

Original Article

Amir Gholami (MD)^{1,2}
Seyyed Ali Hosseini³
Hemmat Gholinia (MSc)⁴
Seyyed Hossein Mousavie
Anijdan (PhD)^{1,5*}

1. Clinical Research Development Unit of Shahid Beheshti Hospital, Babol University of Medical Sciences, Babol, Iran
2. Department of Radiology and Radiotherapy, Shahid Beheshti Hospital, Faculty of Medicine, Babol University of Medical Sciences, Babol, Iran
3. Student Research Committee, Babol University of Medical Sciences, Babol, Iran
4. Health Research Institute, Babol University of Medical Sciences, Babol, Iran
5. Department of Radiation Technology, Allied Medicine Faculty, Babol University of Medical Sciences, Babol, Iran

* Correspondence:

Seyyed Hossein Mousavie
Anijdan, Department of Radiation Technology, Allied Medicine Faculty, Babol University of Medical Sciences, Babol, Iran

E-mail: shmosavia@gmail.com
Tel: +98 1132190104

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Predictive value of serum thyroglobulin after surgery and prior to I-131 therapy in patients with differentiated thyroid carcinoma, examined at two different time intervals

Abstract

Background: Differentiated thyroid carcinoma (DTC) comprises nearly 90% of all thyroid malignancies. The main focus of our study was to examine how measuring Tg at multiple time points could predict the persistence and/or recurrence of both local and distant diseases.

Methods: In this retrospective, single-center, observational study, we examined records of all patients who underwent total thyroidectomy for DTC and received radioactive iodine (RAI) ablation/therapy at the Nuclear Medicine of Shahid Beheshti Hospital. Blood samples were collected at two time, approximately 30 days before RAI (Tg-30 and TSH-30) and the same day of RAI, after TSH-stimulation (Tg-0 and TSH-0). During the follow-up period, patients were categorized into the four groups according to the ATA guideline. Group with an excellent response (ER), nodal disease (ND), distant disease (DD) and partial response (PR).

Results: A significant difference between Tg-0 and Tg-30 was observed only in the ER group and the other 3 groups ($p < 0.001$), and no significant difference was observed between the remaining 3 groups ($p > 0.05$). Cut-off point of 1.35 ng/mL for the Tg-30 and 4.7 ng/mL for the Tg-0 was used with best sensitivity and specificity for differentiation of ER vs. ND. A cut-off point of 14.25 ng/mL for the Tg-30 and 40 ng/mL for the Tg-0 was able to correctly identify ER vs. DD.

Conclusion: By using the cut-off values obtained in this study, it is possible to more accurately predict local or distant recurrences. Maybe these patients need a shorter follow-up period that leads to more appropriate treatment decisions.

Keywords: Differentiated thyroid carcinoma, Serum thyroglobulin, Radioactive iodine therapy, Thyroid remnant ablation.

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According to data from 2020, thyroid carcinoma ranks ninth in global cancer incidence, highlighting its significant prevalence (1-2). The incidence of thyroid cancer has dramatically increased in recent years, primarily attributed to the heightened detection of small tumors (less than 1 centimeter) facilitated by advanced imaging techniques. Additionally, potential environmental and lifestyle factors, such as rising obesity rates, may contribute to this trend. Notably, differentiated thyroid carcinoma (DTC) comprises nearly 90% of all thyroid malignancies (3-4). The established treatment regimen for DTC typically involves a multi-modal approach: total or near-total thyroidectomy, radioactive iodine (RAI) ablation/therapy and levothyroxine (L-T4) therapy with thyroid-stimulating hormone (TSH) suppression (5-6). While these treatments demonstrate efficacy, the prognosis of DTC is impacted by the recurrence of the disease, which can affect up to 30% of patients, varying based on initial therapy and other prognostic factors. The majority of these instances of recurrence happen during the initial 2-3 years following the surgical procedure (7-9).



Local recurrences are frequent, especially in the cervical lymph nodes, followed by residual thyroid remnants, and then the trachea or muscle. The mortality rate among patients with local recurrences is only a mere 8%. In contrast, 21% of patients with DTC develop distant recurrences, primarily in the form of lung metastases. In these cases, the cancer-related mortality rate is approximately 50%. Historically, the standard approach to managing DTC encompassed total thyroidectomy followed by RAI ablation/therapy and prolonged TSH suppression through levothyroxine administration, regardless of the risk of recurrence (10).

However, a lively debate persists regarding the management of these patients, particularly concerning whether to conduct RAI ablation of residual thyroid tissue. Consequently, it is imperative to pinpoint suitable risk stratification systems and specific tumor markers with substantial prognostic significance to inform decision-making tailored specifically to each patient (9-10). Serum thyroglobulin (Tg) is a crucial biomarker for monitoring patients with DTC after surgery and RAI treatment. Since Tg is produced exclusively by thyroid tissue, detectable levels indicate the presence of either residual or recurrent DTC. This makes Tg a valuable tool for early detection of disease recurrence before it can be visualized with imaging studies. Routine follow-up for DTC typically involves a combination of clinical examinations, regular Tg and thyroglobulin antibodies (TgAb), and neck ultrasounds. Additional imaging studies, such as CT, MRI, or PET scans, may be used when necessary (9-12).

The significance of serum Tg as a means to monitor disease status during follow-up is widely acknowledged. Undetectable levels of serum Tg after ablation, regardless of TSH stimulation, indicate a stable remission of the disease. Conversely, a rise in serum post-ablation Tg levels indicates the potential presence of loco-regional or distant disease. Although the role of serum Tg before RAI has not been extensively clarified, an optimal evaluation of post-operative disease status may indicate the need for additional treatment such as RAI ablation/therapy, further surgery, or alternative therapies. Hence, there is a growing interest in assessing its prognostic role in postoperative risk stratification (10, 12). The main focus of our study was to examine how measuring Tg at multiple time points could predict the persistence and/or recurrence of both local and distant disease. Our secondary aim was to pinpoint a consistent cutoff point for Tg levels at each time point, ensuring a dependable distinction between patients with persistent or recurrent disease and those who remain disease-free.

Methods

This research was approved by the Ethics Committee of Babol University of Medical Sciences (ID number: 724135808; IR.MUBABOL.HRI.REC.1403.142). In this retrospective, single-center, observational study, we examined medical records of all patients who underwent total thyroidectomy for DTC, with or without neck node dissection, from 2010 to 2020, and received RAI treatment at the Nuclear Medicine Department of Shahid Beheshti Hospital in Babol, Iran. Furthermore, we documented demographic details, medical backgrounds, records of thyroid and neck ultrasound scans, serum levels of TSH, Tg, and TgAb. Additionally, surgical reports and histopathological results were included, alongside information on RAI therapy, radiological findings, and treatment results.

The inclusion criteria comprised patients aged ≥ 18 years, individuals who underwent total thyroidectomy with or without neck node dissection within 12 weeks before RAI for thyroid remnant treatment, those with papillary histology, availability of Tg, TSH, and TgAb data. All patients underwent a postoperative neck ultrasound using multifrequency probes and Color Doppler to rule out lymph node metastasis. Furthermore, the dosage of levothyroxine substitution therapy administered to all patients was determined based on the American Thyroid Association (ATA) risk assessment and clinical evaluation by the physicians. Patients with aggressive thyroid cancer subtypes, positive TgAb levels, other types of cancer, or Hashimoto's thyroiditis were excluded. Additionally, participants who underwent iodine-based imaging or consumed iodine-altering substances within specific timeframes before the study, as well as pregnant or breastfeeding women, were not included.

The determination of the administered therapeutic RAI activity was based on the postoperative risk stratification of the patient, as outlined in the guidelines provided by the ATA. A serum TSH concentration of >30 mIU/L was considered adequate to confirm the necessity of administering I-131 for ablative or therapeutic purposes. Seven days following the administration of RAI treatment, patients underwent assessment with a post-therapy I-131 whole-body scan (WBS). 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.

Blood samples were collected at various time points to measure serum levels of Tg, TgAb and TSH. Laboratory

tests of patients were often performed in one laboratory using up-to-date kits and ECL method (Electrochemiluminescence) for Tg and TSH and CLIA (Chemiluminescence immunoassay) technique for TgAb. In the euthyroid state, at least 40 days after surgery and approximately 30 days before ablation therapy (referred to as Tg-30, TgAb, and TSH-30). On the same day as RAI ablation/therapy, just before administering I-131, after TSH-stimulation induced by hypothyroidism (referred to as Tg-0, TgAb, and TSH-0). During the follow-up period, if there was suspicion of metastases, a second diagnostic WBS was performed at 6, 12, 24, or 36 months after RAI. This involved orally administering 185 MBq (5 mCi) of I-131.

Neck ultrasound evaluations and blood samples were measured for all patients at intervals of 6, 12, 24, and 36 months during the follow-up period. Ultrasound features used to identify potential malignancy included hypoechoic thyroid lesions, abnormal lymph nodes (round, without hilum, increased blood flow), microcalcifications, irregular borders, and specific nodule shapes. These criteria were crucial for identifying suspicious findings indicative of potential malignancy during the ultrasound assessments. Additional imaging studies, such as X-ray, CT, MRI, and PET scans, were performed on patients with elevated Tg levels but negative WBS to identify potential metastases. We closely monitored patients for signs of disease recurrence or persistence both biochemically (through Tg and TgAb levels) and structurally (using imaging) following initial treatment. This comprehensive approach allowed us to tailor treatment plans based on the specific needs of each patient. After initial treatment and during the follow-up period, patients were categorized into the following four groups according to the ATA guideline.

1. Patients with an excellent response (ER) or disease-free status, which includes the following: no clinical evidence of residual tumor, absence of pathological functioning thyroid tissue in the thyroid bed and/or distant metastases on RAI imaging or ultrasound scan and Tg values < 0.2 ng/mL under TSH suppression, or a stimulated Tg level < 1 ng/mL in the absence of interfering antibodies.

2. Patients with nodal disease (ND): Evidence of cancer spread to nearby lymph nodes.

3. Patients with distant disease (DD): Evidence of cancer spread to distant organs.

4. Patients with a partial response (PR) to treatment: Patients with minimal residual thyroid tissue and indeterminate biochemical status.

Statistical analysis: All statistical analyses were analyzed with SPSS Version 24 software and with descriptive indices including mean, standard deviation, frequency and percentage, and with chi-square tests. Mann-Whitney and Shapiro-Wilk tests or Student's t-test was used to compare the groups and the significance level was considered less than 0.05. Also, with ROC analysis, the optimal cut-off value was determined with the best sensitivity and specificity.

Results

During the period from 2010 to 2020, our institution performed a total or near-total thyroidectomy in 953 patients diagnosed with DTC. Out of these individuals, 820 were excluded from the study due to either incomplete data or insufficient follow-up. Consequently, our analysis comprised 133 patients (104 females and 29 males) who had undergone thorough follow-up, possessing complete clinical and serological records. These patients had an average age of 43.41 ± 15.42 years.

All patients included in the study underwent total thyroidectomy followed by radioiodine remnant ablation. Regarding the histological variants of thyroid carcinoma, the following distribution was observed among the enrolled patients: 129 (97%) patients had a papillary carcinoma, and only 4 (3%) patients had a follicular carcinoma. Even though none of the patients showed signs of metastasis during RAI ablation/therapy. The average dose of RAI administered was 54.59 mCi. This ranged from a minimum of 30 to a maximum of 150 mCi. Approximately 70% of patients received a dose of 30 mCi, while only 3% of patients received a dose of 150 mCi (table 1).

Table 1. Demographic and clinical course characteristics of patients

Variables	n = 133	%
Mean Age ($\pm$ SD)	43.41 (15.42)	
Female	104	78.2
male	29	21.8
Histology		
Papillary carcinoma	129	97
Follicular carcinoma	4	3

RAI dose		
30 mCi	92	69.2
100 mCi	29	21.8
125 mCi	8	6
150 mCi	4	3
Patients groups according to the ATA guideline		
Excellent Response (ER)	92	69.2
Nodal Disease (ND)	23	17.3
Distant Disease (DD)	7	5.3
Partial Response (PR)	11	8.3

Table 2. Relationship between age and four groups

		ER	ND	DD	PR
Age≤ 45 (n=75)	Count	53	14	6	2
	% within Age≤45	70.7%	18.7%	8.0%	2.7%
	% of Total	39.8%	10.5%	4.5%	1.5%
Age≥ 45 (n=58)	Count	39	9	1	9
	% within Age≥45	67.2%	15.5%	1.7%	15.5%
	% of Total	29.3%	6.8%	0.8%	6.8%
Total		92	23	7	11

To investigate the relationship between age and four groups of patients, we divided the patients into two groups under and over 45 years of age (table 2). Based on this, although there was a difference between the groups, this difference was statistically significant only in the PR group ($P=0.026$). Table 3 compares the mean and median level of Tg, and the TSH levels at various points in time for the four patient groups. This difference was observed only between the ER group and the other 3 groups (ND, DD and PR), while there was no significant difference between the remaining groups. Similarity, this difference in the mean and median values of Tg-0 was observed only between the ER group and the other 3 groups, and no significant difference was observed between the remaining 3 groups.

We know that TSH levels can affect Tg values. To account for this, we also analyzed TSH levels across all four

patient groups. The analysis showed no significant difference in TSH-30 and TSH-0 levels between the groups. Therefore, variations in TSH levels in our study population are unlikely to have impacted the observed differences in Tg-30 and Tg-0 levels.

The study compared Tg-30 levels for two ER vs. ND groups. In this comparison, a Tg-30 level of 1.35 ng/mL was used as a cut-off point. With this cut-off point, the test was able to correctly identify all patients with sensitivity 78.3% and specificity 62.0%. Also, a Tg-0 level of 4.7 ng/mL was used as a cut-off point for differentiating the ER vs. ND groups (sensitivity 74% and specificity 65%). In this comparison, a cut-off point of 14.25 ng/mL for the Tg-30 and 40 ng/mL for the Tg-0 was able to correctly identify ER vs. DD groups with sensitivity100% and specificity100% (table 4).

Table 3. Comparisons of the mean and median level of Tg, TSH levels at two time points

Tg-30 (ng/mL)TSH-30 (mIU/L) Tg-0 (ng/mL)TSH-0 (mIU/L)					
Mean (±SD)		1.36 (1.55)	1.02 (0.97)	4.95 (4.85)	71.03 (21.45)
ER	Range (min-max)	0.02 - 8.5	0.01 - 4.3	0.06 - 21	35 -140
	Median	0.95	0.85	2.95	69.5

		Tg-30 (ng/mL)	TSH-30 (mIU/L)	Tg-0 (ng/mL)	TSH-0 (mIU/L)
	Mean (±SD)	7.1 (9.9)	1.12 (0.9)	16.91 (19.103)	66.48 (17.68)
ND	Range (min-max)	0.5 - 41	0.04 - 3	1.5 - 63	39 - 99
	Median	3.6	1	8	67
	Mean (±SD)	83.43 (73.64)	1.1 (0.73)	492.57 (282.2)	75.57 (24.6)
DD	Range (min-max)	20- 220	0.04 -2	59 - 890	42 - 110
	Median	56	1	539	77
	Mean (±SD)	5.91 (6.9)	1.13 (0.94)	15.1 (13.62)	67.45 (18.86)
PR	Range (min-max)	0.8 - 23	0.06 – 3.1	3.7 - 41	42 - 98
	Median	3	1.1	9.5	64
P- Value		<0.001	>0.05	<0.001	>0.05
	Mean (±SD)	7.05 (24.5)	1.05 (0.94)	33.52 (124.62)	70.19 (20.71)
Total	Range (min-max)	0.02 - 220	0.01 – 4.3	0.06 - 890	35 - 140
	Median	1.4	0.9	4.5	69

Table 4. Cut-off points Tg for predicting the disease

	ER vs. ND		ER vs. DD	
	cut-off (Se and Sp)	AUC (95% CI)	cut-off (Se and Sp)	AUC (95% CI)
Tg-30 (ng/mL)	1.35 (78.3 and 62)	0.813 (71.7 to 90.9)	14.25 (100 and 100)	100 (100 to 100)
Tg-0 (ng/mL)	4.7 (74 and 65)	0.757 (65.2 to 86.3)	40 (100 and 100)	100 (100 to 100)

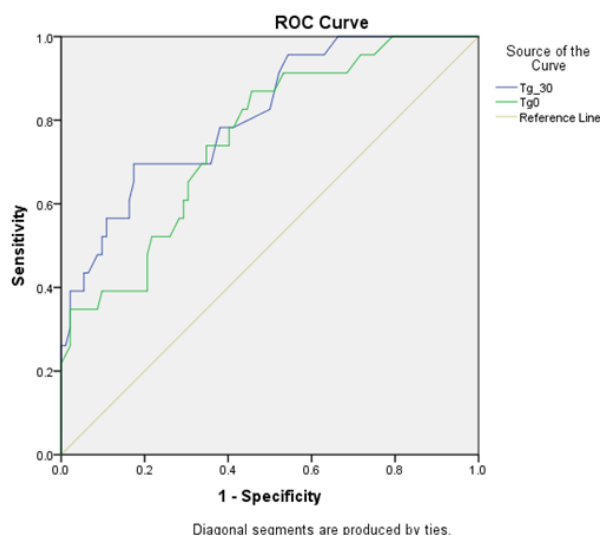


Figure 1. Receiver operating characteristic (ROC) curves of Tg for predicting of disease, at two time points

Discussion

The prognostic value of Tg before RAI treatment remains uncertain due to potential residual thyroid tissue post-surgery. Several factors, including TSH levels, residual

thyroid tissue mass, metastatic risk, and assay sensitivity, influence Tg levels. Additionally, optimal timing for post-operative Tg measurement and definitive cut-off values for diagnosing residual disease have yet to be established (13-

15). Adding to the complexity, there is still no clear consensus on the ideal time to measure Tg levels after surgery (post-operative timing). Additionally, there is no established optimal cut-off point for stimulated or suppressed Tg levels after surgery. These cut-off points would ideally help confirm or rule out the presence of cancerous lesions (16). Because of the existing uncertainties around using Tg levels for predicting future recurrence, our study aimed to assess the usefulness of both suppressed and TSH-stimulated Tg measurements taken at different points in time (Tg-0 and Tg-30). This analysis aimed to clarify whether these measurements could be a better predictor of future recurrence in patients with differentiated thyroid carcinoma.

Our study successfully identified a cut-off value for post-operative Tg-30 and Tg-0 levels that can reliably differentiate between patients with lymph node involvement (ND) or distant metastases (DD) and those who are disease-free (ER). Interestingly, both Tg-30 and Tg-0 proved to be accurate for this purpose (Sec: 78.3%, Sp: 62% vs. Se: 74%, Sp: 65%). In this study, the sensitivity and specificity of the optimal Tg cut-off point were determined at two different time points, and the results were found to be similar to each other. A similar study conducted by Signore in 2023 (10). They aimed to determine if elevated thyroglobulin (Tg) levels could indicate the presence of metastases in two scenarios: 1) early post-surgery (Tg-30) when residual thyroid tissue is still present, and 2) after RAI treatment (Tg+7) when thyroid tissue necrosis might influence Tg levels. The goal was to assess whether Tg levels could reliably detect metastases even in the presence of residual thyroid tissue. In their study, Tg-30 demonstrated better sensitivity and specificity compared to other time points.

The Tg-30 cut-off for distinguishing the disease-free group from the ND and DD groups in our study was 1.35 and 14.25 ng/mL, respectively, while in Signore's study, these values were 1.30 and 16 ng/mL. Similarly, the Tg-0 cut-off for differentiating the disease-free group from the ND and DD groups in our study was 4.7 and 40 ng/mL, respectively, compared to 5.7 and 32.98 ng/mL in Signore's study. Despite the unexpected similarity in the cut-off points between the two studies, Tg-30 and Tg-0 in our study showed similar sensitivity and specificity, with no statistically significant differences.

In the study by de Rosário et al., which examined Tg levels before ablation, it was stated that distant metastases were rarely seen at Tg levels less than 10 ng/mL. Distant metastases were observed in about 31% of patients with values greater than 10 ng/mL. Therefore, this criterion can be considered as a guiding light for the use of other imaging

methods in addition to neck ultrasound in this group of patients. Although their study used a lower cut-off value for distant metastasis compared to ours (10 vs. 40 ng/mL), similar to their study, nodal metastasis can be detected in our study at Tg levels less than 10 ng/mL (4.7 ng/mL as the cut-off). Also, in agreement with their information, it can be stated that, even at low Tg levels, metastasis to lymph nodes may be present, so performing cervical ultrasound when Tg levels are less than 10 ng/mL is necessary (17).

In Signore's study, Tg-30 demonstrated high sensitivity and specificity in distinguishing the disease-free group from the ND group, with sensitivity and specificity of 100% and 89%, respectively. Therefore, they suggested using Tg-30 as a strong prognostic marker for guiding patient follow-up. However, our study did not confirm this finding. In our study, Tg-30 had a sensitivity of 78.2% and specificity of 62%, which were similar to those of Tg-0. In our view, depending on the circumstances and patient comfort, either Tg-30 or Tg-0 could be used, although with such sensitivity and specificity values, they might not be considered strong prognostic markers for planning patient follow-up. In both studies, Tg-30 and Tg-0 demonstrated very high sensitivity and specificity in distinguishing the disease-free group from the DD group. Therefore, it is better to consider using them as a valuable tool in planning current assessments and follow-up of patients, but due to the small number of samples in this group, it is better to conduct a study with a larger number of samples.

According to AJCC 7th Edition/TNM Classification System for DTC, age less than 45 years is associated with a better prognosis in DTC at the time of diagnosis. Almost such a finding was seen in our study. At the age of less than 45 years, the percentage of patients in the ER group was higher, while most of the patients in the PR group were over 45 years old (9). It is important to acknowledge some limitations of this study. First, the follow-up period was relatively short. We know that lymph node metastases (nodal metastases) can sometimes take up to several years after surgery to become detectable. Second, the study involved a relatively small group of patients. Finally, the study design was retrospective and conducted at a single center. Ideally, these findings would be confirmed through larger studies involving multiple centers. This study suggests that a Tg-30 level higher than 1.3 ng/mL and a Tg-0 level higher than 4.7 ng/mL are associated with a higher likelihood of local recurrence (nodal involvement). Therefore, shorter follow-up intervals might be cost-effective, and in cases of indeterminate imaging findings, relying on these levels could lead to more appropriate treatment decisions. Additionally, Tg-30 levels higher than

14.25 ng/mL and Tg-0 levels higher than 40 ng/mL are associated with a higher likelihood of distant metastasis. Therefore, other imaging methods, such as CT scans, MRI, and PET/CT, should be considered for further evaluation.

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