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Original Research Article

Prognostic value of serum stimulating thyroglobulin in metastatic radioactive iodine-refractory differentiated thyroid cancer

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Abstract

Purpose: *To investigate the prognostic value of serum-stimulated thyroglobulin (ps-Tg) before the first ^{131}I therapy in patients with metastatic radioactive iodine-refractory differentiated thyroid cancer (RR-DTC).*
Methods: *From August 2017 to August 2020, the clinical data for 160 patients with thyroid papillary carcinoma (PTC) who received thyroidectomy and ^{131}I treatment were analyzed retrospectively. Differences in clinical data and related thyroid indices were compared. Univariate and multivariate logistic regression analyses were used to analyze the related factors affecting the occurrence of RR-DTC. Receiver-operator characteristic (ROC) curves were used to determine the discriminative power of ps-Tg in predicting RR-DTC, while the Kaplan-Meier survival curve of ps-Tg for RR-DTC was drawn.*
Results: *A total of 160 patients with thyroid cancer were enrolled, including 47 males, and 113 females (70.62 %). Overall mean age was 39 ± 13 years old. The follow-up results showed that 68 patients with thyroid cancer were refractory to radioactive iodine. The ps-Tg of the iodine-refractory group was higher than that of the iodine-receptive group ($p < 0.001$). Multivariate logistic regression showed that ps-Tg was an independent risk factor for RR-DTC (OR = 1.086, $p = 0.000$). The optimal cut-off value of ps-Tg for predicting progression to RR-DTC was 19.21 μg/L. Kaplan-Meier survival curve showed that the risk of iodine refractory in patients with thyroid cancer (≥ 19.21 μg/L) was higher than that of patients with thyroid cancer < 19.21 μg/L ($p < 0.001$).*
Conclusion: *The ps-Tg before the first ^{131}I therapy independently predicts the occurrence of metastatic RR-DTC when ps-Tg is greater than the risk of RR-DTC increase. This finding will be helpful in predicting the occurrence of RR-DTC, in order to determine the best time to start treatment and make individualized treatment decisions.*

Keywords: *Thyroid Cancer, Serum Stimulating Thyroglobulin, Iodine-refractory differentiated thyroid cancer, 131 Iodine therapy*

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INTRODUCTION

From 1990 to 2019, the global incidence of thyroid cancer gradually increased, and has become the most common malignant tumor among endocrine tumors [1]. According to the 2020 Global Cancer statistics, there are 586,000 cases of thyroid cancer in the world, and the

incidence rate ranked ninth among all cancers [2].

Differentiated thyroid carcinoma (DTC) is the main pathological type of thyroid carcinoma, accounting for more than 90 % of cases, including papillary carcinoma and follicular carcinoma. The current guidelines for the treatment of differentiated thyroid cancer include surgery, radioactive iodine (RAI), and thyroid-stimulating hormone (TSH) suppression comprising therapy, with a 10-year survival rate as high as 90 % [3].

Unfortunately, about 15 % of thyroid cancer patients still develop local recurrence and/or distant metastasis, and nearly two-thirds of these patients will transform into iodine-refractory differentiated thyroid cancer (RR-DTC) [4]. In a Long-term follow-up study, it was found that patients with RAI metastatic thyroid cancer had the worst prognosis, with a 10-year survival rate of 10 % [3]. A study has shown that the de-differentiation of tumor cells may be the main reason for the progression of the disease in such patients. Due to the de-differentiation of tumor cells, the expression of thyrotropin receptor and sodium iodide symporter is reduced and their function is abnormal, which makes the patient insensitive to ^{131}I treatment, thus becoming iodine-refractory differentiated thyroid cancer with poor prognosis [5]. Therefore, early detection of RR-DTC, reduction of unnecessary ^{131}I radiation in patients, and changing the treatment regimen could effectively improve the prognosis of iodine-refractory patients [6]. Previous studies have found that ps-Tg could independently predict the risk stratification of metastasis and recurrence in differentiated thyroid cancer [7,8]. At present, there are few studies on whether ps-Tg before the first ^{131}I treatment could predict the risk of RR-DTC in patients with thyroid cancer. Therefore, the aim of this study was to evaluate the prognosis of metastatic RR-DTC by measuring ps-Tg before the first ^{131}I treatment in patients.

METHODS

Study population and ethics approval

From August 2017 to August 2020, a total of 160 patients with papillary thyroid cancer diagnosed by postoperative pathology in the Second Affiliated Hospital of Fujian Medical University, who underwent total thyroidectomy and ^{131}I treatment were retrospectively studied. This retrospective study was approved by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University (approval no. 2022-516), and all study patients signed informed consent. All methods used in this study were in accordance with relevant international guidelines [9].

Inclusion criteria

Patients with thyroid papillary carcinoma that has been confirmed by postoperative pathology, patients that underwent total thyroid cancer resection and lymph node dissection, all patients that underwent postoperative ^{131}I treatment and ^{131}I whole body SPECT scan, and patients with complete clinical information were included in the study.

Exclusion criteria

Patients below 18 years and above 80 years or patients with neck ultrasound or thyroid imaging before the first ^{131}I treatment showed postoperative residual or patients in which thyroglobulin antibody (Tg-Ab) was positive were excluded from this study.

Serological tests

The patients stopped taking levothyroxine sodium tablets (Euthyrox) for 3 - 4 weeks according to the directive of the Physician. When TSH > 30 mIU/L, the Roche electrochemi-luminescence instrument E411 and matching reagents were used to determine the level of Thyroglobulin (Tg). The level of serum thyroid hormones was determined using Siemens automatic chemiluminescence immunoassay analyzer ADVIA Centaur XP and matching reagents. All indicators were tested in the same laboratory.

^{131}I treatment and follow-up

Preparation before treatment

Before ^{131}I treatment, a low iodine diet was taken for 2 - 4 weeks and levothyroxine tablets for 3 - 4 weeks. Serum thyroid hormone, neck color ultrasound, chest CT and thyroid imaging were performed before ^{131}I treatment.

^{131}I therapeutic dose

According to the American Thyroid Association (ATA) 2015 guidelines [9], the dose was determined in line with the patient's individual condition (differentiated thyroid cancer TNM staging and recurrence risk stratification), such as the treatment dose of ^{131}I for nail clearing is 30 - 100 mCi, and the dose of ^{131}I for focus clearing is 100 - 200 mCi (the dose of ^{131}I for

cervical lymph node metastases is between 100 - 150 mCi, and the dose of ^{131}I for lung metastases is between 100 and 150 mCi).

Follow-up after treatment

After 1 month of treatment, the thyroid function was rechecked and the dose of levothyroxine tablets was adjusted. Six months after the first treatment, levothyroxine tablets were discontinued, and when TSH was greater than 30 mIU/L, re-examinations such as serum thyroid hormone, diagnostic ^{131}I scan, cervical color Doppler ultrasound, and cervical and chest CT were performed. The follow-up was reviewed every 6 months, and the follow-up was stopped when the patient developed iodine refractory treatment. The end of follow-up was in August 2020, and none of the patients enrolled in the study were lost to follow-up. The average follow-up time was 19 ± 7 months, and the follow-up results were 68 cases of radioactive iodine-refractory PTC and 92 cases of iodine-receptively PTC.

Diagnostic criteria for iodine-refractory differentiated thyroid cancer

According to the American Thyroid Association (ATA) 2015 guidelines [9], RR-DTC was defined as : (1) The primary lesion/metastasis never concentrated ^{131}I (No iodine accumulation outside the thyroid bed); (2) Despite previous ^{131}I-focused lesions, the lesions lost the ability to concentrate ^{131}I during the treatment (No radioactive iodine contamination); (3) Although ^{131}I was obviously concentrated, it was concentrated in some lesions, but not in other lesions; (4) Despite the obvious ^{131}I concentration, the metastatic lesions progressed.

Statistical analysis

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) (version 25; IBM, Armonk, NY, USA) and MedCalc (version 20.015). The Kolmogorov-Smirnoff test was used to assess the normality of the distribution of continuous variables. Continuous variables are presented as mean ± standard deviation (SD) or median (25^{th} - 75^{th} percentile) and compared using Student's *t*-test or Mann-Whitney U test. Categorical variables are presented as percentages and compared using Chi-square test or Fisher's exact test. The differences in general clinical data, ps-Tg, and other related thyroid indices between iodine-refractory and iodine-receptively groups were compared. Binary univariate and multivariate logistic regression were determined to analyze the related factors affecting the occurrence of RR-DTC. Receiver operator characteristics (ROC) curve was implemented to determine the discriminative ability of ps-Tg in predicting RR-DTC. The Kaplan-Meier survival curve of ps-Tg for RR-DTC was drawn.

RESULTS

Clinical data of the study population

A total of 160 patients with thyroid cancer were enrolled, and all of them were confirmed via postoperative pathology to have papillary carcinoma, including 47 males (29.38 %), and 113 females (70.62 %; Table 1). The overall average age was 39 ± 13 years old, and the average follow-up time was 19 ± 7 months. The results of follow-up showed that 68 patients developed iodine refractory (iodine-refractory group), and 92 patients did not develop iodine refractory (iodine-receptive group). The mean age of the iodine-refractory group was 38 ± 13 years and included 21 male patients and 47 female patients. The mean age of the iodine-receptive group was 40 ± 13 years, and there were 26 male patients and 66 female patients. Compared with the iodine-receptive group, there were no significant differences in age, gender, tumor size and number, extrathyroidal infiltration, T stage, and N stage in the iodine-refractory group ($p > 0.05$). The M stage, TNM stage, recurrence risk stratification, cumulative dose, and number of ^{131}I treatments in the iodine-refractory group were significantly higher than those in the iodine-refractory group, and the differences were statistically significant ($p < 0.05$; Table 1). With regards to the level of thyroid function (Table 2), the ps-Tg of the iodine-refractory group was higher than that of the iodine-receptive group, and the difference was statistically significant ($p < 0.001$). However, there were no statistically significant differences in the remaining thyroid function indicators between the iodine-refractory group and the iodine-receptive group (TgAb, TPO-Ab, T_3, T_4, TSH, FT_3, FT_4, and rT_3) (all $p > 0.05$).

Factors that influence iodine-refractory differentiated thyroid cancer

Univariate logistic regression showed that M_1 stage (OR = 6.858, $p = 0.000$), II-III stage (OR = 10.452, $p = 0.000$), high recurrence risk stratification (OR = 6.071, $p = 0.001$), 3 - 4 times of ^{131}I treatment (OR = 4.284, $p = 0.032$), ps-Tg (OR = 1.098, $p = 0.000$), TgAb (OR = 1.070, $p = 0.015$) were significantly associated with RR-DTC (Table 3).

Table 1: Clinical data of the study population

Parameter	Total population (n=160)	Iodine-refractory group (n=68)	Iodine-receptive group (n=92)	*P*-value
Age, (years)	39±13	38±13	40±13	0.295
Male, (n (%))	47 (29.38)	21 (30.88)	26 (28.26)	0.719
Number of tumor lesions, (n (%))				0.410
Single lesion	79 (49.38)	31 (45.59)	48 (52.17)	
Multiple lesions	81 (50.62)	37 (54.41)	44 (47.83)	
size of tumor lesion, (cm)	1.31 ± 0.42	1.33 ± 0.42	1.29 ± 0.41	0.590
extrathyroidal infiltrates, (n (%))	42 (26.25)	22 (32.35)	20 (20.40)	0.131
T stage, (n (%))				
T_1	77 (48.12)	17 (25.00)	60 (65.22)	
T_2	25 (15.62)	14 (20.59)	11 (11.96)	0.137
T_3	31 (19.38)	18 (26.47)	13 (14.13)	
T_4	21 (13.13)	13 (19.12)	8 (8.70)	
N stage, (n (%))				
N_0	29 (18.13)	6 (11.76)	23 (25.00)	
N_{1a}	48 (30.00)	23 (33.82)	25 (27.17)	0.364
N_{1b}	83 (51.87)	39 (57.35)	44 (47.83)	
M stage, (n (%))				
M_0	122 (76.25)	39 (57.35)	83 (90.22)	
M_1	38 (23.75)	29 (42.65)	9 (9.78)	0.000
TNM stage, (n (%))				
I	101 (63.13)	24 (35.29)	77 (83.70)	
II	50 (31.25)	37 (54.41)	13 (14.13)	0.000
III	9 (5.62)	7 (10.29)	2 (2.17)	
Recurrence risk stratification, n (%)				
low risk	14 (8.75)	6 (8.82)	8 (8.70)	
medium risk	105 (65.63)	35 (51.47)	70 (76.08)	0.001
high risk	41 (25.62)	27 (39.71)	14 (15.22)	
cumulative dose of ^{131}I (mCi)	196 ± 116	288 ± 123	129 ± 42	0.000
Number of ^{131}I treatments, (n (%))				
1	7 (4.37)	2 (2.94)	5 (5.43)	
2	106 (66.25)	30 (44.12)	76 (82.61)	0.000
3	33 (20.63)	25 (36.76)	8 (8.70)	
4	14 (8.75)	11 (16.18)	3 (3.26)	

Table 2: Clinical data of the study population (*contd*.)

Parameter	Total population (n=160)	Iodine-refractory group (n=68)	Iodine-receptive group (n=92)	*P*-value
Level of thyroid function				
ps-Tg, (μg/L)	18.65 (10.89-50.78)	200.37 (100.54-345.89)	10.98 (6.78-18.65)	0.000
TgAb, (mU/L)	10.43 (8.32-15.40)	12.32 (8.24-16.59)	10.23 (8.32-14.32)	0.051
TPO-Ab, (mU/L)	6.78 (5.43-10.32)	7.55 (5.43-10.43)	6.76 (5.32-10.23)	0.083
T_3, (μg/L)	0.61±0.26	0.65±0.28	0.57±0.23	0.061
T_4, (μg/L)	20.85±8.48	22.81±9.60	20.41±7.26	0.076
TSH, (mIU/L)	78.43±33.99	81.71±35.64	76.00±32.72	0.295
FT_3, (pmol/L)	3.35±1.11	3.31±1.13	3.41±1.08	0.593
FT_4, (pmol/L)	6.38±2.34	6.51±2.27	6.28±2.41	0.539
rT_3, (ng/L)	153.16±35.79	155.93±35.92	151.12±34.76	0.402

The above factors with statistical significance in the univariate analysis were in the multivariate logistic regression analysis, and the results showed that ps-Tg (OR = 1.086, p = 0.000) may be used as an independent risk factor for the occurrence of iodine refractory in DTC.

Predictive value of ps-Tg in radioactive iodine-refractory differentiated thyroid cancer

The ROC curve was used to further test the diagnostic performance of ps-Tg and the best cut-off value for predicting RR-DTC (Figure 1).

Table 3: Univariate and multivariate logistic regression analysis of influencing factors of iodine-refractory thyroid cancer

Parameter	Univariate analysis		Multivariate analysis	
	OR (95CI%)	*P*-value	OR (95CI%)	*P*-value
Number of tumor lesions	1.232 (0.579-2.621)	0.588		
Extrathyroidal infiltrates	1.100 (0.478-2.531)	0.823		
T stage				
T_1-T_2	1*			
T_3-T_4	3.322 (0.859-6.652)	0.357		
N stage				
N_0-N_{1a}	1*			
N_{1b}	1.282 (0.684-2.402)	0.438		
M stage				
M_0	1*			
M_1	6.858 (2.963-15.780)	0.000	3.624 (0.987-10.106)	0.809
TNM stage				
I	1*			
II-III	10.452 (4.858-22.490)	0.000	6.132 (0.457-12.085)	0.961
Recurrence risk stratification				
Low-medium risk	1*			
high risk	6.071 (2.102-10.032)	0.001	2.428 (0.942-5.210)	0.170
Cumulative dose of ^{131}I (mCi)	1.026 (1.017-1.035)	0.000	1.003 (0.249-1.018)	0.089
Number of ^{131}I treatments		***0.032***		***1.312***
1-2	1*			
3-4	4.284 (2.361-8.245)	0.032		
Ps-Tg	1.098 (1.050-1.147)	0.000	1.086 (1.062-1.211)	0.000
TgAb	1.070 (1.013-1.129)	0.015	0.453 (0.168-1.021)	0.117

1*, Reference

According to the ROC curve, the critical point corresponding to the maximum value of Youden's index was used as the best cut-off value for judging whether it was RR-DTC. The optimal cut-off value of ps-Tg for predicting progression to RR-DTC was 19.21 μg/L, with a sensitivity of 89.7 %, a specificity of 80.4 %, and an AUC of 0.930 (95 % CI: 0.893 - 0.967, p < 0.001).

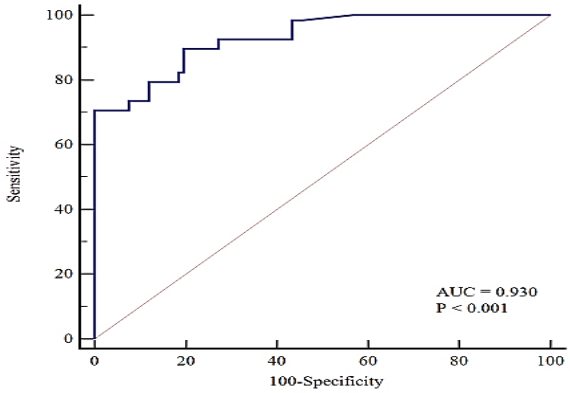

Figure 1: ROC curve of ps-Tg for predicting RR-DTC in 160 patients with papillary thyroid carcinoma

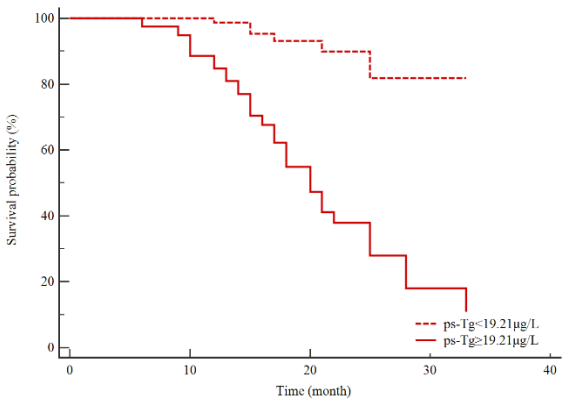

Figure 2: Kaplan-Meier survival curve of RR-DTC based on ps-Tg

Prognostic analysis of metastatic thyroid cancer

In the ps-Tg < 19.21 μg/L group, 7 patients were iodine-refractory, while 74 patients were not iodine-refractory; in the ps-Tg ≥ 19.21 μg/L group, 61 patients were iodine-refractory, and 18 patients were not iodine-refractory. During the follow-up process, the occurrence of iodine

refractory was defined as the end-point event, and the follow-up time was defined as the time period from the first ^{131}I treatment to the end-point event.

The Kaplain-Meier survival curve showed that thyroid cancer patients with ≥ 19.21 μg/L (median time = 21.03 months) had a higher risk of iodine refractory than those with < 19.21 μg/L (median time = 30.73 months) (χ^2 = 38.519, p < 0.001, Figure 2).

DISCUSSION

Currently, most differentiated thyroid cancers are clinically curable with surgery, postoperative radioactive iodine (RAI) therapy, and thyroid-stimulating hormone (TSH) suppression. However, some differentiated thyroid cancers will turn into RR-DTC during the treatment process, and the prognosis is extremely poor, with a 10-year survival rate of less than 10 % [3]. Studies have shown that the de-differentiation of tumor cells may be the main reason for the progression in such patients [10]. Due to the de-differentiation of tumor cells, the function of sodium iodide transporter (NIS) in patients is abnormal and the expression of other iodine processing gene receptors is reduced, such as Tg, thyroid peroxidase (TPO), and thyroid-stimulating hormone receptor (TSHR), resulting in patients being insensitive to ^{131}I therapy and thus becoming RR-DTC [11]. When patients with DTC develop iodine refractory, the follow-up treatment plan should be changed in time, such as local surgery, chemotherapy, targeted therapy, and immunotherapy, etc [12]. Therefore, how to identify radioactive RR-DTC in advance and avoid unnecessary RAI therapy is of great significance, which not only helps to avoid the progression of thyroid cancer caused by discontinuation of levothyroxine tablets but also to help patients switch to other treatment methods as soon as possible.

Thyroglobulin (Tg) is a protein produced by thyroid follicular cells and a specific marker for DTC production. In the case of negative anti-Tg antibodies, Tg is an important indicator for monitoring disease progression. After successful thyroid clearance, elevated Tg levels may indicate disease recurrence and/or metastasis. In recent years, studies have found that the ps-Tg level is used to predict the recurrence and metastasis of thyroid cancer [13,14]. A meta-analysis involving 3947 patients showed that ps-Tg < 10 ng/mL was the best cut-off value for predicting the prognosis of DTC, which suggests that ps-Tg before ^{131}I treatment may serve as a useful negative predictor of persistent and recurrent DTC [15].

Previous studies mainly focused on ps-Tg for the recurrence and metastasis of differentiated thyroid cancer, and there were few studies on the prognosis of iodine-refractory transformation [16]. This present study investigated the relationship between serum-stimulated thyroglobulin and RR-DTC before the first ^{131}I treatment in patients. The univariate logistic regression analysis in this study revealed that the iodine-refractory group had a later TNM stage, higher recurrence risk stratification, more ^{131}I treatment times, and higher ps-Tg and TgAb levels than the iodine-receptive group and the differences were statistically significant. Therefore, it is speculated that patients with advanced thyroid cancer are more likely to develop iodine-refractory thyroid cancer than patients with early-stage thyroid cancer when treated with ^{131}I. After multivariate analysis, it was concluded that ps-Tg was an independent risk factor for iodine refractory in DTC. This study showed that the best cut-off value of ps-Tg for predicting the progression of RR-DTC was 19.21 μg/L, with a sensitivity of 89.7 %, a specificity of 80.4 %, and an AUC of 0.930. When ps-Tg ≥ 19.21 μg/L, patients with DTC were more likely to be refractory to iodine. The Kaplan-Meier survival curve showed that thyroid cancer patients with ≥ 19.21 μg/L (median time = 21.03 months) had a higher risk of iodine-refractory than those with < 19.21 μg/Ls (median time = 30.73 months). This study found that Tg under the first stimulus, was an independent predictor of recurrence risk, and when > 1.6 ng/dL, the recurrence risk increased, which was generally consistent with this study [17]. The difference is that the Amui study [17] focused on disease metastasis and recurrence, and did not predict iodine-refractory transformation. In this paper, the study provides help for early identification of RR-DTC, and helps patients with thyroid cancer to switch to other individualized treatment methods before and after radioactive iodine therapy, which is essential for optimal patient care.

Serum stimulated thyroglobulin (Ps-Tg) before the first ^{131}I treatment can be used to predict the prognosis of differentiated thyroid, but its single level will be affected by other factors such as TSH, and TgAb. This study further evaluated the value of serial ps-Tg measurements in predicting iodine-refractory differentiated thyroid cancer. In a study of 370 patients with DTC with serial ps-Tg measurements, it was observed that even if the interval between continuous ps-Tg measurements was as short as 8 days, the results showed an increase in the identification of

metastatic differentiated thyroid cancer (DM-DTC) [18]. Zhao *et al* [19] further found that ΔTg/ΔTSH was a specific early biochemical marker of DM-DTC (ΔTg is the ps-Tg measurement before radioactive iodine treatment minus the initial ps-Tg measurement, the same notations were applied to ΔTSH), which is better than ps-Tg in predicting DM-DTC and has higher sensitivity and specificity. In addition, the predictive effect of Tg value in suppressed state and Tg value after treatment on iodine refractory requires further study. In a retrospective study of 137 patients with DTC after total thyroidectomy, Miyauchi [20] discovered that even with ^{131}I treatment, patients with Tg doubling time (Tg-DT) less than 1 year were more likely to have local recurrence and metastasis of lesions, and Tg-DT was a significant independent predictor of prognosis.

Limitations of this study

This study still has some limitations. First of all, this study is a single-center study with a small sample size. In the future, multi-center cooperation will be required to expand the sample size. Secondly, this study only focused on papillary carcinomas, and did not include follicular thyroid carcinomas. Finally, this study only focused on the serum Tg level before the first ^{131}I treatment, without follow-up and statistics of the Tg level. In the future, the doubling time of ps-Tg and the continuous monitoring of ps-Tg changes should be further studied for the prediction of RR-DTC.

CONCLUSION

Serum stimulated thyroglobulin (ps-Tg) before the first ^{131}I treatment has been used to predict the occurrence of iodine refractory in patients with DTC after total resection. When ps-Tg ≥ 19.21 μg/L, patients with DTC are more likely to be refractory to iodine. Current advances in RR-DTC diagnosis are limited to post-^{131}I treatment evaluation, in which patients may be exposed to unnecessary ^{131}I radiation and miss opportunities for more effective interventions. It is necessary to be able to predict RR-DTC before ^{131}I treatment, determine the optimal timing of treatment initiation, and make individualized treatment decisions.

DECLARATIONS

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None provided.

Ethical approval

This retrospective study was approved by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University (approval no. 2022-516).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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