Article published online: 2022-05-17

Original article

Stimulated Serum Thyroglobulin Levels versus Unstimulated Serum Thyroglobulin in the Follow-up of Patients with Papillary Thyroid Carcinoma

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Abstract

Serum thyroglobulin (Tg) and thyroid whole-body radioiodine scintigraphy (TWBS) are used in the follow-up of patients with papillary thyroid carcinoma (PTC) after total thyroidectomy. Symptoms of hypothyroidism are frequent as patients discontinue levothyroxine 1 month before visit, favoring the use of unstimulated serum Tg (uSTg) only. This study was done to determine the reliability of stimulated serum Tg levels (sSTg) over uSTg. A total of 650 patients with PTC came for follow-up between June 2011 and 2016. In those who had levels of uSTg and sSTg months measured within an interval of median of 3 months (range from 1 to 8 months), risk stratification was done as per the American Thyroid Association guidelines 2015. Intervention was based on a cutoff value of sSTg >10 ng/ml in our institution and the same was used for data analysis. Out of 650 patients, 106 had paired Tg values. Low-, intermediate-, and high-risk groups comprised 40, 31, and 35 patients, respectively. The sSTg >10 ng/ml with uSTg <10 ng/ml in the same patient was noted in 22.5% (9/40) of the low-risk, 41.9% (13/31) of the intermediate-risk, and 14.2% (5/35) of the high-risk groups. The levels were corroborated with tumor burden as determined by additional clinical, ultrasonography neck, and TWBS findings. Our study highlights the superiority of sSTg over uSTg in the follow-up of PTC patients. Follow-up with uSTg alone may result in underestimating the tumor burden.

Keywords: Papillary thyroid carcinoma, stimulated serum thyroglobulin, unstimulated serum thyroglobulin

Introduction

Differentiated thyroid cancer (DTC), which includes papillary and follicular cancer, comprises the majority (>90%) of all thyroid cancers.[1] Initial management of patients with DTC comprises standard primary treatments including surgery, radioactive iodine (RAI), and thyroid-stimulating hormone (TSH) suppression.[2]

In the recent past, a steady increase in the incidence of thyroid cancer has been observed in both genders and all ethnic populations. This may be attributed to the rise in the incidence of papillary carcinoma as well as the early detection. Mortality rates have supposedly dropped or remained stable, and this has led to increase in the survival rates for thyroid cancer.[3]

In the light of this, it is imperative to have a reliable follow-up strategy for patients with papillary thyroid carcinoma (PTC). Nevertheless, the long-term management of these patients often remains a challenge. The differences in patient and tumor characteristics, risk of recurrence, locoregional, and distant metastases have contributed to the difficulty in

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Access this article online

Quick Response Code:

Website: www.wjnm.org

DOI: 10.4103/wjnm.WJNM_20_17

How to cite this article: Sunny SS, Hephzibah J, Mathew D, Bondu JD, Shanthly N, Oommen R. Stimulated serum thyroglobulin levels versus unstimulated serum thyroglobulin in the follow-up of patients with papillary thyroid carcinoma. World J Nucl Med 2018;17:41-5.

framing a definitive protocol.[4] After exhaustive research over the years, it had been concluded that an accurate estimation of the postoperative disease status would be of utmost importance for an effective management of the patient. The goal for long-term surveillance must also be customized according to individual disease characteristics and risk of recurrence.

The two main modalities currently in use to ascertain the same are thyroid whole-body radioiodine scintigraphy (TWBS) and stimulated serum thyroglobulin (sSTg). The former is employed to assess residual or recurrence of disease and the latter as the tumor marker.[5] The information obtained from both modalities can alter management and possibly benefit outcome.

For the measurement of serum Tg, it has been concluded that the following steps are ensured. First, the recent American Thyroid Association (ATA) guidelines state the use of immunometric assays to measure serum Tg, and it is important that these assays are calibrated against the CRM-457 international standard.[4] Second, TSH stimulation up to ≥30 μIU/ml is essential, as the production and release of Tg from the cells are significantly influenced by the degree of TSH stimulation.[4-6] Third, the Tg assays used require a sufficient detection sensitivity of <1ng/ml. In addition, the same assay technique is to be employed during each follow up visit after excluding the presence of antithyroid antibodies.

If accurate results are to be obtained from the above modalities, it is mandatory for the patient to withdraw suppressive doses of thyroxine supplements for a period of 4 weeks. The drawback of this practice is that most patients if not all complain of symptoms of hypothyroidism such as weight gain, lethargy, generalized edema, and skin changes.[7] In a few, it is significant enough to decrease the quality of life.

Hence, several clinicians resort to follow up with unstimulated serum Tg (uSTg), thereby averting the unpleasant symptoms of hypothyroidism.[8]

In this context, this study was carried out to validate the reliability of uSTg over sSTg values and to compare the two values.

Subjects and Methods

All patients with biopsy-proven PTC who had undergone total thyroidectomy with or without lymph node dissection were included in the study between June 2011 and June 2016.

These patients, irrespective of the initial stage, were advised to follow up in the Nuclear Medicine Outpatient Department for evaluation and TWBS. They were all instructed to withdraw the suppressive dose of thyroxine 4 weeks before their visit to ensure that serum TSH levels exceeded 30 μIU/ml. They were also advised low-iodine diet and avoid iodine-containing drugs for a period of 4–6 weeks. None of the patients had contrast-enhanced computed tomography imaging for at least 3 months before their visit.

Some of the patients were followed up in the surgical outpatient clinic during the interim period, wherein an uSTg value (patient on thyroxine) was obtained. Subsequently, when the patient was evaluated in Nuclear Medicine Department for possible radioiodine scintigraphy/ablation, sSTg was estimated.

Analysis of all the patients fulfilling the criteria was done (n = 650). Of the total, those with paired values (both uSTg and sSTg values measured within an interval of median 3 months) were selected, and their risk stratification was done as per ATA guidelines 2015.

Although ATA guidelines state that an uSTg >1 ng/ml and sSTg >2 ng/ml are considered significant, as per our institutional practice, sSTg >10 ng/ml was considered as a cutoff for intervention.

Statistical analysis

All data were analyzed using Stata software version 12.1 for Windows (StataCorp, College Station, Texas, USA). Frequency distribution was done for categorical variables and presented as number and percentage. Descriptive statistics such as mean, standard deviation, and median with interquartile ranges (IQRs) for continuous variables were calculated. Chi-square test was performed to see the association between risk group and gender. Furthermore, the reliability test was performed for the uSTg and sSTg. The data were also represented graphically using bar charts.

Results

Of the 650 patients with PTC, a total of 106 patients had paired values (both uSTg and sSTg measured within an interval of median 3 months).

The clinicopathological risk stratification of the 106 patients was done as per the ATA guidelines 2015 into low-, intermediate-, and high-risk groups depending on the tumor resection, histology, locoregional or distant metastases, nodal involvement, lymphovascular invasion, avidity on posttherapy scan, and other relevant features.[4]

Tg assay was performed using a Modular Analytics E170 analyzer based on electrochemiluminescence

immunoassay sandwich principle. In our laboratory, the analytical assay range was from 0.04 to 500 ng/ml.

The distribution of the 106 patients was as follows: 40 (38%) - low risk, 31 (29%) - intermediate risk, and 35 (33%) - high risk.

The average age of the study patients was 47 years, ranging from 15 to 78 years. In each individual group, the mean age in the low-risk group was 40 years, 41 years in the intermediate-risk group, and 36 years in the high-risk group.

There was a total of 63 female patients (59%) and 43 male patients (41%). The majority of the male patients were in the high-risk category (19/43, 44.1%), followed by intermediate group (14/43 = 32.5%) and low-risk group (10/43, 23.2%). In the category of the female patients, the majority comprised low-risk patients (30/63, 47.6%), followed by intermediate-risk group (17/63, 27.0%) and high-risk group (16/63, 25.4%) [Tables 1 and 2].

Among the total patients, those with an uSTg <10 ng/ml but with a sSTg >10 ng/ml was selected in each group. It was found that 22.5% (9/40) in the low-risk group, 41.9% (13/31) in intermediate-risk group, and 14.2% (5/35) in high-risk group had an uSTg <10 ng/ml and sSTg >10 ng/ml. Overall, it was 25.4% (27/106) of the total number of patients [Table 3].

The median values of sSTg were also significantly higher overall and in each group as compared to the uSTg values. There was an increase in the median from 0.3 to 2.6 in the low-risk group, 1.3–20.0 in the intermediate group, and 125–920 in the high-risk group. Overall, the median value in the uSTg group was 2.93, the IQR being 0.3–52.2, whereas in the sSTg group, the median value of 30.0 and IQR of 2.3–335.2 significantly higher [Table 4].

Table 1: Patient characteristics (*n*=106)

Patient characteristics	Value
Median age - range (years)	47 (15-78)
Gender (%)	
Females	63 (59)
Males	43 (41)
Distribution according to ATA risk stratification	
Low	40
Intermediate	31
High	35

ATA: American Thyroid Association

Table 2: Distribution of gender across risk

	Male (%)	Female (%)
Overall	43 (40.6)	63 (59.4)
Low	10 (25.0)	30 (76.5)
Intermediate	14 (45.2)	17 (68.8)
High	19 (54.3)	16 (41.2)

Table 3: Distribution of patients with unstimulated serum thyroglobulin <10 ng/mL but with a stimulated serum thyroglobulin >10 ng/mL

	Total	uSTg negative/sSTg positive (%)
Overall	106	27 (25.4)
Low	40	9 (22.5)
Intermediate	31	13 (41.9)
High	35	5 (14.2)

uSTg: Unstimulated serum thyroglobulin; sSTg: Stimulated serum thyroglobulin

Table 4: Median interquartile range of distribution of thyroglobulin levels

	uSTg	sSTg
Overall	2.9 (0.3-52.2)	30.0 (2.3-335.2)*
ATA risk		
Low	0.3 (0.1-20)	2.6 (0.4-19.4)
Intermediate	1.3 (0.3-8.9)	20.1 (2.3-72.0)
High	125 (27-1138)	920 (234-3600)

*$P<0.0001$. uSTg: Unstimulated serum thyroglobulin; sSTg: Stimulated serum thyroglobulin; ATA: American Thyroid Association

Discussion

Serum Tg assay as a tumor marker for DTC plays a vital role in the follow-up of these patients and has become complementary to TWBS.[9]

Withdrawal of thyroxine for a month before TWBS is required resulting in unpleasant symptoms of hypothyroidism.

Conventional practice in nuclear thyroidology suggests the utilization of sSTg and TWBS for the follow-up of these patients. Although recombinant TSH injection is available, the same is not used in several centers due to financial implications. Of late, clinicians have resorted to following up these patients with uSTg alone.

This is not only to avert undue hypothyroidism but also to prevent overaggressive therapy in cases where disease burden and risk of recurrence is low. Hence, this study aimed at determining the reliability and the adequacy of uSTg.

PTC is a relatively slow-growing tumor, and with appropriate management, cure is possible in the majority of the patients. Relying on a single parameter mainly Tg may fail to pick up disease activity, thereby altering the survival outcomes. In view of the same, the emphasis must be laid on tests that are highly specific that permit identification of patients unlikely to experience disease recurrence. This can be utilized to ensure safe, cost-effective, and less aggressive management. Furthermore, in patients with a higher risk of recurrence, more

aggressive surveillance is essential to ensure the early detection of recurrent disease.[4]

Low sSTg level has been proven to indicate the completeness of surgery and ablation, and it predicts low recurrence risk and good prognosis.[10]

According to the ATA and European Thyroid Association guidelines, patients undergoing 131I ablation should be prepared with a preablative TSH level of more than 30 μIU/mL.[4,6] sSTg has been regarded as an important indicator for successful ablation, whose high negative predictive value (NPV) was 98% for predicting disease remission status.[10,11]

Yang *et al*., in their study, emphasized upon the fact that sSTg is highly valuable in predicting therapeutic response and providing incremental value in patients with high sSTg level toward decision-making for RAI therapy.[12]

In our study, it was found that in the low-risk group - 22.5% (9/40), intermediate-risk group - 41.9% (13/31), and high-risk group - 14.2% (5/35) had an uSTg <10 ng/ml and sSTg >10 ng/ml. Overall, it was found to be 25.4% (27/106) of the total number of patients. These are patients who had an undetectable serum Tg on thyroid hormone treatment and a detectable serum Tg after TSH stimulation, obtained following thyroid hormone withdrawal. The results were false negative, and patients would have been falsely assured of a disease-free status if only uSTg was utilized. The importance of sSTg cannot be overlooked in the light of the above findings.

When combining both low- and intermediate-risk groups, almost one-third of the patients would have been false negative.

In the high-risk group, withholding intervention on the basis of a false-negative value is alarming and cannot be overlooked as it can alter the overall prognosis [Figures 1 and 2]. In a recent retrospective analysis by Krajewska *et al*., for assessment of risk factors influencing DTC relapse in 510 patients with a median follow-up of 12.1 years, it was summarized that high stimulated Tg level above 30 ng/mL, evaluated before RAI ablation, was the most potent, independent prognostic factor.[13]

Some authors have demonstrated the use of a highly sensitive STg, wherein uSTg is sensitive enough. According to the meta-analysis of nine studies with 3178 DTC patients by Giovanella *et al*., basal high sensitive Tg measurement has a very high NPV but an insufficient positive predictive value for monitoring DTC patients.[14] These authors have proposed that sSTg is avoided in patients with an undetectable basal high sensitive Tg, whereas a stimulated Tg measurement is considered when basal high sensitive Tg levels are detectable.

In a study by Lamartina *et al*., the authors concluded that continued monitoring of stimulated Tg levels should be considered a key component of follow-up, not because of its capacity to identify patients with persistent/recurrent disease, which is, in fact, limited, but because it allows the confident exclusion of this outcome in a substantial proportion of this population.[15]

The significant *P* value and rise in median sSTg values over uSTg in all three groups and overall produce a

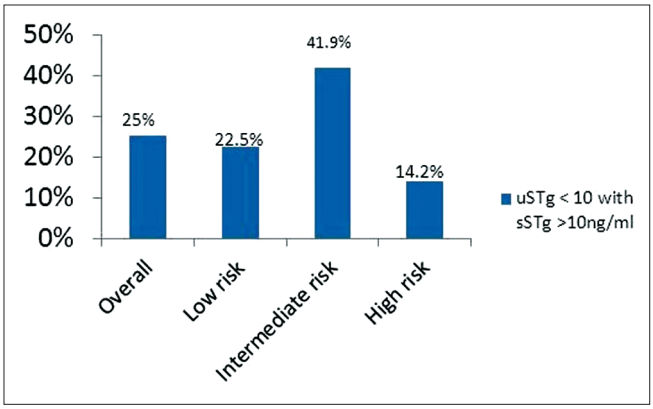

Figure 1: Histogram depiction of patients after risk stratification whose unstimulated serum thyroglobulin <10 ng/ml and stimulated serum thyroglobulin levels >10 ng/ml

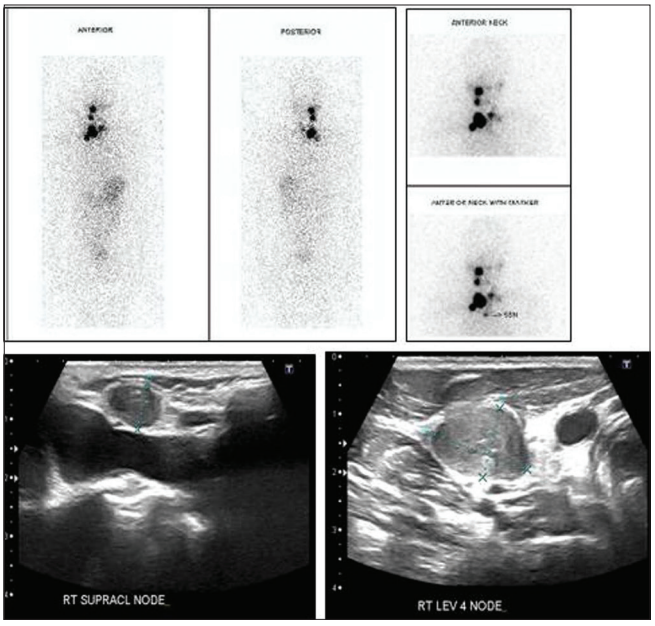

Figure 2: A 23-year-old male with biopsy-proven papillary thyroid carcinoma and posttotal thyroidectomy. His unstimulated serum thyroglobulin value was 19.14 ng/ml. Stimulated serum thyroglobulin levels obtained after 6 months were 1380 ng/ml. Ultrasonography neck and thyroid whole-body radioiodine scintigraphy revealed nodal recurrence

strong evidence to denote that sSTg is a much more reliable and sensitive marker in accurately predicting the postoperative disease status which was also stated in the structured meta-analysis by Eustatia-Rutten *et al*.[16] There is also an additional benefit of complementation with TWBS to assess disease persistence/recurrence.

The limitation of this study is that of its small sample size and a single institutional study; perhaps a larger sample size would have been ideal in the given setting.

Conclusion

From the results obtained, it can be concluded that sSTg is a more reliable test than uSTg in the follow-up of patients with PTC irrespective of their risk stratification. Hence, it is prudent to consider the same during evaluation of these patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Kumar V, Abbas AK, Astar JC. Robbins and Cotran Pathologic Basis of Disease. 9th ed. Philadelphia: Elsevier Saunders; 2014.
2. Haugen BR. Initial treatment of differentiated thyroid carcinoma. Rev Endocr Metab Disord 2000;1:139-45.
3. La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, *et al.* Thyroid cancer mortality and incidence: A global overview. Int J Cancer 2015;136:2187-95.
4. 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.
5. Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, *et al.* Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2005;90:1440-5.
6. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W; European Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154:787-803.
7. Papadakis G, Kalaitzidou S, Triantafillou E, Drosou A, Kakava K, Dogkas N, *et al.* Biochemical effects of levothyroxine withdrawal in patients with differentiated thyroid cancer. Anticancer Res 2015;35:6933-40.
8. Pelttari H, Laitinen K, Schalin-Jäntti C, Välimäki MJ. Long-term outcome of 495 TNM stage I or II patients with differentiated thyroid carcinoma followed up with neck ultrasonography and thyroglobulin measurements on T4 treatment. Clin Endocrinol (Oxf) 2008;69:323-31.
9. Hephzibah J, Theodore B, Shanthly N, Oommen R, Nair A, Seshadri MS. Follow up of patients with differentiated carcinoma thyroid: Is serum thyroglobulin alone enough? Aust N Z Nucl Med J 2009;40:2-5.
10. Lee JI, Chung YJ, Cho BY, Chong S, Seok JW, Park SJ. Postoperative-stimulated serum thyroglobulin measured at the time of 131I ablation is useful for the prediction of disease status in patients with differentiated thyroid carcinoma. Surgery 2013;153:828-35.
11. Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, *et al.* The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: A meta-analysis involving 3947 patients. J Clin Endocrinol Metab 2012;97:2754-63.
12. Yang X, Liang J, Li T, Zhao T, Lin Y. Preablative stimulated thyroglobulin correlates to new therapy response system in differentiated thyroid cancer. J Clin Endocrinol Metab 2016;101:1307-13.
13. Krajewska J, Jarzab M, Czarniecka A, Roskosz J, Kukulska A, Handkiewicz-Junak D, *et al.* Ongoing risk stratification for differentiated thyroid cancer (DTC) – Stimulated serum thyroglobulin (Tg) before radioiodine (RAI) ablation, the most potent risk factor of cancer recurrence in M0 patients. Endokrynol Pol 2016;67:2-11.
14. Giovanella L, Treglia G, Sadeghi R, Trimboli P, Ceriani L, Verburg FA. Unstimulated highly sensitive thyroglobulin in follow-up of differentiated thyroid cancer patients: A meta-analysis. J Clin Endocrinol Metab 2014;99:440-7.
15. Lamartina L, Montesano T, Trulli F, Attard M, Torlontano M, Bruno R, *et al.* Papillary thyroid carcinomas with biochemical incomplete or indeterminate responses to initial treatment: Repeat stimulated thyroglobulin assay to identify disease-free patients. Endocrine 2016;54:467-75.
16. Eustatia-Rutten CF, Smit JW, Romijn JA, van der Kleij-Corssmit EP, Pereira AM, Stokkel MP, *et al.* Diagnostic value of serum thyroglobulin measurements in the follow-up of differentiated thyroid carcinoma, a structured meta-analysis. Clin Endocrinol (Oxf) 2004;61:61-74.