

# Can the basal serum thyroglobulin level be used to predict the recombinant human TSH-stimulated thyroglobulin level in differentiated patients with thyroid cancer?

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## Abstract

This study investigated the correlation between basal thyroglobulin (Tg) and recombinant human thyroid-stimulating hormone (rhTSH)-stimulated Tg in differentiated patients with thyroid cancer, and sought to determine whether the basal Tg level predicts the rhTSH-stimulated Tg level.

We retrospectively enrolled 177 patients with papillary thyroid cancer (mean age = 44 years; 50 males, 127 females) who received rhTSH before radioiodine therapy (RIT). Serum Tg levels were measured 7 days before the 1st rhTSH injection (basal Tg) and on the days of RIT (rhTSH-stimulated Tg). Patients were divided into 3 groups according to rhTSH-stimulated Tg cut-off levels of 2, 5, and 10 ng/mL. The correlation between basal Tg and rhTSH-stimulated Tg levels was assessed, and whether basal Tg was useful in predicting the rhTSH-stimulated Tg level was determined.

A significant positive correlation was observed between basal and rhTSH-stimulated Tg levels ( $|r_{ho}| = 0.48, P < .0001$ ). The basal Tg level had significant diagnostic ability in predicting an rhTSH-stimulated Tg level of 2 ng/mL or higher, and the optimal basal Tg level for this prediction was 0.3 ng/mL (AUC = 0.77,  $P < .0001$ ). A basal Tg level of 0.5 ng/mL was optimal for predicting rhTSH-stimulated Tg levels of 5 ng/mL or higher (AUC = 0.81,  $P < .0001$ ), and of 10 ng/mL or higher (AUC = 0.82,  $P = .0171$ ).

The basal Tg level was significantly correlated with the rhTSH-stimulated Tg level. If the basal Tg level is  $>0.3$  or  $0.5$  ng/mL, then the rhTSH-stimulated Tg level can be expected to be sufficiently high to necessitate clinical examination.

**Abbreviations:** AJCC = American Joint Committee on Cancer, AUC = area under the ROC curve, DTC = differentiated thyroid cancer, IQR = interquartile range, rhTSH = recombinant human thyroid-stimulating hormone, RIT = radioiodine therapy, ROC = receiver-operating characteristic, SD = standard deviation, Tg = thyroglobulin, TgAb = antithyroglobulin antibody.

**Keywords:** papillary, recombinant human thyroid-stimulating hormone, thyroglobulin, thyroid cancer

## 1. Introduction

Patients with differentiated thyroid cancer (DTC) are typically treated with total thyroidectomy followed by radioiodine therapy (RIT), using I-131, for thyroid remnant ablation.<sup>[1]</sup> Although patients with DTC generally have a good prognosis, relapse, or

distant metastasis may occur within the first 5 years after treatment, necessitating clinical follow-up.<sup>[2]</sup> Thyroglobulin (Tg) is a highly specific tumor marker in the management of DTC. An increase in the serum Tg level after RIT is an early and reliable indicator of local recurrence or metastasis.

In patients with DTC, Tg level with thyroid-stimulating hormone (TSH) stimulation ( $\geq 30$  mU/L), which is considered to be a significant tumor marker.<sup>[3]</sup> Such TSH elevation can be achieved by inducing hypothyroidism after discontinuing thyroid hormones for approximately 4 to 5 weeks. This traditional thyroid hormone withdrawal method causes hypothyroid symptoms persisting for weeks to months in most patients, damaging their physical and psychologic health and thus decreasing quality of life.<sup>[4,5]</sup> Exogenous stimulation with recombinant human TSH (rhTSH) has been approved to measure Tg levels as an alternative to thyroid hormone withdrawal; it strongly stimulates iodine uptake and Tg production without inducing the side effects associated with hypothyroidism. Numerous studies<sup>[6–8]</sup> have indicated that rhTSH and thyroid hormone withdrawal are equally effective as markers of recurrence. In addition, rhTSH appears to decrease the radiation exposure of extra-thyroid tissues and red marrow after ablation.<sup>[9–12]</sup> The therapeutic use of rhTSH has been approved by the European Thyroid Association for low-risk patients; it was also proposed as an alternative to hormone withdrawal by the American Thyroid Association.<sup>[13]</sup>

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Recently, several clinicians have followed-up patients with DTC to determine the reliability of basal Tg values, with the goal of reducing the burden of thyroid hormone withdrawal.<sup>[14–16]</sup> In addition, measuring rhTSH-stimulated Tg is costly, so we use basal Tg as a tumor marker in daily clinical practice. However, there are still doubts regarding how well basal Tg reflects TSH-stimulated Tg, and how seriously basal Tg levels should be taken as a marker of recurrence or metastasis. In this study, we investigated the relationship between the basal Tg level (without TSH stimulation) and the rhTSH-stimulated Tg level. We also examined the clinical utility of basal Tg levels for predicting the risk of future recurrence, and sought to determine the optimal basal Tg threshold.

## 2. Materials and methods

### 2.1. Subjects

This study included patients with papillary thyroid carcinoma ( $n=177$ ) who were transferred to our department between March 2016 and March 2018 for RIT after surgery. The mean age of the patients was 44 years, and about 72% were women. All patients received 2 intramuscular injections of 0.9 mg rhTSH (Thyrogen; Genzyme Corporation, Cambridge, MA), 24 and 48 hours before RIT without discontinuation of levothyroxine. The blood sampling was done 7 days before, and 48 hours after, the 1st rhTSH injection (Fig. 1). We collected the patients' clinical information through a chart review and the cancer stages were established based on the American Joint Committee on Cancer (AJCC) 8th edition.<sup>[17]</sup> All patients included in this study had cervical lymph nodes metastases (N1a or N1b), which required postoperative RIT.<sup>[3]</sup> They had no clinical suspicion of distant metastasis prior to RIT and were in the M0 stage. Patients with a basal blood antithyroglobulin antibody (TgAb) level  $>60$  IU/mL in were excluded from this study. To facilitate statistical analysis, a Tg of  $<0.1$  ng/mL was recorded as zero.

The clinical design of this retrospective study was approved by the Institutional Review Board of Ajou University (AJIRB-MED-MDB-18-224). The need for informed consent was waived.

### 2.2. Laboratory measurements

Serum TSH concentrations was measured by immunoradiometric assay using a sandwich-type assay (TSH IRMA kit; Beckman Coulter, Prague, Czech Republic). Serum Tg was checked using Tg-S IRMA CT (ZenTech, Angleur, Belgium). Serum TgAb was measured with a radioligand assay for quantitative determination of antibodies to Tg in human serum (BRAHMS anti-Tg RIA kit; Thermo Scientific, Hennigsdorf, Germany).

### 2.3. Statistical analysis

All statistical analyses were done using MedCalc Statistical Software (ver. 18.5; MedCalc Software bvba, Ostend, Belgium). First, we performed a power analysis to calculate the appropriate sample size for this study using a significance ( $\alpha$ ) level of 5% and statistical power ( $1-b$ ) of 80%. A sample size of 145 was required to attain an appropriate confidence level; thus, the sample size of our study ( $n=177$ ) was sufficient.

The Kolmogorov–Smirnov test was used to assess whether our dataset differed significantly from a normal distribution. Data with a normal distribution are presented as the mean and standard deviation (SD), and data that do not follow a normal distribution are presented as the median and interquartile range (IQR). Statistical methods were applied according to whether the data were parametric or nonparametric.

Spearman coefficient of rank correlation test was used to examine the correlation between basal and rhTSH-stimulated Tg levels. Correlations were classified as very weak ( $|\rho| < 0.20$ ), weak ( $|\rho| = 0.20–0.39$ ), moderate ( $|\rho| = 0.40–0.59$ ), strong ( $|\rho| = 0.60–0.79$ ), or very strong ( $|\rho| \geq 0.80$ ).<sup>[18]</sup>

Patients were grouped according to rhTSH-stimulated Tg cut-off levels of 2, 5, and 10 ng/mL, which can be considered to indicate remaining cancer cells.<sup>[3,19,20]</sup> We used univariate logistic regression analysis to determine the significant risk factors for exceeding each rhTSH-stimulated Tg cut-off. Furthermore, multiple stepwise regression was used to search for independent risk factors. The diagnostic efficacy of basal Tg level for predicting rhTSH-stimulated Tg level was assessed using receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) was compared with 0.5, and the value with the highest Youden index was used as the cut-off value. All  $P$ -values  $< .05$  were considered significant.

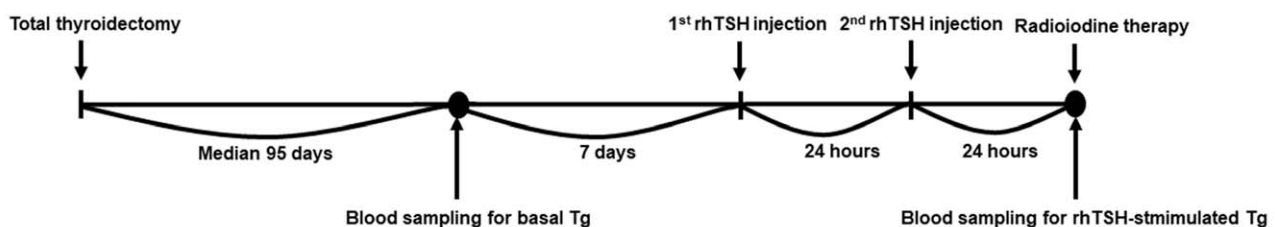
## 3. Results

### 3.1. Patients' characteristics

Regarding the AJCC stage, 80.2% of patients (142/177) were stage I and 19.2% (34/177) were stage II. Basal Tg was examined postoperatively after a median of 95 days. Among all patients, the median basal Tg level was 0.0 ng/mL and the median rhTSH-stimulated Tg level was 0.5 ng/mL. The detailed clinical characteristics of the patients are summarized in Table 1.

### 3.2. Correlation between basal and rhTSH-stimulated Tg levels

The Spearman coefficient of rank correlation  $\rho$  value between basal and rhTSH-stimulated Tg was 0.48. The 95% confidence



**Figure 1.** Schematic of blood sampling. The blood tests for checking basal thyroglobulin (Tg) were performed 7 days before the first injection of recombinant human thyroid-stimulating hormone (rhTSH). The blood test to evaluate rhTSH-stimulated Tg was performed 48 hours after the first rhTSH injection.

**Table 1**  
**Clinical characteristics of patients.**

Characteristics	Number
Papillary thyroid carcinoma, n (%)	177 (100%)
Age, mean ± SD, yrs	44 ± 11.6
Sex, n (%)	
Female/male	127 (71.8%)/50 (28.2%)
T stage, n (%)	
T1/T2/T3a/T3b/T4a/T4b	128 (72.3%)/37 (20.9%)/6 (3.4%)/4 (2.3%)/2 (1.1%)/0 (0%)
N stage, n (%)	
N0/N1a/N1b	0 (0%)/78 (44.1%)/99 (55.9%)
M stage, n (%)	
M0/M1	177 (100%)/0 (0%)
AJCC stage, n (%)	
I/II/III/IV	142 (80.2%)/34 (19.2%)/1 (0.6%)/0 (0%)
Interval between surgery and basal blood test, median (IQR), d	95 (82–110)
Basal TSH, median (IQR), μIU/mL	0.08 (0.05–0.18)
Basal Tg, median (IQR), ng/mL	0.0 (0.0–0.4)
rhTSH-stimulated TSH, median (IQR), μIU/mL	94.4 (73.1–113.3)
rhTSH-stimulated Tg, median (IQR), ng/mL	0.5 (0.0–1.6)

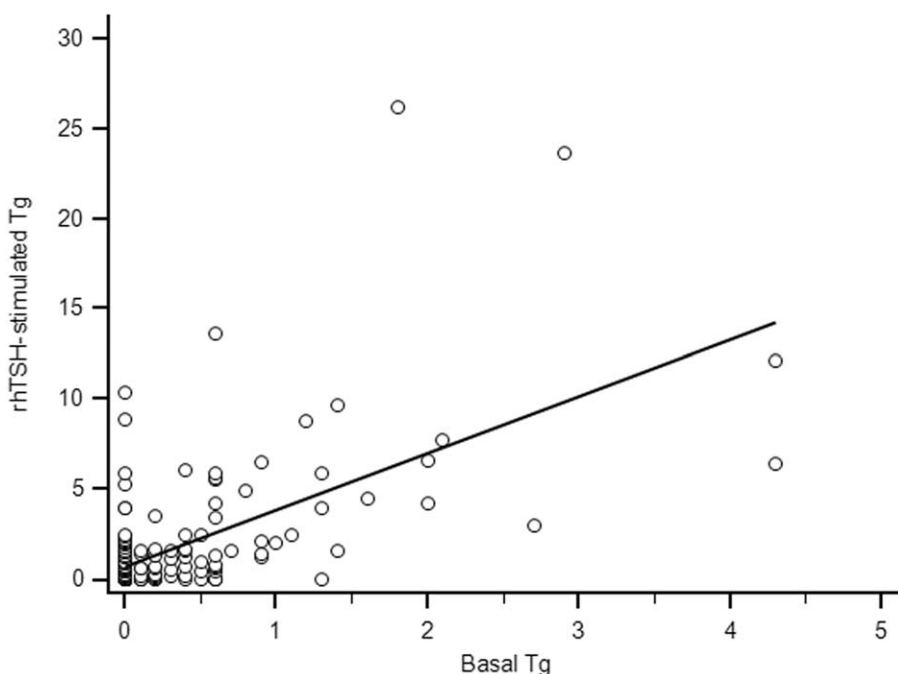
AJCC=American Joint Committee on Cancer, IQR=interquartile range, rhTSH=recombinant human TSH, SD=standard deviation, Tg=thyroglobulin, TSH=thyroid-stimulating hormone.

interval (CI) ranged from 0.36 to 0.59. The associated *P*-value was <.0001, suggesting a positive relationship between basal and rhTSH-stimulated Tg levels (Fig. 2).

**3.3. Regression analyses for risk factors for rhTSH-stimulated Tg levels**

With a cut-off rhTSH-stimulated Tg level of 2 ng/mL, 137 patients were in the risk-free group (rhTSH-stimulated Tg < 2 ng/mL) and 40 were in the risk group (rhTSH-stimulated Tg ≥ 2 ng/mL). In the univariate regression analysis, male (*P* = .0249), advanced T stage (T3 and T4; *P* = .0267), higher basal TSH level

(*P* = .0325), and higher basal Tg level (*P* < .0001) were risk factors for an rhTSH-stimulated Tg level of 2 ng/mL or higher. Using a cut-off rhTSH-stimulated Tg level of 5 ng/mL, 158 patients were in the nonrisk group (rhTSH-stimulated Tg < 5 ng/mL) and 19 were in the risk group (rhTSH-stimulated Tg ≥ 5 ng/mL). The risk of an rhTSH-stimulated Tg level of 5 ng/mL or higher was significantly greater in males than in females (*P* = .0041). An advanced T stage (*P* = .0162), high basal TSH level (*P* = .0393) and high basal Tg level (*P* < .0001) were also significant risk factors for a high rhTSH-stimulated Tg level. When the cut-off level of rhTSH-stimulated Tg was 10 ng/mL, 172 subjects were included in the nonrisk group (rhTSH-



**Figure 2.** Correlation between basal thyroglobulin (Tg) and recombinant human thyroid-stimulating hormone (rhTSH)-stimulated Tg. Spearman coefficient of rank correlation analysis showed a moderate positive correlation between basal Tg and rhTSH-stimulated Tg levels (*P* < .0001, |rho| = 0.48, 95% CI: 0.36–0.59).

**Table 2**  
Univariate logistic regression analysis of factors predicting the various rhTSH-stimulated Tg level groups.

Parameters	rhTSH-stimulated Tg ≥ 2 ng/mL			rhTSH-stimulated Tg ≥ 5 ng/mL			rhTSH-stimulated Tg ≥ 10 ng/mL		
	Coefficient	OR (95% CI)	P-value	Coefficient	OR (95% CI)	P-value	Coefficient	OR (95% CI)	P-value
Age (≥55 yrs)	-1.15	0.31 (.09–1.09)	.0701	-1.43	0.23 (.03–1.84)	.1693	-18.73	1.42 (.79–3.68)	.9978
Male	0.85	0.33 (1.11–4.88)	.0249*	1.43	4.20 (1.57–11.17)	.0041*	1.38	3.98 (.64–24.63)	.1363
T stage (T3, T4 vs T1, T2)	1.34	3.85 (1.16–12.70)	.0267*	1.60	5.00 (1.34–18.57)	.0162*	1.29	3.65 (.37–35.59)	.2637
N stage (N1b vs N1a)	0.34	1.42 (0.69–2.92)	.3428	0.09	1.09 (.42–2.86)	.8553	-0.66	0.51 (.08–3.16)	.4741
AJCC stage (II–IV vs I)	-0.96	0.37 (0.13–1.15)	.0869	-0.81	0.44 (.09–2.02)	.2956	-18.76	2.42 (.91–4.18)	.9976
Basal Tg	2.70	14.97 (5.32–42.08)	<.0001*	1.82	6.18 (2.75–13.87)	<.0001*	1.26	3.52 (1.71–7.24)	.0006*

AJCC=American Joint Committee on Cancer, CI=confidence interval, NV=no value, OR=odds ratio, rhTSH=recombinant human TSH, Tg=thyroglobulin, TSH=thyroid-stimulating hormone.  
\* P<.05.

stimulated Tg < 10 ng/mL) and the remaining 5 (rhTSH-stimulated Tg ≥ 10 ng/mL) were in the risk group. In the risk analysis based on an rhTSH-stimulated Tg level of 10 ng/mL, only basal Tg was a statistically significant contributor to the risk of a high rhTSH-stimulated Tg level (P = .0006). The detailed results of the univariate regression analysis are shown in Table 2.

In the multivariate regression analysis, higher basal Tg level and advanced T stage were independent risk factors for an rhTSH-stimulated Tg level of 2 ng/mL or higher and 5 ng/mL or higher. Only the basal Tg level was a statistically significant risk factor for an rhTSH-stimulated Tg cut-off level of 10 ng/mL or higher (Table 3).

**3.4. ROC curve analysis results**

In ROC curve analysis, basal Tg level had a statistically significant ability to predict an rhTSH-stimulated Tg level of 2 ng/mL or higher (AUC=0.77, 95% CI: 0.70–0.83, P < .0001).

The optimal basal Tg value for this prediction was 0.3 ng/mL, with 67.5% sensitivity and 83.2% specificity (Fig. 3A). When risk groups were distinguished according to an rhTSH-stimulated Tg cut-off level of 5 ng/mL, basal Tg again had a statistically significant ability to predict risk group (AUC=0.81, 95% CI: 0.75–0.87, P < .0001). In this case, the optimal basal Tg value for this prediction was 0.5 ng/mL, with sensitivity of 73.7% and specificity of 84.8% (Fig. 3B). Finally, basal Tg level had a statistically significant ability to predict an rhTSH-stimulated Tg level of 10 ng/mL or higher (AUC=0.82, 95% CI: 0.76–0.87, P = .0171). A basal Tg level of 0.5 ng/mL was optimal for this prediction, with sensitivity and specificity of 80.0% and 80.2%, respectively (Fig. 3C).

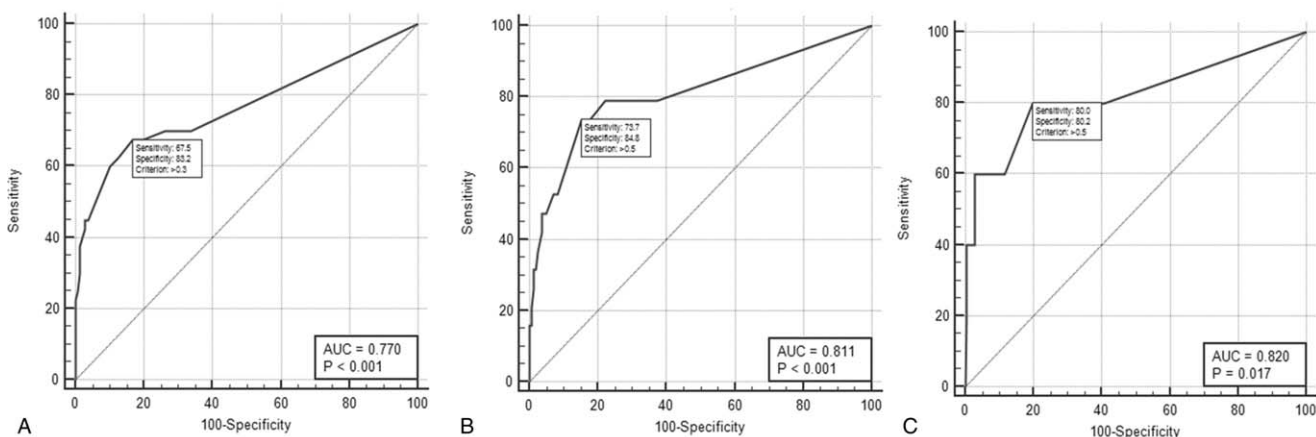
**4. Discussion**

There have been few studies on the relationship between basal Tg and rhTSH-stimulated Tg levels. A study by Spencer et al<sup>[21]</sup>

**Table 3**  
Multivariate logistic regression analysis of factors predicting the various rhTSH-stimulated Tg level groups.

Parameter	rhTSH-stimulated Tg ≥ 2 ng/mL			rhTSH-stimulated Tg ≥ 5 ng/mL			rhTSH-stimulated Tg ≥ 10 ng/mL		
	Coefficient	OR (95% CI)	P-value	Coefficient	OR (95% CI)	P-value	Coefficient	OR (95% CI)	P-value
Basal Tg	2.94	18.93 (6.27–57.15)	<.0001*	1.98	7.25 (2.97–17.69)	<.0001*	1.25	3.52 (1.71–7.24)	.0006*
T stage (T3, T4 vs T1, T2)	2.03	7.63 (1.96–29.65)	.0033*	2.27	9.73 (2.06–45.83)	.0040*			

CI=confidence interval, OR=odds ratio, rhTSH=recombinant human TSH, Tg=thyroglobulin.  
\* P<.05.



**Figure 3.** Receiver operating characteristic (ROC) curves of basal thyroglobulin (Tg) for predicting risk groups based on cut-off recombinant human thyroid-stimulating hormone (rhTSH)-stimulated Tg. Basal Tg values had significant diagnostic ability in predicting rhTSH-stimulated-Tg levels equal to or exceeding 2 (A), 5 (B), and 10 ng/mL (C).



demonstrated that basal Tg level was strongly correlated with rhTSH-stimulated Tg level ( $r=0.85$ ). In our study, the trend was not as strong, but there was a significant correlation between basal Tg and rhTSH-stimulated Tg levels. Our study included a well-controlled, homogenous sample with constant blood sampling interval and timing. Future studies with larger sample sizes may demonstrate this relationship more clearly.

We used several TSH-stimulated Tg cut-off values in our study. According to the American Thyroid Association guidelines, a serum Tg level exceeding 2 ng/mL following TSH elevation is considered significant to warrant further investigation of DTC recurrence.<sup>[3]</sup> Most authors agree that if the rhTSH-stimulated Tg level remains below 2 ng/mL, the likelihood of detectable recurrence is small.<sup>[22]</sup> Furthermore, when Tg levels are above 5 ng/mL after rhTSH stimulation, therapeutic RIT should be considered, even if all the imaging studies are negative.<sup>[23–25]</sup> Schluter et al<sup>[26]</sup> indicated that a TSH-stimulated Tg level exceeding 10 ng/mL could be used a cut-off point for implementation of F-18 fluorodeoxyglucose positron-emission tomography. Momesso and Tuttle<sup>[27]</sup> defined a biochemically incomplete response as a TSH-stimulated Tg level >10 ng/mL. We believe that all of these cut-offs, of 2, 5, and 10 ng/mL, are clinically meaningful, so applied all 3 in this study.

Our study found that sex, advanced T-stage, and high basal Tg level were risk factors for rhTSH-stimulated Tg levels of 2 ng/mL or higher and 5 ng/mL or higher. In the patients included in our study, the proportion of female was about 2.5 times higher than in male, which is not surprising based on previous reports that the incidence of thyroid cancer is 2.9 times higher in women than in men.<sup>[28,29]</sup> Sex and tumor size are well-known prognostic factors of DTC,<sup>[30,31]</sup> consistent with our findings. It is important to note that the independent risk factor for exceeding all rhTSH-stimulated Tg cut-offs in our multivariate analysis was the basal Tg value. Although it is well known that serum Tg level is an important marker for predicting disease progression in patients with DTC,<sup>[32,33]</sup> it was unclear whether basal Tg had sufficient predictive power to replace the TSH-stimulated Tg test. Our results have shown that basal Tg can play an important role in predicting elevated rhTSH-stimulated Tg levels, which may be clinically useful.

Our data also suggested 0.3 ng/mL as an appropriate basal Tg cut-off for predicting an rhTSH-stimulated Tg level above 2 ng/mL. This basal Tg level is almost identical to the 0.28 ng/mL suggested by Trimboli et al<sup>[16]</sup> and matches the level of 0.3 ng/mL mentioned by Rosario et al,<sup>[34]</sup> which enhances its reliability. In both of those previous studies, persistent disease was rarely present when the basal Tg level was <0.28 and 0.3 ng/mL, respectively, such that it is not necessary to check the TSH-stimulated Tg level in these cases.<sup>[16,34]</sup> Here we present another basal Tg cut-off level, of 0.5 ng/mL, which may be useful for predicting an rhTSH-stimulated Tg level exceeding 5 or 10 ng/mL. We found no previous study suggesting that 0.5 ng/mL is a dangerous basal Tg level. TSH-stimulated Tg cut-off values of 5 and 10 ng/mL are mainly used to determine the RIT dose, or in a clinical context to assess the response after RIT. We cautiously suggest that a basal Tg level of 0.5 ng/mL may be more meaningful than 0.3 ng/mL for clinicians dealing with RIT patients.

The limitations of this study were as follows. First, the timing of the rhTSH-stimulated Tg measurement was not consistent with the recommended sampling time. It is widely known that serum Tg levels should be measured at 72 hours after the second

rhTSH injection. Unfortunately, we evaluated serum Tg levels at 48 hours after the 1st rhTSH injection, where the blood sampling timing could not be adjusted as this study was conducted retrospectively. The reasons for this earlier sampling point than the standard guideline are because it is inconvenient for patients to visit the hospital again for a blood test after RIT, and there is a risk to laboratory staff of radiation exposure while sampling blood from post-RIT patients. In fact, a recent study by Sager et al<sup>[35]</sup> reported little difference between Tg values at day 3 after the 1st rhTSH injection date (equivalent to the time of the blood sampling in this study) and day 5 (equivalent to the standard guideline), such that a day 5 blood sample may not be necessary. Thus, there is still debate about the timing of blood tests after rhTSH injection. However, we admit that the risk of an elevated rhTSH-stimulated Tg level may have been underestimated in this study due to the early timing of blood sampling, and a well-designed prospective study will be needed for validation of our findings. Another limitation of this study was the lack of patient outcome data. DTC is known to have a good prognosis,<sup>[36]</sup> and the study period was too short to analyze prognosis or survival in our patients according to recurrence or metastasis. Thus, we will conduct a continuous follow-up study including clinical outcome data. The final limitation was that this study lacked data on the amount of remnant thyroid tissue prior to RIT. Remnant thyroid tissue may contribute to Tg production,<sup>[37,38]</sup> which may have influenced our results. Unfortunately, our institution did not perform ultrasonography prior to RIT, and we did not obtain data on remnant thyroid tissue. To further clarify our results, prospective studies including data on remnant thyroid tissue are needed in the future.

The main conclusion of this study is that the basal Tg level (without TSH stimulation) was significantly correlated with the rhTSH-stimulated Tg level, and the rhTSH-stimulated Tg level appears clinically meaningful when the basal Tg value is  $\geq 0.3$  or 0.5 ng/mL.

## Author contributions

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**Writing – original draft:** Eugene Jeong.

**Writing – review & editing:** Young-Sil An.

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