Effect tracking of ^{131}I treatment in Graves' disease patients within 1 year and analysis of the factors that may influence the cure

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Abstract

Objective: To observe the disease development and outcome of Graves' disease (GD) patients within 1 year after iodine-131 (^{131}I) treatment, and analyze the factors affecting the treatment effect. **Subjects and Methods:** Clinical data of 221 patients who received the first treatment with ^{131}I in our department from June 2016 to October 2018 were retrospectively analyzed and they were followed up at 3 months, 6 months and 1 year after the treatment. According to the three follow-up records, the cure rate was calculated and the follow-up chart was drawn. The factors that may affect the clinical cure were analyzed according to the follow-up results after 1 year: Independent risk factors affecting the prognosis were screened out by Logistic regression analysis, and the effects of the above factors on the prognosis were further analyzed by Chi-square test, and the cure multiple relationship caused by the influencing factors was analyzed by Logistic regression analysis. **Results:** The cure rate was 58.82% and the effective rate was 71.95%. At the 3-month follow-up, 11 patients (4.98%) presented complete response, 99 patients (44.80%) presented hypothyroidism, 93 patients (42.08%) presented partial response, and 18 patients (8.14%) presented no effect or recurrence. At 6 months, 18 cases (8.14%) had complete response, 90 cases (40.72%) had hypothyroidism, 59 cases (26.70%) had partial response, and 54 cases (24.43%) had no effect or recurrence. At 12 months, 36 cases (16.29%) had complete response, 94 cases (42.53%) had hypothyroidism, 29 cases (13.12%) had partial response, and 62 cases (28.05%) had no effect or recurrence. Thyroid weight and thyroid peroxidase antibody (TPOAb) were the influencing factors. Among all patients, patients with thyroid weight ≤28.70g were 4.25 times more likely to achieve clinical cure than patients with >28.70g [OR (95%CI):4.252 (2.383-7.588), P<0.01)], female patients with the thyroid weight ≤28.70g was 5.78 times than those with >28.70g [OR (95%CI): 5.776 (2.951-11.308), P<0.01]. In male, patients with TPOAb≤449.00IU/mL were 0.27 times more likely to achieve clinical cure than those with >449.00IU/mL [OR (95%CI): 0.274 (0.081-0.919), P<0.05]. **Conclusion:** Iodine-131 was an effective treatment to GD. Thyroid weight before treatment was the influencing factor for all patients and female patients, while TPOAb was the influencing factor for male patients.

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Introduction

Graves' disease(GD) is an autoimmune disorder in which thyrotropin receptor antibodies (TRAb) stimulate the thyroid stimulating hormone (TSH) receptor, increasing thyroid hormone production and release [1]. It often occurs in genetically susceptible populations (especially women) and people with smoking, iodine-rich dietary stress, infection, and pregnancy [2]. Iodine-131 (^{131}I), antithyroid drugs (ATD) and surgery are the common treatment methods for GD [3]. Iodine-131is favored by many doctors for its efficacy and safety, especially when patients contraindicated ATD use or failure to achieve euthyroidism during treatment with ATD [1]. The purpose of this study is to observe the development and outcome of hyperthyroidism patients after ^{131}I treatment, and to analyze the factors that influence the therapeutic effect of the treatment.

Subjects and Methods

Ethics statement

This is a retrospective clinical study. It presents a summary and analysis of a large number of clinical data. The study was approved by the Ethics Committee for Medical Research Tianjin Medical University General Hospital and was carried out in accordance

with the Good Clinical Practice. Informed consents were provided by all patients participating in this study.

Patients

Clinical data of patients receiving ^{131}I treatment in the Department of Nuclear Medicine, General Hospital of Tianjin Medical University from June 2016 to October 2018 were retrospectively analyzed. Inclusion criteria: (1) All the patients diagnosed with GD that met the criteria of the Chinese guideline: Guideline for ^{131}I Treatment of Graves' Hyperthyroidism (2013 Edition) [4]; (2) Patients who received ^{131}I treatment for the first time and had follow-up records at 3, 6 and 12 months after treatment. Exclusion criteria: (1) Patients with hyperthyroidism caused by toxic adenoma or other causes; (2) Patients with previous cervical radiation history or previous ^{131}I treatment. A total of 221 cases were reported, including 49 males and 172 females, aged from 16 to 70 (42.03±13.72).

Data collection

Before the ^{131}I treatment, the patients had undergone routine eligibility examinations, including the assessment of standard clinical symptoms of GD, effective^{131}I half-life in thyroid gland (T_{eff}), tri-iodothyronine (T3), thyroxine (T4), free tri-iodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroglobulin antibody (TGAb), thyroid microsome antibody (TMAb), thyrotropin receptor antibody (TRAb) as well as iodine uptake tests: 24-h (T24).

The therapeutic dose of radioiodine was calculated with the formula [5]: Dose=estimated gland weight (g)×absorption dose (Gy/g)×0.67/$T_{1/2eff}$ (days)×Max% uptake. Absorption dose=100Gy/g, 0.67 is a correction factor. Thyroid weight (g)=0.479×thyroid volume (cm^3), the total volume of thyroid was the sum of the product of the length, width and thickness of the double-lobe thyroid. GE Ving Med Ultrasound Vivid Five Ultrasound instrument was used to measure the thyroid size of each patient [6, 7] (all were remeasured by more than two physicians). All the patients took the calculated dose of ^{131}I orally. They all fasted for 2 hours before and after administration of ^{131}I to achieve higher absorption.

Patients were followed up at 3, 6 and 12 months after treatment, and the follow-up was mainly based on outpatient review records. Patients' symptoms, signs, medication status and laboratory test results, such as FT3, FT4 and TSH, were recorded. At the same time, part of the patients who did not attend the clinic was followed-up by telephone.

Efficacy was assessed according to the criteria of the Guideline for the ^{131}I Treatment of Graves' Hyperthyroidism (2013 Edition) [4]: (a) Complete response (CR): symptoms and signs of hyperthyroidism completely disappeared. FT3, FT4 and TSH returned to normal; (b) Partial response (PR): symptoms of hyperthyroidism were alleviated, signs partially disappeared, serum FT3 and FT4 significantly decreased, but not to the normal level; (c) No effect: the patient's symptoms and signs were not improved or aggravated, and the serum thyroid hormone level was not significantly reduced; (d) Recurrence: After ^{131}I treatment, the disease reached the standard of complete response, but symptoms and signs of hyperthyroidism appeared again, and serum thyroid hormone level increased again; (e) Hypothyroidism: after ^{131}I treatment, symptoms and signs of hypothyroidism were observed, and serum thyroid hormone levels were lower than normal and TSH levels were higher than normal. In this study, (a)(e) was defined as cured and (b)(c)(d) as uncured [8, 9]. (a)(b)(e) was defined as effective treatment; (c)(d) was defined as ineffective treatment [5, 10].

Statistical analysis

Statistical analysis was carried out using SPSS for windows, version 25.0 (SPSS Inc., Chicago, Illinois, USA). Logistic regression analysis was used to screen independent risk factors affecting patient prognosis. The Chi-square test was applied to investigate the influence of count data. Moreover, logistic regression analysis was used to evaluate the impact that particular parameters had on the success of treatment with ^{131}I (clinically cured and clinically uncured).

Results

Follow-up of efficacy of patients in this study

Follow-up records of 221 patients were plotted into a tree, as shown in Figure 1.

At the initial stage of treatment, i.e., 3 months after treatment, 11 patients (4.98%) presented complete response, 99 patients (44.80%) presented hypothyroidism, 93 patients (42.08%) presented partial response, and 18 patients (8.14%) presented no effect or recurrence. At the middle stage of treatment, namely 6 months after treatment, 18 cases (8.14%) had complete response, 90 cases (40.72%) had hypothyroidism, 59 cases (26.70%) had partial response, and 54 cases (24.43%) had no effect or recurrence. At the late stage of treatment, namely 12 months after treatment, 36 cases (16.29%) had complete response, 94 cases (42.53%) had hypothyroidism, 29 cases (13.12%) had partial response, and 62 cases (28.05%) had no effect or recurrence.

Of the 11 patients who showed complete response at 3 months, 4 (36.36%) showed complete response, 4 (36.36%) showed hypothyroidism, 2 (18.18%) showed partial response, and 1 (9.09%) showed no effect or recurrence at 12 months. Of the 99 patients who showed hypothyroidism at 3 months, 14 cases (14.14%) had complete response, 67 cases (67.68%) had hypothyroidism, 6 cases (6.06%) had partial response, and 12 cases (12.12%) had no effect or recurrence at 12 months. Of the 93 patients who showed partial response at 3 months, 18 cases (19.35%) had complete response, 23 cases (24.73%) had hypothyroidism, 21 cases (22.58%) had partial response, and 31 cases (33.33%) had no effect or recurrence at 12 months.

The effect of clinical and biochemical data before treatment on the cure at 12 months after treatment

The results of univariate continuous logistic regression analysis (Table 1) showed that among all patients, the factors related to the recovery of GH included: thyroid weight and TRAb; In women, thyroid weight and TRAb was associated with treatment status. In men, TPOAb was associated with treatment status, but thyroid weight and TRAb was not associated with treatment status.

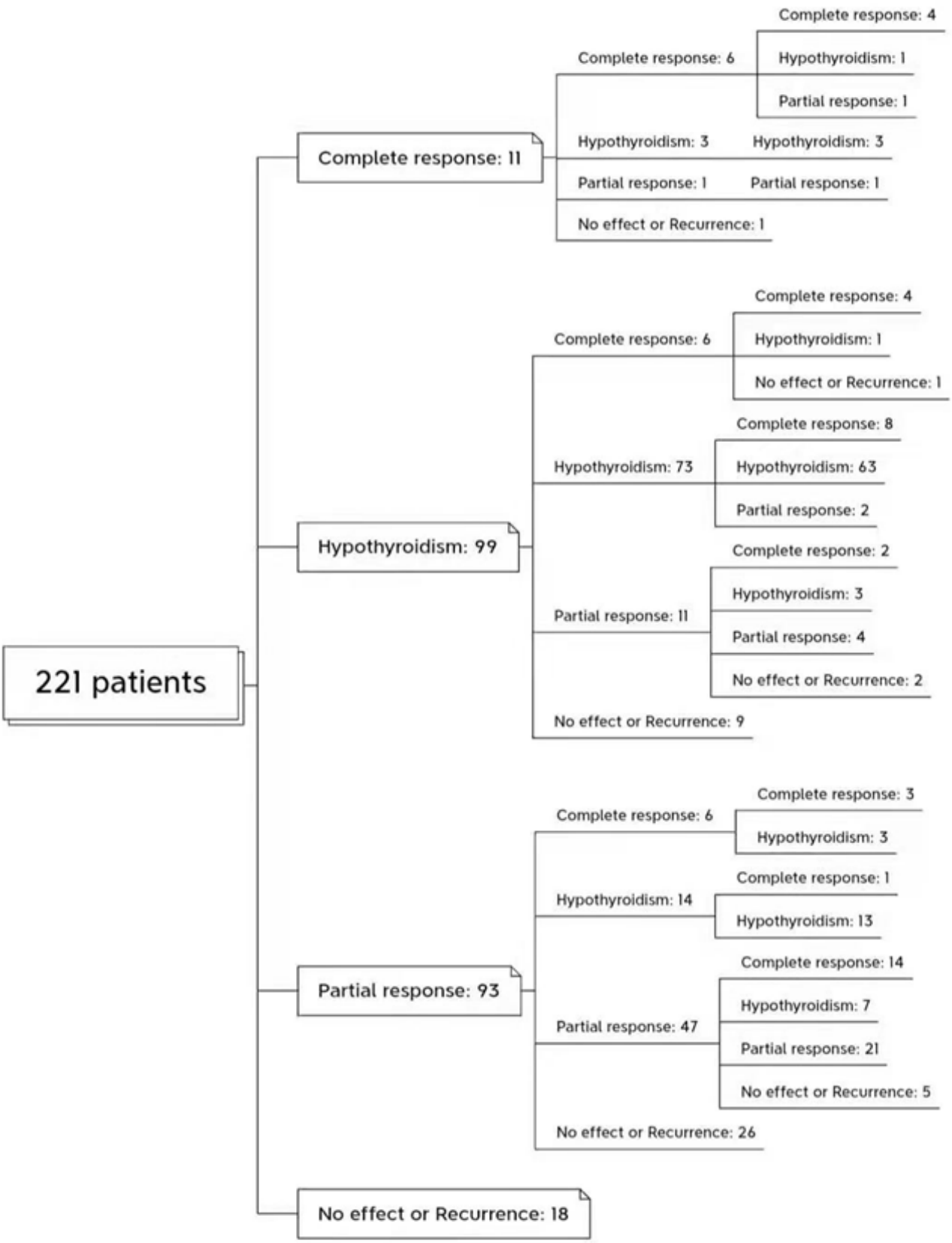

Figure 1. Follow-up results of 221 patients at 3, 6, and 12 months after treatment.

Table 1. *Factors influencing prognosis of GD patients, screened by Logistic regression univariate analysis.*

Factors	All patients	Female patients	Male patients
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Gender	0.915 (0.481-1.739)	0.987 (0.966-1.009)	1.018 (0.971-1.068)
Age (year)	0.993 (0.973-1.012)		
Thyroid weight (g)	1.040 (1.023-1.057)**	1.064 (1.038-1.092)**	1.007 (0.985-1.030)
Urinary iodine (μg/L)	0.999 (0.996-1.002)	1.002 (0.998-1.006)	0.991 (0.982-1.001)
FT3 (pmol/L)	1.016 (0.994-1.039)	1.024 (0.998-1.051)	0.994 (0.951-1.039)
FT4 (pmol/L)	1.008 (0.999-1.016)	1.008 (0.998-1.017)	1.012 (0.987-1.037)
TGAb (IU/mL)	1.016 (0.987-1.046)	1.026 (0.993-1.060)	0.976 (0.910-1.046)
TPOAb (IU/mL)	0.990 (0.927-1.057)	1.027 (0.954-1.106)	0.855 (0.734-0.995)*
TRAb (IU/L)	1.020 (1.000-1.041)*	1.027 (1.004-1.051)*	0.995 (0.951-1.040)
Highest iodine uptake rate (%)	1.000 (0.976-1.024)	1.008 (0.982-1.035)	0.921 (0.837-1.013)
24h iodine uptake rate (%)	0.988 (0.964-1.013)	0.996 (0.969-1.023)	0.946 (0.886-1.010)
Half-life (days)	0.917 (0.755-1.113)	0.941 (0.755-1.171)	0.803 (0.513-1.257)
ATD treatment△	1.358 (0.875-2.106)	1.353 (0.820-2.231)	1.363 (0.543-3.419)

△: *ATD treatment was grouped by: no medication, medication and withdrawal ≤7 days, medication and withdrawal >7 days; **P<0.01; *P<0.05*

Continuous variables were divided into two groups according to ≤median and > median, namely, thyroid weight (group 1≤28.70g, group 2 >28.70g), TRAb (group 1≤11.94IU/L, group 2 >11.94IU/L), TPOAb (group 1≤449.00IU/mL, group 2 <449.00IU/mL), Chi-square test was performed, and the results were shown in Table 2. For all patients and for female patients, thyroid weight was statistically different between cured and uncured patients (P<0.01), there was no significant difference in other factors (P>0.05). For male patients, TPOAb was statistically different between cured and uncured patients (P<0.05) and there was no significant difference in other factors.

In this study, the factor with statistical difference between the above two methods was taken, that is, thyroid weight was a related factor affecting the recovery of ^{131}I treatment for GD in all patients and female patients, while it had no effect on male patients. TPOAb was a related factor affecting the recovery of ^{131}I treatment for GH in male patients, but had no effect in female patients or all patients.

Thyroid weight (group 1≤28.70g, group 2 >28.70g) and TPOAB (group 1≤449.00IU/mL, group 2 >449.00IU/mL) were labeled as grouping variables to perform Logistic regression analysis. The results were shown in Table 3. For all patients, subjects with thyroid weight ≤28.70g were 4.25 times more likely to achieve clinical cure than those with >28.70g. For female patients, subjects with thyroid weight ≤28.70g were 5.78 times more likely to achieve clinical cure than those with >28.70g. For male patients, subjects with TPOAb≤ 449.00IU/mL were 0.27 times more likely to achieve clinical cure than those with >449.00IU/mL.

Discussion

In China, ^{131}I, antithyroid drugs and surgery are all the first-line treatment methods for GD [4]. Iodine-131 has the advantages of definite efficacy, predictable clinical outcome, safety and convenience. Guideline for ^{131}I Treatment of Graves' Hyperthy-

Table 2. *Factors influencing prognosis of GD patients, screened by Chi-square test.*

Factors		All patients	Female patients	Male patients
		Cured (Uncured)	Cured (Uncured)	Cured (Uncured)
Thyroid weight (g)	≤ 28.70	82 (27)	73 (22)	9 (5)
	> 28.70	45 (63)**	27 (47)**	18 (16)
TRAb (IU/L)	≤ 11.94	70 (39)	55 (28)	15 (11)
	> 11.94	59 (49)	47 (41)	12 (8)
TPOAb (IU/mL)	≤ 449.00	61 (48)	53 (35)	8 (13)
	> 449.00	67 (41)	49 (33)	18 (8)*

*Continuous variables were divided into two groups based on ≤median and > median. **P < 0.01; *P < 0.05*

Table 3. *Logistic regression analysis of influencing factors.*

Factors	All patients	Female patients	Male patients
	OR (95% C.I.)	OR (95% C.I.)	OR (95% C.I.)
Thyroid weight (g)	4.252 (2.383-7.588)**	5.776 (2.951-11.308)**	1.600 (0.443-5.778)
TPOAb (IU/mL)	0.990 (0.927-1.057)	1.020 (0.552-1.885)	0.274 (0.081-0.919)*

*Thyroid weight (group 1 ≤28.70g, group 2 > 28.70g) and TPOAb (group 1≤449.00IU/mL, group 2 > 449.00IU/ mL) were labeled as group variables for Logistic regression analysis. **P< 0.01; *P< 0.05*

roidism (2013 Edition) pointed out that the evaluation of treatment efficacy should be carried out at least 6 months after treatment, and this study was evaluated at 12 months after treatment, and the effective rate was basically consistent with the relevant studies. The study of Kuanrakcharoen et al. (2017) [11] showed that the cure rates after 6 months and 12 months were 46.0% and 66.3%, and the total response rate after 12 months accounted for 11.5%, which was consistent with the results of this study. The study of Wang RF et al. (2010) [5] showed that the incidence of hypothyroidism was about 33.2% within 6-12 months of treatment, which was basically consistent with our study. The study of Xing YZ et al. (2020) [12] showed that the cure rate was 62.2% at 12 months after treatment, among which complete response was 28.9% and hypothyroidism was 33.3%. The cure rate was consistent with our study, but the complete response accounted for a higher proportion, which may be related to the fact that they used a fixed dose while we used the calculated dose of ^{131}I. In the study of Brito et al. (2020) [13] in the United States, they defined the requirement for follow-up treatment within two years after treatment as treatment failure, and their treatment success rate was 93%, which was quite different from our study and may be related to ethnic differences and different doses of ^{131}I administration.

There are many factors influencing the therapeutic effect of ^{131}I. A retrospective analysis of the treatment of GD with a fixed dose of 15mCi [14] showed that thyroid weight was the only factor affecting the cure, and the median thyroid weight of patients with successful treatment was 44.6g. The study of Kuanrakcharoen et al. (2017) [11] showed that the 1-year cure rates of the groups with gland weight <30g, 30-60g and >60g were 60.0%, 46.7% and 36.1%, respectively, which was consistent with our results of higher cure rates with thyroid weight ≤ 28.70g. Thyroid volume is related to a number of factors, such as thyroid disease severity, thyroid immune disorder degree, thyroid disease duration, gender, individual sensitivity, etc., which may influence the outcome of ^{131}I treatment in a complex interaction [15]. In this study, the initial thyroid weight of male patients was a non-influencing factor for the treatment effect, which may be due to the fact that the average thyroid weight of male patients was greater than that of female patients (male thyroid weight: 16.30~170.10g, 44.66±26.07g; Female thyroid weight: 8.70~142.00g, 34.03±23.79g), which caused the difference of sensitivity to ^{131}I in males.

In this study, it was found that male patients with high TPOAb level had higher clinical cure rate, which was consistent with the findings of Q. Dong et al. (2017) [16]. Q. Dong et al. (2017) reported that TPOAb in patients with hypothyroidism after ^{131}I treatment was significantly higher than that in other patients, indicating that TPOAb may play a promoting role in the occurrence and development of hypothyroidism. However, other investigators had the opposite findings. In the study of Gomez-Arnaiz et al. (2003) [17], the change of TPOAb level did not show any predictive value; A study of transient hyperthyroidism in children with Hashimoto's thyroiditis [18] found that higher TPOAb level at the time of diagnosis was related to longer duration of hyperthyroidism. The effect of TPOAb on the therapeutic effect of ^{131}I still needs to be further studied.

In the process of ^{131}I treatment of GD, internal thyroid dosimetric factors and some potential confounding factors may interfere with the efficacy, and they may even interact or counteract with each other. Many studies have evaluated the effects of ^{131}I therapy, but the results were inconsistent due to differences in design, sample size, patient selection, and dose calculation [9, 19, 20]. It is difficult to predict the outcome of ^{131}I therapy by a single factor [15]. In clinical treatment, physicians still need to handle the treatment flexibly according to their treatment experience.

In conclusion, the results of our retrospective study showed that the cure rate of ^{131}I treatment in GD patients was 58.82% and the effective rate was 71.95%. The thyroid weight before ^{131}I treatment was the influencing factor of ^{131}I treatment efficacy for all patients and female patients, and the treatment success rate was higher for patients with smaller thyroid weight. TPOAb was the influencing factor of the efficacy for male patients, and the cure effect was better for patients with higher TPOAb value. The sample size of this study was small, especially for male patients, and the follow-up time was only 12 months after treatment. Therefore, more cases should be accumulated to extend the follow-up time and more complete studies will be conducted for verification.

The authors declare that they have no conflicts of interest.

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