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Predictive value of thyroglobulin after radioiodine therapy for excellent response to treatment in postoperative thyroid cancer

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Objective **This study aimed to assess the usefulness of thyroglobulin (Tg) after radioiodine (RAI) therapy in predicting excellent response (ER) to therapy in postoperative differentiated thyroid cancer (DTC).**

Methods **A retrospective observational study was conducted on postoperative DTC patients who underwent RAI from August 2018 to December 2022. Various factors were analyzed to predict ER to treatment. This involved Tg under stimulation (sTg) before RAI, Tg immediately (imTg) 112 h post-RAI and imTg/sTg(rTg). Based on the efficacy of RAI, patients were categorized into two groups: ER and non-ER (NER). Univariate logistic analysis was utilized to compare parameters between the two groups, followed by binary logistic regression analysis on factors associated with ER. Receiver operating characteristic (ROC) curves were employed to evaluate the sensitivity, specificity, and optimal diagnostic cutoff points for parameters affecting ER.**

Results **The analysis included 45 ER patients and 56 NER patients. Statistical significance was found in the binary logistic regression analysis for the number of lymph nodes in the lateral cervical region ($P = 0.016$), sTg ($P = 0.021$), and rTg ($P \leq 0.001$) concerning ER. ROC curve analysis revealed that the rTg area under the curve was 0.845, with an optimal cutoff value of 11.78, sensitivity of 82.6%, and specificity of 74.5%.**

Conclusion **Post-RAI therapy, significant value is demonstrated by rTg with high sensitivity and specificity. This provides a foundation for the evaluation and decisions about DTC treatment in advance.** ***Nucl Med Commun*** **46: 146–151**

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Keywords: excellent response, predictive value, radioiodine, rTg, thyroid cancer

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Introduction

Differentiated thyroid cancer (DTC) generally boasts a favorable prognosis [1], with a 93% 10-year survival rate. Nonetheless, approximately 30% of patients encounter recurrence or metastasis, underscoring the necessity for ongoing and vigilant monitoring. Thyroglobulin (Tg), derived from thyroid follicular epithelial cells, plays a pivotal role in the synthesis and release of thyroid hormones, maintaining the body's normal physiological functions [2]. Tg is released not only by normal thyroid tissue but also by thyroid cancer cells and their metastatic lesions. While Tg remains stable in normal thyroid tissue, its levels significantly rise after the occurrence of thyroid tumors, potentially linked to the proliferation of thyroid cancer cells and the loss of follicular structures [3,4]. The established normal reference range for Tg is 1.40–78.00 μG/L. As serum Tg exclusively originates from thyroid or thyroid cancer tissue, it serves as a crucial indicator in the treatment and follow-up of DTC [5].

Typically, individuals with DTC undergo radioiodine (RAI) therapy postsurgery to eliminate normal thyroid tissue, diminish the risk of recurrence, and enhance the sensitivity and specificity of monitoring tools [6,7]. Currently, assessing the efficacy of RAI therapy involves discontinuing thyroid hormone tablets after 6 months of treatment to stimulate thyroid-stimulating hormone (TSH) and subsequently measuring thyroid function and conducting a ^{131}I whole-body scan (WBS) [6]. Presently, most studies focus on Tg levels or the Tg to TSH ratio under TSH stimulation after subtotal thyroidectomy or before ^{131}I treatment. Additionally, Tg levels under TSH inhibition are explored to evaluate disease status and predict the effectiveness of iodine therapy [8–10]. While Tg under stimulation (sTg) reflects the patient's disease status, it does not indicate the treatment's effectiveness. Currently, no

research article in China addresses the changes in Tg within 1 week after ^{131}I treatment and its response to iodine therapy.

In theory, following RAI therapy, thyroid tissue and metastatic thyroid cancer cells should absorb ^{131}I. As a consequence of radiation effects, both thyroid and tumor cells are expected to undergo destruction, leading to the release of Tg stored in the tissue into the bloodstream, causing a transient increase in Tg levels [11].

Some articles have reported that elevated serum Tg level after RAI therapy is a good indicator for predicting treatment outcomes. These researches have examined the significant rise in Tg levels at 48 h, 3 days, 5 days, 9 days, and 14 days post-RAI therapy [11–14]. Changes in Tg levels indicate the patient's response to RAI therapy and predict therapeutic efficacy. However, the number of cases studied was small, and related influencing factors were not controlled. There are few cutoff points for measuring Tg after ^{131}I treatment, and there is a lack of research on the dynamic changes of Tg increase and decrease after RAI therapy. It is difficult to determine the optimal Tg cutoff value for predicting the effectiveness of RAI therapy and the patient's condition.

As cellular recovery has been identified at day 5 after radiation damage [15], and taking into account the investigation of the maximum time point for the increase in Tg levels and the necessities of clinical practice, this study measured the serum Tg levels of patients at 112 h (4 days and 16 h) post-RAI therapy. By investigating the changes in serum Tg levels, this study addresses the current gap in research on Tg alterations after iodine treatment in China. A comparison with the traditional monitoring of Tg and iodine scan results under TSH stimulation or inhibition after 6 months was conducted. The study aims to explore the predictive value of serum Tg levels at 112 h post-RAI therapy, providing insights into patients' responses to RAI therapy and predicting long-term treatment effects in advance. This approach seeks to offer more reliable evidence-based medical information for patients to formulate accurate treatment plans.

Methods

General data: patient selection

A retrospective observational study was conducted, involving 101 patients diagnosed with DTC who underwent their initial RAI therapy at our hospital from August 2018 to December 2022. Inclusion criteria comprised patients who underwent total thyroidectomy or subtotal thyroidectomy, expressed willingness for RAI therapy, and agreed to follow TSH suppression therapy post-RAI. Additionally, patients underwent RAI therapy 1 month after surgery, abstained from thyroid hormone tablets for a minimum of 3 weeks, adhered to a low-iodine diet, and maintained TSH stimulation (TSH > 30 mIU/L). Exclusion criteria included the presence of local or distant metastatic lesions revealed through medical image examinations [^{131}I WBS after RAI therapy, diagnostic WBS, neck ultrasound, chest computed tomography (CT)], TgAb (anti-thyroglobulin antibodies) positivity (TgAb > 115.00 kIU/L) [16], Tg measurements exceeding the specified limits, and incomplete clinical data. This study adheres to the principles of the Helsinki Declaration and has undergone ethical review at our institute.

Data collection

Operative pathological data included the presence of goiter, Hashimoto's disease, tumor deposit, extraglandular invasion, capsule invasion, single or multiple lesions, maximum tumor diameter, and the number of metastatic lymph nodes (LN no.) in central and lateral regions.

Imaging data comprised ultrasonography and CT scans of the neck and chest without contrast 1 day before RAI therapy, ^{131}I WBS on day 4 post-RAI therapy. SPECT/CT (Infinia Hawkeye, GE Healthcare, Milwaukee, Wisconsin, USA) used gamma camera equipped with high-energy collimators and 3/8 inch NaI crystals. Anterior and posterior WBS were acquired at a speed of 10 cm/min using a 1024 × 256 matrix and a 364 keV photopeak with a 10% window and diagnostic WBS or neck ultrasound 6 months post-RAI therapy. Ultrasound measurements were utilized to assess the residual thyroid dimensions.

Thyroid function tests encompassed serum levels of free triiodothyronine (FT3), free tetraiodothyronine (FT4), TSH, TgAb, and Tg on 1 day before RAI therapy, designated as sFT3, sFT4, sTSH, sTgAb, and sTg. On 112 h ± 20 min post-RAI therapy, immediate serum thyroid function tests were conducted, designated as (imFT3, imFT4, imTSH, imTgAb, and imTg), with Tg changes represented by dTg = imTg – sTg. The Tg change rate was calculated as rTg = imTg/sTg. Six months post-RAI therapy, serum thyroid function tests were performed under TSH stimulation or inhibition.

Thyroid function tests were conducted using electrochemiluminescence immunoassay with reagents provided by Roche, Switzerland. Normal reference values were set as follows: Tg: 1.40–78.00 μG/L, TSH: 0.27–4.20 mIU/L, TgAb: 0.00–115.00 kIU/L.

Outcome

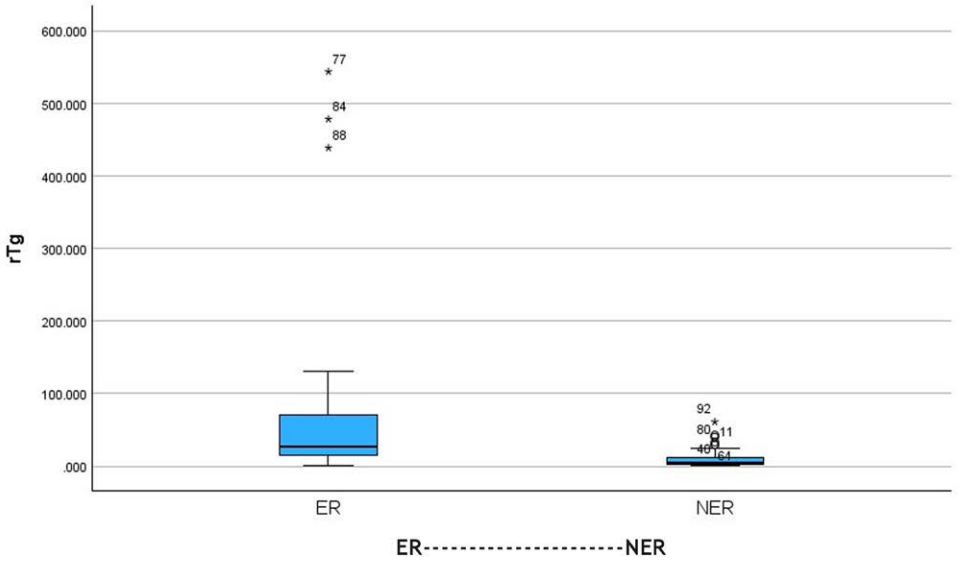
According to the 2015 ATA guidelines [6], criteria for the excellent response (ER) group were determined through a comprehensive analysis of serological (Tg, TgAb) and imaging (neck ultrasound, chest CT, and ^{131}I WBS) results obtained during regular follow-ups. Meeting the following two points classified a case as ER: negative imaging and either suppressed Tg <0.2 ng/ml or sTg <1 ng/ml. For the non-excellent response (NER) group, judgment criteria included three situations: indeterminate

Table 1 Parameters based on differentiated thyroid cancer patients and postoperative routine pathology: univariate analysis comparing possible parameters that affect excellent response or non-excellent response

Parameters	Total	ER	NER	$\chi^2/F/u$	*P* value
Sex, M/F	18/83	6/40	12/43	1.317[a]	0.251
Age (years)	43 ± 11.59	43.41 ± 10.47	42.65 ± 12.54	0.580[b]	0.745
Goiter (yes/no)	57/44	28/18	29/26	0.675[a]	0.411
Hashimoto's disease(yes/no)	21/80	11/35	10/45	0.500[a]	0.480
Tumor deposit (yes/no)	8/93	1/45	7/48	3.825[a]	0.050*
Single/multiple lesions	41/60	21/25	20/35	0.896[a]	0.344
Extraglandular invasion (yes/no)	10/91	4/42	6/49	0.138[a]	0.711
Capsule invasion (yes/no)	44/57	18/28	26/29	0.675[a]	0.411
Maximum tumor diameter	0.8 (0.60, 1.50)	0.70 (0.50, 1.00)	1.00 (0.70, 2.00)	−3.145[c]	0.002**
LN no. in central regions	2.00 (1.00, 4.00)	2.00 (1.00, 3.25)	3.00 (1.00, 4.00)	−1.551[c]	0.121
LN no. in lateral regions	0.00 (0.00, 2.00)	0.00 (0.00, 0.25)	1.00 (0.00, 4.00)	−3.174[c]	0.002**
Total LN no.	3.00 (1.00, 6.00)	2.00 (1.00, 4.25)	4.00 (2.00, 8.00)	−2.732[c]	0.006**
Residual thyroid (l × w × h)	0.00 (0.00, 1.00)	1.00 (0.00, 1.00)	0.00 (0.00,0.00)	−2.950	0.003**
^{131}I dosage (mCi)	100.00 (80.00, 100.00)	100.00 (80.00, 100.00)	100.00 (80.00, 100.00)	−1.437[c]	0.151
sTg (μG/L)	9.48 (2.05, 18.73)	6.32 (0.86, 14.45)	13.15 (3.45, 30.42)	−2.741[c]	0.006**
imTg (μG/L)	109.50 (11.79, 500.00)	323.15 (9.97, 500.00)	61.99 (7.27, 246.10)	−2.249[c]	0.025*
dTg (μG/L)	76.00 (4.67, 473.67)	314.90 (19.20, 491.96)	35.10 (2.08, 212.53)	−3.045[c]	0.002**
rTg	12.09 (3.36, 32.88)	26.75 (14.57, 71.02)	4.04 (1.60, 12.64)	−5.953[c]	<0.001**

dTg = imTg − sTg, rTg = imTg/sTg, l × w × h length × width × height.
ER, excellent response; imTg, Tg immediately 112 h post-RAI; LN no., number of metastatic lymph nodes; M/F, male/female; NER, non-excellent response; RAI, radioiodine; sTg, Tg under stimulation.
[a]χ^2 value.
[b]*F* value.
[c]*u* value.
*$0.01 < P \leq 0.05$.
**$P \leq 0.01$.

Fig. 1



Differences between ER and NER. rTg:imTg/sTg. ER, excellent response; imTg, Tg immediately; NER, non-excellent response; sTg, Tg under stimulation.

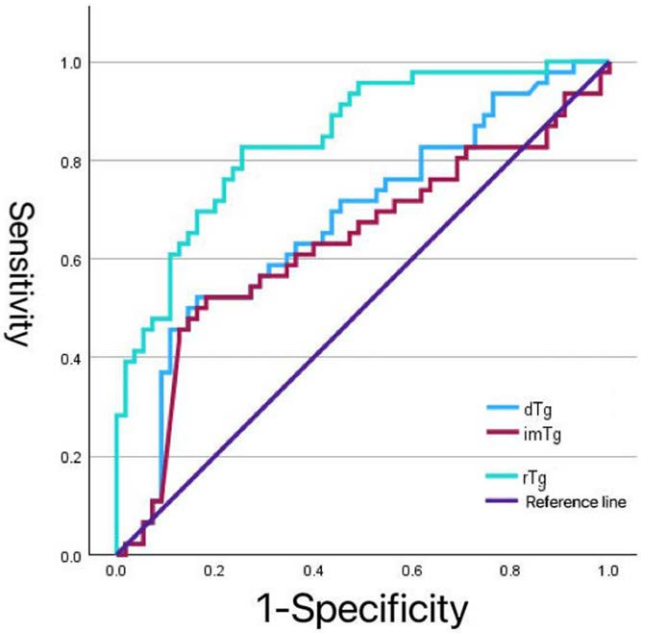
response (IDR), biochemical incomplete response (BIR), and structural incomplete response (SIR). IDR indicates nonspecific findings on imaging studies, faint uptake in thyroid bed on RAI scanning, 1 μG/L < sTg < 10 μG/L or 0.2 μG/L < suppressed Tg < 1 μG/L or TgAb stable or declining in the absence of structural or functional disease. BIR indicates negative imaging and sTg >10 μG/L or suppressed Tg >1 μG/L, or continuous TgAb increase. SIR encompassed structural or functional imaging positivity at any Tg± or TgAb± level. The results underwent independent analysis by two attending physicians with over 5 years of experience in the nuclear medicine department. Disagreements were resolved through discussion, and in cases of persistent

Table 2 **Binary logistic regression analysis: assessment of significant variables influencing excellent response**

Parameters	Classification	*P* value	OR	OR (95% CI) Lower	Upper
LN no. in lateral regions		0.016	1.711	1.106	2.645
sTg		0.021	1.065	1.009	1.123
rTg		<0.001	0.917	0.873	0.962

rTg = imTg/sTg.
CI, confidence interval; imTg, Tg immediately; LN no., number of metastatic lymph nodes; OR, odds ratio; sTg, Tg under stimulation.

Fig. 2



ROC curve of the relationship between imTg, dTg, and rTg and ER. imTg Tg immediately 112 h post-RAI, dTg = imTg − sTg, rTg = imTg/sTg. ER, excellent response; imTg, Tg immediately; RAI, radioiodine; ROC, receiver operating characteristic; sTg, Tg under stimulation.

disagreement, the results were submitted to a chief physician for a final ruling.

Statistical analysis

Statistical analysis utilized SPSS 29.0.1.0 statistical software (IBM Corp., Armonk, New York, USA). The Kolmogorov–Smirnov normality test was applied initially. Data conforming to normal distribution were presented as mean ± SD, whereas nonnormally distributed data were presented as median (p25 and p75). Independent sample *t*-test, chi-square analysis, and Mann–Whitney *U* rank sum tests were employed to compare statistical differences between the two groups. Binary logistic regression analysis (forward: conditional) assessed significant variables influencing ER. Receiver operating characteristic (ROC) curve analysis identified statistically significant ($P < 0.05$) parameters, determining the area under the curve (AUC), *P*-value, cutoff value, sensitivity (%), and specificity (%). The threshold for statistical significance was set at $P < 0.05$.

Results

General information of patients and univariate analysis comparing possible parameters that affect excellent response or nonexcellent response

A total of 101 patients with DTC underwent RAI therapy for postsurgical thyroid ablation, with 45 were classified in the ER group and 56 in the NER group. Patient and thyroid carcinoma characteristics are summarized in Table 1. Univariate analysis was conducted to compare potential parameters influencing ER or NER, and the results are presented in Table 1. Statistical differences were observed in the presence or absence of tumor deposit and imTg between the two groups ($P \leq 0.05$). Moreover, significant variations were noted in the maximum diameter of the tumor, LN no. in lateral regions, total number of LN no., residual thyroid (length × width × height), sTg, dTg, and rTg, all with $P \leq 0.01$.

Binary logistic regression analysis

Binary logistic regression analysis was performed on meaningful parameters identified in the single-factor analysis. Of the nine candidate variables, rTg retained strong statistical significance, with a *P*-value of less than 0.001. The median of rTg, illustrating the difference between ER and NER, is depicted in Fig. 1. LN number in lateral regions and sTg exhibited *P*-values ranging between 0.05 and 0.01, demonstrating statistical significance, as summarized in Table 2.

Receiver operating characteristic curve analysis

Continuous variables, including the maximum diameter of the tumor, LN number in lateral regions, total LN number, residual thyroid (l × w × h), sTg, imTg, dTg, and rTg, were categorized based on cutoff values through ROC curve analysis. The analysis aimed to identify statistically significant parameters and determine AUC, *P*-value, sensitivity (%), and specificity (%). ROC curve analysis revealed the following outcomes: rTg demonstrated the most favorable statistical value in predicting successful ablation, exhibiting 82.6% sensitivity and 74.5% specificity with a cutoff of 11.78 (AUC = 0.845). Parameters with lower AUC values are not presented (Fig. 2 and Table 3).

Table 3 Receiver operating characteristic curve analysis of continuous parameters related to excellent response

Diagnosis index	AUC	Cutoff	Sensitivity	1-specificity	Youden index
imTg	0.630	287.75	0.522	0.182	0.340
dTg	0.676	292.12	0.522	0.164	0.358
rTg	0.845	11.78	0.826	0.255	0.572

dTg = imTg − sTg, rTg = imTg/sTg.
imTg, Tg immediately 112 h post-RAI; RAI, radioiodine; sTg, Tg under stimulation.

Discussion

This study highlights a substantial elevation in Tg levels post-RAI therapy. The novel metric, rTg, derived from comparing Tg values at 112 h to those before RAI therapy, demonstrated notable sensitivity and specificity in predicting a positive response to RAI therapy. This contrasts with the limited predictive value observed for sTg in assessing thyroid residual ablation efficacy. Earlier studies [17,18] often failed to exclude patients with distant metastasis, leading to elevated sTg levels and a poorer treatment response. Consequently, in our study, elevated sTg did not accurately reflect the response to RAI therapy in the cohort of DTC patients who were free from metastasis.

Currently, most research focuses on Tg levels under stimulation before iodine therapy [9,19]. The levels of Tg under TSH stimulation in postoperative DTC patients may be linked to residual thyroid tissue volume and disease status pre-RAI therapy. However, these levels are not directly associated with the treatment response. At this juncture, Tg originates from both normal thyroid tissue and thyroid cancer cells, offering insights into residual thyroid tissue volume and the thyroid cancer situation [18]. While this indirect information proves valuable in predicting RAI therapy outcomes, it falls short in directly reflecting the response to radiation therapy, highlighting a limitation in predicting the effectiveness of RAI therapy.

Apoptosis in thyroid tissue subsequent to radiation therapy results in damage to cell membrane integrity [20,21]. The findings indicate that the release of Tg in thyroid tissue post-RAI therapy contributes to an acute-phase elevation in Tg levels. Consequently, imTg offers valuable insights into RAI ablation efficacy on residual thyroid tissue postsurgery. Previous studies observed a significant increase in Tg levels 48 h after RAI therapy, with a median increase of 6.8 ng/ml and a 1.3 times median increase in rTg in patients without distant metastasis [12]. Similarly, in a study 3 days after RAI therapy, the average Tg levels increased to 62.7 ng/ml, with a remarkable 31.2 times average increase in rTg observed in the successful ablation group. Contrarily, no significant difference in imTg was noted between the successful ablation and residual tissue groups [13]. A 5-day post-RAI therapy study demonstrated that rTg increased by 14.8 times in all patients studied. Unfortunately, the Tg changes in the successful ablation group were not provided [14]. The findings of this research align closely with the aforementioned results, indicating that the median imTg level for all patients, irrespective of grouping, was 109.5 ng/ml, with a median rTg that was 12.09 times this value. Furthermore, in the ER group, the imTg level escalated to 323.15 ng/ml, accompanied by a median rTg that was 26.75 times greater. The elevation in Tg after RAI therapy is influenced by the size of residual thyroid tissue, with more thyroid tissue leading to higher Tg release through destruction and subsequently higher imTg values [10]. To mitigate the impact of residual thyroid volume, a ratio, rTg, was introduced, providing a better indication of the extent of thyroid response to RAI. A high rTg signifies early Tg release from residual thyroid tissue, indicating early tissue destruction and a positive response to RAI treatment [11]. The study suggests that rTg is a specific indicator of RAI treatment response, surpassing sTg as a marker of residual thyroid tissue. The optimal predictive value for rTg in this study was 11.78, slightly lower than a reference literature [13] with rTg (cutoff ≥12.0) as a significant predictor of successful ablation. However, the area under the ROC curve and sensitivity are higher than the reference literature.

Our research has certain limitations. This article did not delve into the impact of TSH levels on Tg, and varying doses of ^{131}I administered to patients may also influence Tg changes. To calculate rTg, some data with Tg measurements below the minimum value were excluded. Additionally, our study did not encompass investigations on metastatic patients. Notably, ongoing research on Tg heterogeneity presents a promising avenue for distinguishing differences between normal thyroid tissue and tumor tissue [22]. In the future, our research will take these factors into account and seek more robust indicators to predict treatment response.

The clinical significance of this study includes (1) investigating changes in serum Tg levels at 112 h after RAI therapy in patients with DTC and (2) exploring the correlation between rTg and the prognosis 0f RAI therapy, determining the optimal predictive cutoff point for rTg. This enables short-term evaluation of treatment efficacy following RAI therapy, enabling timely formulation of effective treatment. It is expected to replace the traditional prediction method that can only be conducted 6 months after RAI therapy, thereby reducing the time needed for efficacy and alleviating the economic burden.

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Y.Z., X.Y., and H.Z. carried out the studies, participated in collecting data, and drafted the manuscript. Z. Liu and Q.Z. performed the statistical analysis and participated in its design. Z. Li and X.H. participated in acquisition, analysis, or interpretation of data. All authors read and approved the final manuscript.

The study was approved by the Medical Ethics Committee, Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL485-01). The requirement for informed consent was waived by the Institutional Review Board of the Affiliated Hospital of Xuzhou Medical University Hospital because of the retrospective nature of the study.

All data generated or analyzed during this study are included in this published article.

Conflicts of interest

There are no conflicts of interest.

References

1 Hundahl SA, Cady B, Cunningham MP, Mazzaferri E, McKee RF, Rosai J, *et al*. Initial results from a prospective cohort study of 5583 cases of thyroid carcinoma treated in the United States during 1996. U.S. and German Thyroid Cancer Study Group. An American College of Surgeons Commission on Cancer Patient Care Evaluation study. *Cancer* 2000; **89**:202–217.
2 Di Jeso B, Arvan P. Thyroglobulin from molecular and cellular biology to clinical endocrinology. *Endocr Rev* 2016; **37**:2–36.
3 Lin JD. Thyroglobulin and human thyroid cancer. *Clin Chim Acta* 2008; **388**:15–21.
4 Christensen SB, Bondeson L, Ericsson UB, Lindholm K. Prediction of malignancy in the solitary thyroid nodule by physical examination, thyroid scan, fine-needle biopsy and serum thyroglobulin. A prospective study of 100 surgically treated patients. *Acta Chir Scand* 1984; **150**:433–439.
5 Citterio CE, Rivolta CM, Targovnik HM. Structure and genetic variants of thyroglobulin: pathophysiological implications. *Mol Cell Endocrinol* 2021; **528**:111227.
6 Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al*. 2015 American Thyroid Association Management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016; **26**:1–133.
7 Tuttle RM, Ahuja S, Avram AM, Bernet VJ, Bourguet P, Daniels GH, *et al*. Controversies, consensus, and collaboration in the use of (131)I therapy in differentiated thyroid cancer: a joint statement from the American Thyroid Association, the European Association of Nuclear Medicine, the Society of Nuclear Medicine and Molecular Imaging, and the European Thyroid Association. *Thyroid* 2019; **29**:461–470.
8 Li Y, Rao M, Zheng C, Huang J, Fang D, Xiong Y, Yuan G. Analysis of factors influencing the clinical outcome after surgery and (131)I therapy in patients with moderate-risk thyroid papillary carcinoma. *Front Endocrinol* 2022; **13**:1015798.
9 Wu R, Liu W, Li N, Wang X, Sun D, Ji Y, *et al*. Analysis of correlation factors influencing the outcome of initial 131I remnant ablative therapy in intermediate- to high-risk patients with papillary thyroid microcarcinoma. *Nucl Med Commun* 2022; **43**:669–674.
10 Karvounis E, Kappas I, Angelousi A, Makris GM, Siamatras TD, Kassi E. The diagnostic and predictive accuracy of thyroglobulin to TSH ratio and TSH to thyroglobulin ratio in detecting differentiated thyroid carcinoma in normothyroid patients with thyroid nodules: a retrospective cohort study and systematic review of the literature. *Oncol Rev* 2020; **14**:439.
11 Muratet JP, Giraud P, Daver A, Minier JF, Gamelin E, Larra F. Predicting the efficacy of first iodine-131 treatment in differentiated thyroid carcinoma. *J Nucl Med* 1997; **38**:1362–1368.
12 Choi JH, Lim I, Lee I, Byun BH, Kim BI, Choi CW, Lim SM. An enhanced treatment effect can be expected from a higher serum thyroglobulin level after radioactive iodine therapy. *Ann Nucl Med* 2019; **33**:128–134.
13 Kim YI, Im HJ, Paeng JC, Cheon GJ, Kang KW, Lee DS, *et al*. Serum thyroglobulin level after radioiodine therapy (day 3) to predict successful ablation of thyroid remnant in postoperative thyroid cancer. *Ann Nucl Med* 2015; **29**:184–189.
14 Bernier MO, Morel O, Rodien P, Muratet JP, Giraud P, Rohmer V, *et al*. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2005; **32**:1418–1421.
15 Jadhav SS, Meeks CJ, Mordwinkin NM, Espinoza TB, Louie SG, diZerega GS, Rodgers KE. Effect of combined radiation injury on cell death and inflammation in skin. *Apoptosis* 2015; **20**:892–906.
16 Spencer CA, Takeuchi M, Kazarosyan M, Wang CC, Guttler RB, Singer PA, *et al*. Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 1998; **83**:1121–1127.
17 Kendler DB, Vaisman F, Corbo R, Martins R, Vaisman M. Preablation stimulated thyroglobulin is a good predictor of successful ablation in patients with differentiated thyroid cancer. *Clin Nucl Med* 2012; **37**:545–549.
18 Tamilia M, Al-Kahtani N, Rochon L, Hier MP, Payne RJ, Holcroft CA, Black MJ. Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. *Nucl Med Commun* 2011; **32**:212–220.
19 Lima N, Cavaliere H, Tomimori E, Knobel M, Medeiros-Neto G. Prognostic value of serial serum thyroglobulin determinations after total thyroidectomy for differentiated thyroid cancer. *J Endocrinol Invest* 2002; **25**:110–115.
20 Ramakrishnan N, McClain DE, Catravas GN. Membranes as sensitive targets in thymocyte apoptosis. *Int J Radiat Biol* 1993; **63**:693–701.
21 Nishiyama K, Kozuka T, Higashihara T, Miyauchi K, Okagawa K. Acute radiation thyroiditis. *Int J Radiat Oncol Biol Phys* 1996; **36**:1221–1224.
22 Xavier AC, Maciel RM, Vieira JG, Dias-da-Silva MR, Martins JR. Insights into the posttranslational structural heterogeneity of thyroglobulin and its role in the development, diagnosis, and management of benign and malignant thyroid diseases. *Arch Endocrinol Metab* 2016; **60**:66–75.