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Determining A Thyroglobulin Cut-Off Value to Predict Distant Metastases in Differentiated Thyroid Carcinoma

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ABSTRACT

Background and Objective: Serum thyroglobulin (Tg) is a biochemical marker for the diagnosis of persistent or recurrent differentiated thyroid carcinoma (DTC) after total thyroidectomy. The purpose of this study is to determine the thyroglobulin cut-off value in distant metastases in patients with DTC.

Methods: Of patients with DTC who referred to the nuclear medicine department for radioactive iodine therapy after total thyroidectomy from 2008 to 2023, 424 patients were enrolled to this cross-sectional study. For follow-up of high-risk patients with distant metastases, only patients with postoperative stimulated thyroglobulin (ps-Tg) above 10 ng/ml with negative anti-thyroglobulin antibodies were selected.

Findings: Of these 424 patients, 335 (79%) were female and 89 (21%) were male. Based on the location of involvement, metastases were seen in lungs, bones and brain in the order of prevalence. According to ROC analysis, the optimal ps-Tg cut-off value 41.5 ng/ml predicted the presence of distant metastases with the highest sensitivity (90%) and specificity (88.5%) with an area under the curve of 0.959.

Conclusion: The results demonstrated that the serum level of Ps-Tg can be considered as a suitable and reliable indicator in showing the recurrence risk and distant metastasis. This value may be the only indicator to be used for this purpose.

Keywords: *Differentiated Thyroid Carcinoma, Radioactive Iodine Therapy, Stimulated Serum Thyroglobulin Level, Distant Metastasis.*

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Introduction

Thyroid cancer is a rare neoplasm, accounting for approximately 1% of all cancers. However, it is the most common malignant neoplasm of the endocrine glands. Statistical data indicate an increase in the incidence of thyroid cancer in recent decades (1). Over the past 10 years, the incidence of thyroid cancer has increased by an average of 1.3% per year in the United States (2). Radioiodine remnant ablation (RRA) aims to achieve three major goals: (A a therapeutic goal; for irradiating any neoplastic microfoci that may be present in the 50% of the thyroid remnants, particularly in the case of papillary thyroid carcinoma (PTC), (B a diagnostic goal; because of the possibility of performing a whole-body scan after RRA to identify additional sites of disease that were not identified before RRA (3-5), and (C a facilitative goal; because the destruction of the normal tissue of thyroid remnant that usually produces thyroglobulin (Tg) makes serum Tg measurement much more sensitive and can predict recurrent or persistent.

The half-life of serum Tg is 1-3 days. The time required for Tg levels to decline after surgery is approximately 3-4 weeks after that (6, 7). After treatment with radioactive iodine (I^{131}), it takes several months for Tg to disappear from the circulation. The serum Tg level after surgery is an important prognostic factor that can inform patient management, especially in the decision-making process for radioactive iodine ablation therapy, and also predict successful ablation of the thyroid remnants. Postoperative serum Tg levels greater than 10 ng/mL indicate the possibility of persistent or recurrent disease, the presence of distant metastases, failure of I^{131} ablation, and mortality, and therefore needs further evaluation and treatment. However, the Tg level alone is not the only criterion for successful ablation, and the patient's risk level should also be considered (6-8).

The most common sites of distant metastases are the lungs and bones. Early detection of these metastases is essential for adequate treatment and better response to therapy. Distant metastases are seen in a small number of patients with DTC, but still account for the majority of disease-related mortality. However, in addition to the staging system, the status of the disease in the postoperative period is also important in deciding on the proposed treatment. As part of this assessment, measurement of Postoperative Stimulated Thyroglobulin (ps-Tg) is of great importance (9-12).

Several studies have shown an association between an increased risk of recurrent and persistent disease after total thyroidectomy and RRA and high ps-Tg levels. In addition, ps-Tg is often considered an independent predictor of persistent or recurrent disease. High ps-Tg levels in the postoperative period may be associated with poor survival and, if these levels are greater than 5-10 ng/ml, they are associated with increased risk of distant metastases (11, 13). However, the level of ps-Tg associated with distant metastases at the time of postoperative evaluation is not well defined, and few studies have evaluated the predictive value of ps-Tg associated with distant metastases (11, 13-17). Since clinical detection of distant metastases is of great importance for treatment decisions, any additional data on the refinement of postoperative risk prognostic indicators such as ps-Tg would be a valuable tool to improve patient outcomes. Therefore, this study aims to determine a ps-Tg cut-off value that would more accurately identify distant metastases and, consequently, high-risk patients.

Methods

After approval by the Ethics Committee of Babol University of Medical Sciences with the code IR.MUBABOL.HRI.REC.1403.100, this cross-sectional study was conducted on 424 DTC patients who underwent total thyroidectomy with or without neck dissection from 2008 to 2023 and were referred to the Nuclear Medicine Department of Shahid Beheshti Medical Center in Babol for Post-Therapy Whole-Body

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Scan (ptWBS) with or without Radioactive iodine (RAI) therapy. Patients with Tg antibody levels above 100 IU/ml and patients lacking complete information about ps-Tg or TgAb levels were excluded from the study. Patients with other malignant tumors or Hashimoto thyroiditis (due to high TgAb levels), consumption of iodine-containing medications or foods that affect iodine absorption or metabolism within 4 weeks prior to RAI treatment, as well as cases of pregnancy or breastfeeding were also excluded from the study.

Based on TNM and the American Thyroid Association (ATA) guidelines, patients were divided into 3 groups according to the initial risk level: low, intermediate, and high risk. Patients received I^{131} doses ranging from 30 to 200 mCi according to the initial risk level and ATA recurrence risk classification. For radioactive iodine treatment, patients underwent levothyroxine discontinuation and a low-iodine diet for at least 2 to 4 weeks until serum TSH levels were greater than 30 μU/L. After thyroxine tablets were discontinued, ps-Tg, TgAb, and TSH levels were measured before the first I^{131} ablation of thyroid remnants. When TSH levels were elevated, serum ps-Tg was determined using a high sensitivity quantitative luminescence immunoassay (Immulite Tg, Roche Diagnostics, Germany). To avoid misinterpretation of Tg measurements, all patients were screened for circulating anti-Tg antibodies using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH). Patient characteristics including age, sex, histology, distant metastasis, residual uptake in ptWBS, TSH, ps-Tg, and TgAb were collected. Color Doppler ultrasound of the neck was performed in all patients before RRA. A whole-body scan was performed after iodine therapy using a large-field-of-view single-head gamma camera (SIEMENS Orbiter 75 ZLC) equipped with a high-energy, high-resolution collimator.

Since the target was high-risk patients with distant metastases, only patients with ps-Tg values above 10 ng/mL and negative antithyroglobulin antibodies were included. Considering that previous studies have shown an association between ps-Tg values above 10 ng/mL and poor overall survival, poor disease-free survival, and in some multivariate analyses, a higher risk of persistent or recurrent disease, this parameter was used to initiate patient selection. The presence of pathologically confirmed distant metastatic lesions, the presence of focal or diffuse lesions on ptWBS with or without positive findings on other complementary imaging modalities, and negative findings on ptWBS with the presence of structural lesions on CT scan, MRI, bone scan, or FDG PET/CT were considered as distant metastases.

The ps-Tg cut-off value was obtained using receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using SPSS version 24 with descriptive statistics including mean and standard deviation, frequency and percentage, and chi-square tests and multivariate logistic regression analysis. Mann-Whitney or Student's t-test were used to compare groups, and $p<0.05$ was considered significant.

Results

A total of 424 patients were included in the study, of whom 335 (79%) were female and 89 (21%) were male. The mean age of the patients participating in this study was 43.4±14.2 years (range 17 to 81). Thyroid remnant in ptWBS was only absent in 11 (2.6%) patients and was present in 413 (97.4%).

Histological examination showed that papillary pattern was seen in 387 (91.1%) patients, with the classic variant being the most common subtype. Regarding the initial treatment, 82% of the patients underwent total thyroidectomy without neck dissection. The radioactive iodine dose used varied as 30, 100, 125, 150, 175, and 200 mCi, with approximately half of the patients receiving a dose of 150 mCi. The mean time from surgery to the first dose was 4.5 months. Distant metastasis was seen in 12 (13.5%) of 89 men and 28 (8.4%) of 335 women, and this difference was not significant.

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Based on the site of involvement, distant metastasis was seen in the lungs, bones, and brain in order of prevalence. Distant metastasis was seen in 40 patients (9.5%), of whom 25 (62.5%) had lung metastasis, 8 (20%) had bone metastasis, 4 (10%) had simultaneous lung and bone metastasis, 2 (5%) had brain metastasis, and 1 (2.5%) had simultaneous brain and lung metastasis (Table 1).

Table 1. Location of distant metastases in order of prevalence in the studied patients (n=40)

Involved area	Number(%)	Median Tg	Tg Mean±SD
Lung	25(62.5)	91	109.84±68.97
Bone	8(20)	404	456.00±366.79
Lung-bone	4(10)	517.5	575.25±165.71
Brain	2(5)	217.5	217.50±36.06
Lung-brain	1(2.5)	248	248.00

The mean ps-Tg level in the study population was 47.24±107.5 ng/ml (range 10 to 1143), which was 27.73±49.85 in the group without distant metastasis and 234.45±247.33 in the group with distant metastasis, which was statistically significant (p<0.001). The highest ps-Tg level was in the group with simultaneous distant metastasis to bone and lung (575.25±165.71 ng/ml). Simultaneous lung-bone and bone metastases alone exhibited the highest ps-Tg levels, respectively.

A significant association was observed between the age of the patients and the prevalence of distant metastasis. In people over 40 years of age, 29 people had distant metastasis (13.1%), while in people under 40 years of age, this number was 11 people (5.4%) (p<0.008) (Table 2).

Table 2. Association between age, gender, and serum ps-Tg levels with distant metastases

Variable	Without distant metastasis Number(%)	With distant metastasis Number(%)	p-value
Gender			
Male	77(86.5)	12(13.5)	0.154
Female	307(91.6)	28(8.4)	
Age (years)			
Over 40	192(94.6)	11(5.4)	<0.008
Below 40	192(86.9)	29(13.1)	
Stimulated Thyroglobulin (Mean±SD) (Mean value)	27.73±49.85 (194.19)	234.45±49.85 (388.61)	<0.001

A multivariate logistic regression analysis was performed to investigate whether ps-Tg was an independent predictor of distant metastasis in DTC patients. Gender, age, histology, and serum ps-Tg levels were assessed. Ps-Tg was a strong independent predictor of possible metastasis after excluding other risk factors (p=0.001) (Table 3).

Since the metastasis pattern of differentiated papillary and follicular thyroid carcinomas is different, subgroup analyses were also performed. Patients with FTC pathology were more likely to have metastasis than those with PTC (p=0.068).

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Table 3. Logistic regression analysis of distant metastases according to clinicopathological factors

Variable	OR	OR (95% CI)	p-value
(PTC/FTC) Pathology	2.86	0.92-8.82	0.068
Age (over 40/ below 40)	1.64	0.66-4.04	0.279
Gender (male/female)	0.82	0.3-2.19	0.692
Tg (<41.5/ >41.5)	60.55	20.39-179.83	<0.001

To evaluate the most sensitive and specific ps-Tg cut-off value for detecting the presence of distant metastases, ROC curve was used for data analysis (Figure 1). Accordingly, the optimal cut-off value of 41.5 ng/mL was obtained with the highest sensitivity (90%) and specificity (88.5%) with an area under the curve of 0.959 for predicting the presence of distant metastases.

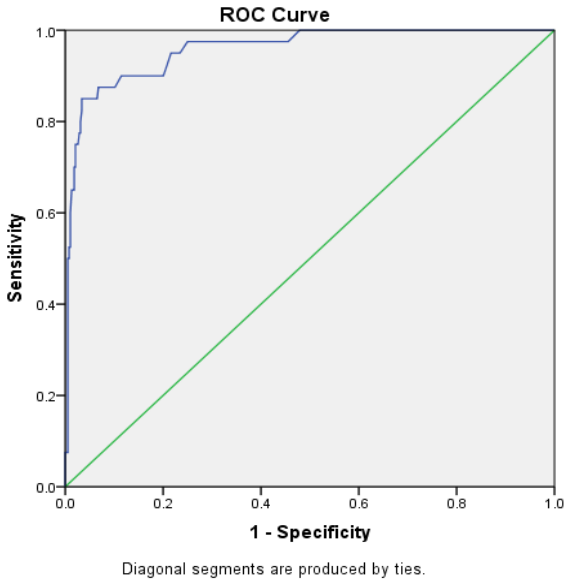

Figure 1. ROC curve for distinguishing between the presence of distant metastases and the groups without distant metastases. Area under the curve: ROC cut-off value of Ps-Tg, 41.5 ng/ml, sensitivity 90% (81-99%), specificity 88.5% (81-99%), PPV=45% (34-56%) and NPV=99% (98-100%).

Discussion

According to the ATA guideline, serum ps-Tg levels can be a predictor of persistent disease or distant metastasis after surgery, but the optimal cut-off value for making treatment decisions with an appropriate dose of radioactive iodine is still not well defined (6). Several studies have demonstrated the clinical use of serum thyroglobulin measurements as a suitable tool for stratifying the initial risk level for appropriate treatment and predicting the course of the disease (5, 8, 11).

Since serum ps-Tg levels are an important prognostic factor that can help in the decision-making process for RRA and also predict successful ablation of the thyroid remnant, several recent studies have attempted to provide a cut-off value for serum ps-Tg levels to predict the presence of distant metastasis (8, 11). Several recent studies have considered ps-Tg as a factor for post-operative reassessment, linking ps-Tg levels to the initial risk stratification system. A meta-analysis showed that serum ps-Tg levels are an easy, accessible, and inexpensive tool with a high negative predictive value (NPV) for future disease-free status. Low ps-Tg

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levels can be considered as a favorable prognostic factor for patients with DTC (18). In some studies, there was an association between high ps-Tg levels and poor overall survival and poor prognosis (11, 19, 20). Other studies also showed significant differences in ps-Tg concentrations in patients with and without distant metastases (17, 21, 22).

In a study by Li et al., a cut-off value of 52.75 ng/ml with a sensitivity of 87.90% and a specificity of 91.70% was proposed based on ROC analysis for predicting distant metastases (16). In another similar study, Yang et al. found that a cut-off value of 1.47 ng/ml could be a good predictor for detecting distant metastases. Furthermore, a high specificity (93.7%) and a very high OR (42.5) were found for this cut-off value, which distinguished distant metastases in all patients. They also suggested that if this cut-off value was measured before radioactive iodine treatment, it could prevent low-dose iodine treatment in about 10% of patients who had no evidence of distant metastases on pre-ablation evaluation (15). In our study, the cut-off value was 41.5 ng/mL with a sensitivity of 90%, specificity of 88.5%, and a very high OR (60.55), which was very similar to the study by Yang et al. (15), and the findings of these two studies may provide a specific definitive cut-off value for further detection of distant metastasis in high-risk patients in the absence of metastatic evidence before ablation.

In the study of Couto et al., a cut-off value of 117.5 ng/ml with a high NPV (93.7%) was used to detect distant metastases (11). This cut-off value was for lung and bone metastases. Therefore, similar to our study, a high level of ps-Tg was observed for distant metastases in this study. The higher level of ps-Tg in this study may be due to different TSH levels at the time of testing, which may be influenced by various factors such as thyroid tissue remnant and different times between thyroidectomy and thyroglobulin measurement. On the other hand, this difference in cut-off values between our study and that of Couto et al. (11) may be related to the fact that there were fewer cases with lung and bone metastases in our study. Therefore, further studies with a larger number of bone and lung metastases are needed to confirm these findings.

In a study by Kim et al. to determine the predictive value of preoperative Tg for detecting distant metastases, the optimal cut-off value was 4.63 ng/mL with an area under the ROC curve of 0.914, a sensitivity of 84.2%, and a specificity of 90.6% in ROC analysis. In multivariate logistic regression analysis, the OR for the cut-off value of 4.63 ng/mL as a predictor of distant metastases was 24.62, and the effect size was significantly larger than other variables such as age, tumor size, pathology, and type of surgery. They suggested that preoperative serum Tg may be a strong indicator of distant metastases from DTC (23).

Although our study was performed on patients after surgery, the results were almost similar. In multivariate logistic regression analysis, people with ps-Tg levels higher than 5.41 had a significantly increased risk of distant metastasis. People with FTC pathology had a higher risk of metastasis than the PTC group, which is noteworthy. However, other variables (gender and age) did not show a significant association with the prediction of distant metastasis.

Our findings showed that higher ps-Tg levels indicate a more advanced stage of the disease and a higher risk of distant metastasis. In our study, a cut-off vaue of 41.5 ng/mL for ps-Tg has high sensitivity and specificity in distinguishing patients with distant metastasis from those without metastasis. In addition, high specificity (88.5%) and very high OR (55.60) were identified in relation to the cut-off value, so that it can distinguish distant metastasis in most patients. Moreover, ps-Tg may be the only available indicator for the detection of distant metastasis. If the postoperative serum Tg is very high, patients should be informed about the possibility of distant metastasis and appropriate imaging studies should be requested, which can prevent low-dose iodine therapy.

In the present study, our results showed that higher ps-Tg levels more accurately predicted a high risk of recurrence. A cut-off value of 41.5 ng/mL with a high negative predictive value, NPV=99% (98-100%), could reliably rule out the presence of distant metastasis in patients with DTC.

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One of the limitations of our study was its retrospective design. Moreover, although our study included a relatively large number of patients with DTC, the number of samples included in the study was relatively insufficient due to the low prevalence of distant metastasis in DTC patients. Also, the patients were selected from a teaching hospital, so there was a possibility of sample selection bias, and on the other hand, the dose of iodine therapy was not only influenced by the physician's perspective, but also to some extent by the patient's choice of outpatient or inpatient treatment. Another limitation was that recurrence and survival after ablation were not examined. Long-term follow-up is necessary to determine the effect of ablation therapy, so a prospective multicenter study is recommended to confirm the findings of our study. In our study, the cut-off value of 41.5 ng/mL for ps-Tg is suggested as the optimal cut-off value with the highest accuracy for practical use in the clinic. This study showed that the serum level of ps-Tg is helpful in predicting the presence of distant metastasis in DTC patients.

The Ps-Tg index can be considered as a suitable and reliable marker in showing the different risks of recurrence and distant metastasis and may be the only parameter used for this purpose. Furthermore, it can provide useful changes in the decision-making process of radioiodine therapy.

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