



ORIGINAL RESEARCH ARTICLE

The thyroglobulin to TSH ratio to predict successful ablation after iodine therapy in papillary thyroid carcinoma

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ABSTRACT

Introduction: In recent years, thyroidectomy and radioactive iodine remnant ablation and thyroid-stimulating hormone suppression therapy with thyroxine have emerged as the optimal treatment for differentiated thyroid cancer. The aim of the study was to analyze the sTg/TSH ratio to predict the value of successful ablation and also to evaluate whether this ratio can be used as a suitable predictor and compared with stimulated thyroglobulin (sTg).

Methods: We investigated patients who underwent total thyroidectomy for DTC, with or without neck lymph node dissection, from 2015 to 2024. The administered dose was determined by experienced nuclear medicine physician based on thyroid remnant status and the presence of distant metastases. Four to six months after I-131 treatment, all patients underwent follow-up assessments. Successful ablation was defined as the absence of detectable lesions on diagnostic iodine scan, neck ultrasound, Tg levels below 1 ng/mL and negative TgAb results.

Results: Of the total 154, 115 patients (74.7%) achieved successful ablation, while 39 patients (25.3%) had unsuccessful ablation. Primary tumor size, multifocality and cervical lymph node involvement were associated with a higher rate of failure to successful ablation ($P = 0.004$). Patients were classified based on a Tg cutoff of 2.25 ng/mL. At sTg levels greater than 2.25 ng/mL, the chance of successful ablation decreased by 89% ($OR=0.11$). At a Tg/TSH ratio cutoff of 0.046, patients with ratios below this value had a success rate of 70.4%, which was statistically significant compared to those with higher ratios ($P < 0.001$).

Conclusion: The present study showed that both sTg and sTg/TSH ratio can predict ablation outcome in the PTC patients. With the equal specificity (70.4%), the sensitivity of sTg/TSH ratio (82%) is slightly higher than sTg (79.5%) as a better predictor of the efficacy of RAI treatment and successful ablation.

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, with differentiated thyroid cancer (DTC) accounting for approximately 90% of all cases. DTC, which includes the papillary and follicular subtypes, generally presents with a favorable prognosis and high long-term survival rates. However, the risk of disease recurrence or distant metastasis remains a significant challenge for patients and clinicians [1]. Standard treatment strategies for DTC typically include total or near-total thyroidectomy, radioactive iodine therapy (RAI), and thyroid-stimulating hormone (TSH) suppression with levothyroxine [2]. These approaches have been widely utilized to improve disease-free survival and reduce recurrence rates. Among them, RAI plays a pivotal role in eliminating residual thyroid tissue or microscopic tumor cells and facilitates the detection of disease recurrence or metastasis through serum thyroglobulin (Tg) measurements and whole-body scans (WBS).

Thyroglobulin serves as a critical serum marker in the follow-up of patients after thyroidectomy and RAI, providing valuable insights into treatment response and identifying persistent or recurrent disease [3, 4]. Although pre-ablation stimulated thyroglobulin (sTg) is recognized as a reliable predictor of success RAI, its accuracy can be influenced by various factors, including tumor staging, TSH levels, and individual patient characteristics.

Given the strong dependency of Tg production on TSH levels, the sTg/TSH ratio has been proposed as a potentially more precise predictive model for assessing RAI success [5, 6]. Initial investigations suggest that this ratio might provide enhanced predictive accuracy compared to standalone sTg levels, offering a more comprehensive understanding of treatment outcomes [7].

Previous studies have primarily focused on the individual effects of sTg or TSH levels in predicting RAI success. However, there is limited data directly comparing the predictive efficacy of sTg and the sTg/TSH ratio in this context. Furthermore, the variability in predictive criteria and interpretation of treatment outcomes highlights the need for a more robust and standardized model [7-10].

In this study, we aim to bridge this knowledge gap by evaluating the impact of TSH levels on the predictive efficiency of sTg and investigating the potential of the sTg/TSH ratio as a novel and accurate predictor of the success of the first RAI dose in patients with DTC. Our findings are expected to contribute to optimizing treatment decision-making and improving predictive approaches for assessing treatment response in DTC patients.

METHODS

In this retrospective, single-center, observational study, we investigated patients who underwent total thyroidectomy for DTC, with or without neck node dissection, from 2015 to 2024. Patients received RAI treatment at the Nuclear Medicine Department of Shahid Beheshti Hospital in Babol, Iran. This research was approved by the Ethics Committee of Babol University of Medical Sciences (ID number: 724135814; IR.MUBABOL.HRI.REC.1403.201). Furthermore, we documented demographic details, medical backgrounds, records of thyroid and neck ultrasound scans, serum levels of TSH, sTg, thyroglobulin antibodies (TgAb), and specifics of levothyroxine therapy. Additionally, surgical reports and histopathological results were included, alongside information on RAI therapy, radiological findings, and treatment results. A total of 154 patients diagnosed with DTC were included based on specific eligibility criteria. All patients were adults who had undergone total thyroidectomy, with postoperative pathology confirming papillary thyroid carcinoma (PTC). The RAI was performed 3-4 weeks following surgery, and thyroxine replacement therapy was discontinued during the same period.

Patients were excluded if they tested positive for TgAb, if measurements of TgAb, TSH, and sTg were taken at different times or from separate samples, or if they had undergone contrast-enhanced CT within one month prior to RAI. Additional exclusion criteria included loss to follow-up, failure to perform total thyroidectomy, or diagnostic WBS conducted prior to RAI, as this could cause a potential stunning effect. Serum indices, including TSH, sTg, and TgAb levels, were measured before RAI using a fully automated chemiluminescence analyzer in a clinical laboratory.

The administered dose was determined by experienced nuclear medicine physician based on thyroid remnant status and the presence of distant metastases. Typical doses ranged from 1.11 to 3.7 GBq (30–100 mCi) for low-risk cases, 3.7 to 5.55 GBq (100–150 mCi) for intermediate-risk cases. To enhance intestinal absorption of I-131, patients were advised to fast for two hours before and after the treatment. Adequate rest and nutritional support during hospitalization were also recommended. Post-treatment WBS was performed 5-7 days after the therapeutic dose, with imaging covering the whole body, cervical region, and chest. The WBS was conducted using a gamma camera featuring a large field of view and a high-energy collimator, alongside a 128 × 128 matrix. Interpretation of the images involved

qualitative assessment through visual examination of the size and intensity of tracer uptake in residual tissue or distant metastases. The settings included an energy peak of 364 keV, a window width of 20%, a 64×64 matrix, and a magnification factor of 1.5. Four to six months after I-131 treatment, all patients underwent follow-up assessments, including neck ultrasound, diagnostic WBS, and measurement of serum indices. Successful ablation was defined as the absence of detectable lesions on diagnostic WBS and neck ultrasound and sTg levels below 1 ng/mL.

Statistical analysis

Data analysis was conducted using SPSS version 24.00. Continuous variables with a normal distribution were analyzed with the unpaired Student's t-test and presented as mean \pm standard deviation. For non-normally distributed data, the results were expressed as median (M) and interquartile range (IQR), with comparisons performed using the Mann–Whitney U test. Receiver operating characteristic (ROC) analysis was utilized to create ROC curves and determine the optimal cutoff values for sTg and the sTg/TSH ratio. Univariate and multivariate logistic regression analyses were carried out to identify predictors of successful RAI. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included 154 patients, of whom 119 were female (77.3%) and 35 were male (22.7%), and their

ages ranged from 21 to 80 years (mean 43.6 ± 14.7 years). Of the total participants, 115 patients (74.7%) achieved successful ablation or excellent response (ER) groups, while 39 patients (25.3%) had unsuccessful ablation or incomplete response (IR) groups. Demographic and clinical course characteristics of patients showed in Table 1. No significant differences were observed between the ER and IR groups in terms of age or gender. The primary tumor size ranged from 0.4 to 6.4 cm, and 91.6% of patients had a tumor size smaller than 4 cm. Of the 13 patients with a size larger than 4 cm, 8 were in the ER group and 5 were in the IR group, which was a significant difference ($P = 0.004$). In the IR group, 46% of patients had multifocal disease, compared with 28% in the ER group, which was borderline significant ($P = 0.051$). Lymphatic invasion was reported in 40 patients (26%), with a higher incidence in the IR group ($P < 0.001$). As a result, multifocality and cervical lymph node involvement were associated with a higher rate of failure to successful ablation. Most patients in the IR group received a high dose (150 mCi) (38%), whereas most patients in the ER group received a low dose (30 mCi) (60%), a difference that was statistically significant ($P < 0.001$). This difference seems to be due to a significant difference in the two groups based on American Thyroid Association (ATA) risk, as most patients in the IR group were in the intermediate risk group (48.7%) who received higher doses, but in the ER group, most patients had a low risk level (80%) who received lower doses ($P < 0.001$).

Table 1. Demographic and clinical course characteristics of patients (n=154)

Variables		Excellent Response (ER)	Incomplete Response (IR)	P-Value
Mean Age (\pm SD)	43.6 (14.7)	43.09 (14.80)	45.13 (14.68)	0.455
Gender	Female	93	26	0.079
	Male	22	13	
Tumor size>4	Yes	5	8	0.004
	No	110	31	
Lymphatic invasion	Yes	20	20	< 0.001
	No	95	19	
Multifocality	Yes	33	18	0.051
	No	82	21	
RAI dose (mCi)	30	69	9	< 0.001
	100	24	11	
	125	5	4	
	150	17	15	
ATA Risk	Low	103	20	< 0.001
	Intermediate	12	19	
sTg and sTg/TSH	Mean sTg	2.07	15.19	< 0.001
	Mean sTg/TSH	0.044	0.341	< 0.001

Complete ablation was observed in 83.7% of low-risk patients and 61.3% of intermediate-risk patients. The success rate was significantly higher in the low-risk group ($P < 0.001$). The ablation success rate did not increase with higher doses of iodine-131. Patients who received a dose of 30 mCi had a success rate of 88.5%, while the success rates for doses of 100, 125, and 150 mCi were 68.6%, 55.6%, and 53.1%, respectively ($P > 0.05$).

The sTg levels ranged from 0.04 to 126 ng/mL, with a mean of 14.3 ± 5.4 ng/mL and a median of 1.85 ng/mL. The TSH levels ranged from 25 to 110 mIU/mL, with mean and median values of 55.6 ± 19.7 mIU/mL and 50.95 mIU/mL, respectively. The sTg/TSH ratio ranged from 0.0004 to 2.74, with mean of 0.33 ± 0.12 and median of 0.033. The mean sTg level in the ER group was 2.38 ± 2.07 ng/mL and in the IR group was 26.03 ± 15.19 . The mean sTg/TSH ratio in the ER group was 0.065 ± 0.044 ng/mL and in the IR group was 0.59 ± 0.34 , and the difference between these two indices was significant between the two groups ($P < 0.001$).

To assess the sensitivity and specificity of sTg and sTg/TSH for identifying successful and unsuccessful ablation, ROC curve was used to analyze the data (Figure 1). Accordingly, a sTg value of 2.25 ng/mL was obtained with the highest sensitivity (79.5%) and specificity (70.4%) with an area under the curve

(AUC) of 0.839 (0.758-0.919) for this prediction. Also, a sTg/TSH value of 0.0457 ng/mL was obtained with the highest sensitivity (82%) and specificity (70.4%) with an AUC of 0.843 (0.766-0.920) for this prediction (Table 2).

Patients were classified based on a sTg cutoff of 2.25 ng/mL. Of the 89 patients (57.8%) whose sTg levels were below this threshold, 81 (70.4%) had successful ablation, while only 8 (20.5%) had incomplete ablation ($P < 0.001$). At sTg levels greater than 2.25 ng/mL, the chance of successful ablation decreased by 90% ($OR=0.108$). For the sTg/TSH ratio, 81 patients had ratios below 0.046, while 34 patients had ratios above that. Patients with a ratio below 0.046 had a success rate of 70.4%, with only 8% incomplete ablation, which was statistically significant ($P < 0.001$).

In univariate logistic regression analysis, initial ablation dose with iodine-131, tumor size, lymphatic invasion, tumor multifocality, sTg level, and sTg/TSH ratio were predictors of successful ablation (all $P < 0.05$). In multivariate regression analysis, only sTg level and sTg/TSH ratio remained significantly associated with ablation success ($P < 0.001$). The correlation coefficient for Tg with ablation success was $OR 0.069$ (0.023-0.207), and for sTg/TSH ratio it was $OR 0.065$ (0.021-0.201) (Table 3).

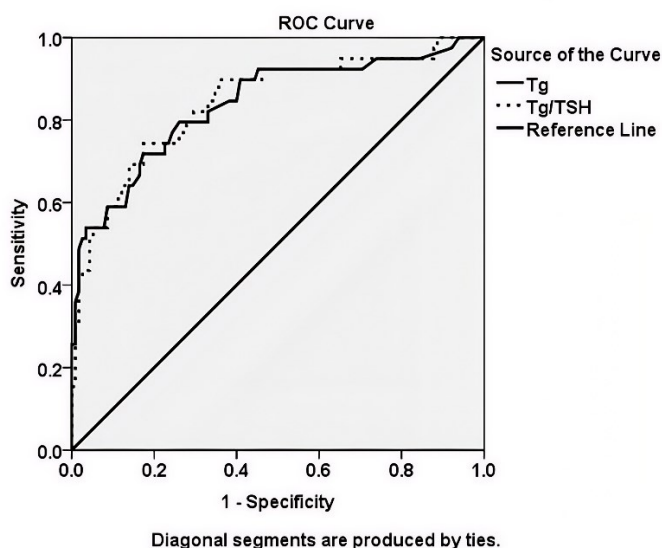


Figure 1. Receiver operating characteristic (ROC) curves of sTg and sTg/TSH ratio predicting successful ablation with papillary thyroid cancer

Table 2. Cutoff values of sTg and sTg/sTSH ratio with their sensitivity and specificity

	Cut - off	AUC	Std. Error	Asymptotic 95% Confidence Interval	P-Value
sTg	2.25	0.839	0.041	0.758 - 0.919	$P < 0.001$
sTg/TSH	0.046	0.843	0.039	0.766 - 0.920	$P < 0.001$

Table 3. Association between sTg level and sTg/TSH ratio with response to ablation therapy: Frequency distribution, odds ratio (OR), and P-values

		ER	IR	OR	P-Value
sTg	<2.25	81(91)	8(9)	1	P<0.001
	>2.25	34(52.3)	31(47.7)	0.11 (0.04-0.26)	
sTg/TSH	<0.0457	81(92)	7(8)	1	P<0.001
	>0.0457	34(51.5)	32(48.5)	0.09 (0.03-0.22)	

ER: Excellent response; IR: Incomplete response

DISCUSSION

Ablation therapy with I-131 plays a crucial role in significantly lowering rates of loco-regional recurrence, distant metastasis, and disease-specific mortality. However, the response to therapy varies widely among patients with well-differentiated thyroid cancer due to factors that remain only partially understood. This variability has resulted in inconsistent outcomes for I-131 ablation across different studies [11, 12].

Reported success rates for thyroid remnant ablation range from 43% to 87.2%. In cases of PTC, low-dose ablation has shown success rates between 76% and 79.3% (8). Research by El Rasd et al. revealed a success rate of 59.4% among DTC patients with a median baseline sTg level of 16.9 ng/mL, whereas Lee et al. and Salama et al. reported a higher success rate of 82.7% with a median sTg level of 2.6 ng/mL and 74.6% with a median sTg level of 7.41 ng/mL respectively [8, 13, 14]. In our study, we observed a success rate of 74.7% with a median sTg level of 1.85 ng/mL. The discrepancies in ablation outcomes can largely be explained by differences in sTg levels, a marker that indicates the volume of residual functional thyroid tissue and the adequacy of thyroidectomy [11]. Rosario et al. reported that ablation success exceeded 80% in patients with minimal thyroid remnants (<2% thyroid bed uptake) but decreased to 67% in patients with larger remnants [15, 16].

The outcomes of ablation are influenced by multiple factors that have been identified by several studies. Lin et al. highlighted age, clinical stage, extent of surgery, and postoperative sTg levels as significant predictors of success [5]. Similarly, Claimon et al. emphasized that female gender, absence of lymph node involvement or distant metastases, surgical margins, age below 45, and sTg levels below 20 ng/mL are associated with higher ablation success rates [17]. Wang et al. and Lubin et al. reported that tumor size, pre-ablation sTg levels, lymph node involvement, and multifocality independently predicted ablation failure [18]. Additionally, Lubin et al. observed that

elevated thyroglobulin antibody levels and lymph node invasion significantly contributed to resistance to I-131 therapy. In Salama et al. study, demographic factors such as age and gender had no statistically significant impact on ablation outcomes [8, 18]. However, unfavorable pathological factors like tumor size greater than 4 cm, lymph node involvement, and multifocality were associated with poorer ablation results [8].

In our study, similar to Wang and Salama's study, demographic factors such as age and gender had no statistically significant effect on ablation outcomes. However, factors such as larger tumor size, lymphatic invasion, and multifocality were associated with poorer ablation outcomes. Also, in the present study, only patients with low and intermediate risk levels were evaluated based on the ATA guidelines. Most patients were classified as low risk group (79.9%), with success rates of 83.7%. But in the intermediate group (20.1%), the success rate was 38.7%. There was significant difference between these groups ($P < 0.001$). This finding suggests that the initial risk level alone can independently predict the effectiveness of ablation. This is inconsistent with the findings of Wang et al. and Salama et al. that risk stratification alone cannot independently predict the effectiveness of ablation [8, 12].

The Cutoff value of sTg for ablation outcomes is widely recognized. Watanabe et al. demonstrated that sTg levels above 10 ng/mL were significantly associated with ablation failure [19]. Tamilia et al. and Bernier et al. identified cutoff values of 5–6 ng/mL as indicators of failure, with sensitivities of 67–76.7% and specificities around 79%, which were similar to the sensitivity and specificity of the present study [20, 21]. In our study, the sTg cutoff value was 2.25 ng/mL, with a sensitivity of 79.6% and specificity of 70.4%. The cutoff values in Liu et al. and Salama et al. studies were 38.18 (sensitivity 93.75% and specificity 56.45%) and 8.25 (sensitivity 77.4% and specificity 47%), respectively [7, 8]. The relatively low specificity in both studies may be due to confounding factors such as multifocality, lymph node involvement, and suboptimal TSH levels. Different cutoff values have been mentioned in

various studies. Variations in measurement techniques, regional iodine intake, and treatment protocols likely explain these differences.

Patients whose Tg was greater than 2.25 ng/mL had an 89% reduced chance of successful ablation (OR=0.108). These findings suggest that lower sTg levels prior to ablation significantly improve the likelihood of success of ablation, underscoring the importance of thoroughly removing thyroid lesions and residual tissue during surgery for DTC patients. According to ROC analysis, the study identified an optimal sTg/TSH cutoff value of 0.046. The area under the curve (AUC) was 0.839 (95% CI: 0.758–0.919) for the sTg level and 0.843 (95% CI: 0.766–0.920) for the sTg/TSH ratio respectively. These values are comparable to other studies in this field. Among patients with a sTg/TSH ratio below this threshold, 92% achieved successful ablation, compared to just 51.5% of those with higher ratios. Additionally, patients with a sTg/TSH ratio greater than 0.046 had a 91% reduced chance to achieve successful ablation, with sensitivity and specificity of 82% and 70.4%, respectively. This finding is consistent with studies by Zheng et al. (cutoff value of 0.11), Liu et al. (cutoff value of 0.969) and Salama et al (cutoff value of 0.1050), who reported that a higher sTg /TSH ratio predicts poorer outcomes [5, 7-9].

In the present study, with the equal specificity (70.4%), the sensitivity of the sTg/TSH ratio was higher than that of sTg (82% vs. 79.5%), while in the study by Yin et al., the sensitivity and specificity of the sTg/TSH ratio were higher than that of sTg [22]. Unexpectedly, in the study by Salama et al, they reported lower sensitivity (72.3% vs. 77.6%) and much higher specificity (75% vs. 47%) [8]. They stated that the low specificity may be due to the presence of other relevant factors such as multifocality, lymph node involvement, low I-131 dose, and most importantly, relatively lower TSH levels that affect the outcome of ablation.

Some studies have identified the sTg/TSH ratio as a stronger prognostic factor than sTg; conversely, some researchers have noted that the sTg/TSH ratio, although predictive of ablation success, is slightly less predictive than sTg [23-26]. In our study, both factors had almost the same predictive power, which is roughly consistent with the study by Zhou et al [27].

This study, similar to the study by Liu et al., showed that the sTg/TSH ratio was more correlated with ablation outcomes than sTg alone [7]. This slightly stronger correlation suggests the potential utility of the sTg/TSH ratio in predicting successful ablation efficacy. These findings suggest that the sTg/TSH ratio is a slightly more effective predictor of

ablation success than sTg alone, while Tg alone still provides approximately equivalent sensitivity and specificity, such that it is currently useful as a predictive marker in this group of patients.

CONCLUSIONS

The present study showed that both sTg and sTg/TSH ratio can predict ablation outcome in the PTC patients. With the equal specificity, the sensitivity of sTg/TSH ratio is slightly higher than sTg as a better predictor of the efficacy of RAI treatment.

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