Variability of Serum Thyroglobulin Levels in Post-Thyroidectomy Patients with Well-Differentiated Thyroid Cancer: the ATA Guidelines

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Objective: Evaluate the variability of stimulated serum thyroglobulin (Tg) levels in post-thyroidectomy patients with well-differentiated thyroid cancer (WDTC) and determine the frequency of undetectable Tg in patients with evidence of functional thyroid tissue after a 131-I whole-body scan (WBS).

Methods: A retrospective record review of patients with WDTC referred to our clinic from 1990 to 2010. Demographic data, histology, staging, imaging studies, stimulated Tg values, and the presence if applicable of Tg antibodies (TgAb) were documented. The images of whole-body radioiodine scans were reviewed to assess the extent of functional thyroid tissue.

Results: A total of 142 cases were evaluated with 417 studies. There were 112 women and 30 men; the median age was 47 years. The tumor histologies included 97 papillary (4 had the Hurthle cell variant), 33 papillary-follicular tumor, and 12 follicular tumors; 7 were multifocal. ATA classification was used; groups were divided into low (55%) and intermediate-high risk (45%). The final analysis comprised 84 patients, having among them 170 studies that included Tg values in their records. The cut-off value for Tg was 2.0 ng/ml, and for TgAb, it was 20 IU/ml or more. Residual functional tissue was present in 105 (62%) cases. Discordant Tg results were found in 55% of the low-risk patients; of those, only 3 had TgAb. In the intermediate- and high-risk group, 47% had discordant results; 2 cases had TgAb.

Conclusion: The variability of the Tg levels and the high frequency of discordant results (positive WBSs with undectable Tg levels) bring into question the standard recommendation of conservative management for low-risk patients. Follow-ups should include a Tg assay and imaging studies. [*P R Health Sci J 2016;35:142-146*]

Key words: Thyroid Cancer, Serum Thyroglobulin, Low-risk thyroid cancer

For many years post-thyroidectomy patients with well-differentiated thyroid cancers (WDTC), which include papillary, follicular, and papillary-follicular tumors, have been referred to nuclear medicine for radioiodine ablation therapy and/or annual follow-up with diagnostic whole-body imaging. The initial and follow-up evaluations entail the measurement of thyroid-stimulating hormone (TSH) and stimulated serum thyroglobulin (Tg) levels and a neck sonogram, all prior to the administration of radioiodine (for diagnostic or therapeutic purposes), as recommended by the current American Thyroid Association (ATA) guidelines (1,2,3). Serum thyroglobulin is a well-known tumor-specific marker indicative of functional thyroid tissue remnants and/or residual thyroid cancer or recurrent disease.

The ATA taskforce guidelines for the evaluation of thyroid cancer have evolved over the past 10 years. The current guidelines recommend that a patient with WDTC be classified as belonging to a low-, intermediate-, or high-risk group. Patient management is then guided based on the risk of recurrence (3).

The guidelines for the evaluation and management of thyroid cancer vary according to the risk levels. Both surgery and post-surgical radioiodine ablation are recommended for the intermediate- and high-risk groups, with subsequent follow-up including the measurement of serum Tg levels and whole-body radioiodine scintigraphy. Patients in the intermediate-risk group experience the microscopic invasion of the tumor into the peri-thyroidal soft tissues at the initial surgery or cervical lymph node metastases, while high-risk patients are those with large tumors with extra-thyroidal extension, lymph node invasion or distant metastasis. The low-risk group includes patients whose tumors

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are confined to the thyroid (less than 4 cm) and no lymph node or distant metastasis. The recommended management of this last group is more conservative in terms of both the extent of surgery required and the use of post-surgical radioiodine ablation. The follow-up recommendations are limited to doing serial neck sonograms and measuring serum Tg levels (3).

In our clinical experience over the last 20 years evaluating WDTC patients with post-therapeutic or diagnostic 131-iodine whole body scan, we have observed great variability in the results of the stimulated Tg values of these patients. It is our understanding that Tg measurements are often not concordant with the clinical, sonographic, and scintigraphic findings. This observation is particularly worrisome as this discordance could have an impact on the management and follow-up of patients (whose risk of recurrence has been classified according to the 2009 and 2015 ATA guidelines), especially those in the low-risk group. It is important to emphasize that prior to the 2009 revision of the guidelines, many of these low-risk patients, in their follow-ups, would have received the benefit of radioiodine ablation therapy and diagnostic whole-body imaging.

The aim of the study was to retrospectively evaluate the variability of TSH-stimulated (TSH ≥ 30 IU/dL) serum Tg levels in post-thyroidectomy patients with WDTC and to determine the frequency of normal Tg levels in patients with evidence of functional thyroid tissue in I-131whole body scans (WBSs) in order to explore our concerns regarding the management of low-risk patients.

Materials and Methods

We performed a retrospective record review of patients who had been diagnosed with WDTC and had been referred to the UPR School of Medicine Nuclear Medicine Section during the period ranging from January 1990 to December 2010. All patients diagnosed with WDTC and total thyroidectomy who had undergone therapeutic and/or sequential diagnostic whole-body radioiodine studies and Tg measurements during the study period were included. All post-therapeutic 131-Iodine WBSs had been performed 7 to 10 days after the oral administration of radioiodine, while the diagnostic WBSs had been done 48 hours after the iodine dose. The diagnostic studies were done in accordance with the Society of Nuclear Medicine and Molecular Imaging Procedure Guidelines (4), at approximately 1-year intervals for a period of 3 to 5 years. A dual head nuclear camera with a high energy collimator and a 20% symmetric window centered at the 364 kev peak was used.

Patients with fewer than 2 follow-up diagnostic radioiodine whole-body scans were excluded, as were those patients with other histological types of disease, including medullary, poorly differentiated, or anaplastic thyroid cancers.

The demographic data extracted from each patient's record included the patient's age and sex, the tumor histology and stage, imaging-study findings, TSH, stimulated Tg values, and the presence (when applicable) of Tg antibodies. All the available Tg values were obtained with TSH values equal to or above 30 IU/dL. The cut-off value for a positive serum Tg was greater than or equal to 2.0 ng/ml; for TgAb, it was 20 IU/ml or greater. All the cases were revised to establish the ATA classification for the risk of recurrence level (4).

The WBS images of patients having undetectable serum Tg levels but positive WBS results were reviewed by 2 experienced nuclear medicine physicians. These individuals determined the extent and intensity of the functional thyroid tissue, classifying each case according to a visual tissue-burden scale that was developed by the authors for the purpose of this study. The scale consisted of a visual evaluation of the intensity and extension of the abnormal tracer concentration in the region of the thyroid bed in the whole-body images. The scale classifies tissue burden in a range going from 1 to 3, with a tissue burden of 1, corresponding to small size and mildly intense activity; 2, corresponding to moderate size and moderately intense activity; and 3, corresponding to large size and intense activity. The scale was used exclusively for the study as a descriptive tool.

The study was approved by the University of Puerto Rico Medical Sciences Campus Institutional Review Board.

Statistical analysis

Stata Statistical Software, Release 11 (College Station, TX: StataCorp LP), was used to perform the statistical analyses. Descriptive statistics were used to describe the study population. Continuous variables were described using the mean, standard deviation, median, and range. Frequencies and proportions were used to describe categorical variables (sex, histology type), TNM stage, metastasis (local, distant), and disease status (disease free, residual disease, or recurrent disease). To evaluate the association of the study parameters with the WBS, chi-squared or Fisher's exact test (as appropriate) was used for categorical variables.

Results

A total of 142 patients were initially identified, with 417 diagnostic and/or post-therapy whole-body studies. There were 112 women and 30 men; median age was 47 (6–83 years). The overall tumor histology consisted of 97 papillary (4 of these had the Hurthle cell variant), 33 papillary-follicular, and 12 follicular tumors; 7 tumors were multifocal. Cases without corresponding Tg levels or with fewer than 2 years of follow-up were excluded. The final analysis was based on 84 patients who, among them, had 170 laboratory reports of both Tg and TgAb in their medical records.

In this group of patients we found, based on the ATA classification guidelines for recurrence risk, that 55% of the patients were low risk, while 45% were classified as belonging in the intermediate- high-risk group. The mean age for the low-risk group was 46 years (16–79 years); for the intermediate-high-risk group, it was 45 years (6–80 years). All the patients in the low-risk group were older than 15 years.

Lymph node invasion was reported in 26% (n = 22) of the cases and distant metastasis in 4.4% (n = 6). Residual functional thyroid tissue in the neck was visible in the WBS of 105 cases (62%). The tissue that was located in the thyroid bed was considered to be thyroid remnant. Tissue elsewhere in the neck (lateral or midline) was considered to be lymph node disease. Discordant Tg results (meaning that the WBS showed functional tissue though Tg levels remained undetectable) were found in 47% (n = 38) of the study population (Table 1). Thyroglobulin antibodies were present in only 25% of the total population.

Table 1. Relation of thyroglobulin (Tg) values and whole-body scan (WBS) results in all patient groups

All WBSs with Tg Value		
	Tg-	**Tg+**
WBS-	52.9%	22.9%
WBS+	47.1%	77.1%
Total	100	100

p value <0.5. WBS was significantly associated with Tg (Fisher's exact test).

Table 2. Comparison of thyroglobulin (Tg) levels and whole-body scans (WBSs) in the low-risk group

Low-Risk Group: WBS vs. Tg		
	Tg-	**Tg+**
WBS-	44.8%	11.5%
WBS+	55.2%	88.5%
Total	100	100

p value was <0.5 (Fisher's exact test).

In the low-risk group, 55% (n = 23) of the patients had undetectable Tg levels; of those, only 13% (n = 3) had TgAb (Table 2). In the intermediate- high-risk group, 47% had undetectable Tg values; only 22% (n = 2) of the cases had TgAb. The WBS results were significantly associated with the Tg values (p value <0.5). During the follow-up evaluations, 2 patients in the low-risk discordant group had recurrent disease in the neck and in the lungs.

The tumor burden in the discordant cases was evenly distributed in the intermediate-high-risk group as follows: mild (tumor burden 1) in 40% (n = 14), moderate (tumor burden 2) in 44.4% (n = 4), and severe (tumor burden 3) in 43.6% (n = 17). In the low-risk group, patients with undetectable levels of Tg had a tumor burden distribution of 15% in the mild, 23% in the intermediate, and 62% in the severe category.

Discussion

WDTC is a slow-growing tumor with a good survival rate, particularly when diagnosed at an early stage. Its incidence has been rising during the past 10 years in the United States and Puerto Rico, with an average annual increase of 6%. The tumor is more frequent in women than in men, with a male-to-female ratio of 3:1. The most common histologic type is the papillary type, representing approximately 75 to 85% of the cases in the United States, followed by the papillary-follicular variant and the follicular type (1,2,3,5).

It is well known that several risk factors, including gender, age, tumor histology and size, and disease extension, influence the recurrence rate of this kind of tumor and the long-term prognosis of the adults and children who suffer from it; in children the exposure to ionizing radiation is the most important risk factor. Recurrence rates are higher in patients with early local lymph node invasion, as well as in patients under 20 or over 60 years (2). Patients with distant metastasis at diagnosis have a higher mortality rate.

The recommended initial therapy for most cases is thyroidectomy (total or subtotal), the exception being the micro-carcinoma. Radioiodine ablation therapy is the second step in many cases. This treatment eliminates post-surgical, residual functioning thyroid tissue, reduces recurrences, and optimizes follow-up (1,2,3). Ablating any residual functioning

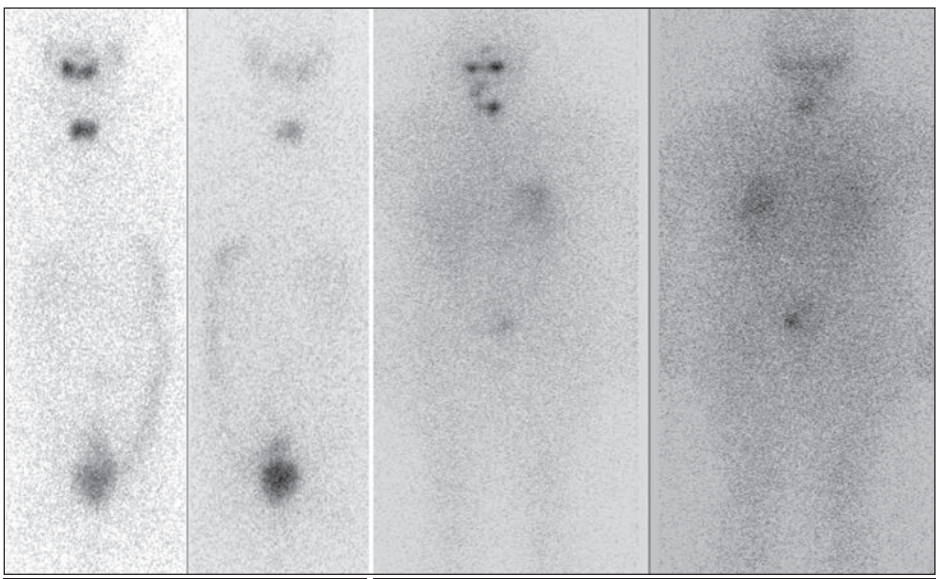

Figure 1. Anterior and posterior 131-I whole-body scintigraphy images showing evidence of tissue burden. The large remnant of functional thyroid tissue with intense tracer uptake presented in the left 2 panels is scored as a 3 on our visual scale. The right 2 panels display a moderately sized mass of functional thyroid tissue having a moderate intensity; its visual score is a 2.

thyroid tissue improves follow-up, for it allows the measurement of serum Tg. After a total thyroidectomy and radioiodine ablation therapy, thyroglobulin serum levels should be undetectable. Thyroglobulin is then employed as a specific marker for functional thyroid tissue in the follow-up of these patients. Any increase in Tg levels is indicative of remnant or recurrent functional thyroid tissue, either local or distant (6,7).

Most of the Tg assays used today are done using the immunometric method. Thyroglobulin assays are calibrated against the CRM-457 international standard. It is known that 1 gram of well-differentiated thyroid tumor releases about 0.5 ug/L of Tg when TSH is suppressed, and the functional sensitivity of most test is 1 ug/liter (5,6). The measurement of stimulated Tg is performed after thyroid hormone therapy withdrawal or after the injection of recombinant TSH. The production of Tg is even higher with TSH stimulation, making Tg levels a more sensitive marker for detecting the presence of persistent or recurrent disease. In our study population, TSH levels were above 30 IU/dL, as recommended by the ATA Guidelines. The Tg assays in our study were all done using the immunometric technique; most were done in reference laboratories.

Despite improvements in the standardization of Tg assays, there is still as much as a twofold difference between some assays. Serum Tg levels have a high positive predictive value; however, studies have reported false-negative rates of between 4 to 35%. Several factors have been associated with the false-negative rates of Tg assays, including technical problems with the assay, heterogeneity of the circulating Tg, a small tumor mass with a low production of Tg, inadequate TSH stimulation, the interference of anti-TgAb, and the "hook effect," in which a falsely low assay response is seen in the presence of high concentrations of Tg (6, 7).

One of the contributing factors interfering with the measurement of Tg is the presence of endogenous TgAb. The reported values for circulating antibodies in thyroid cancer patients range from 10 to 25%. Endogenous antibodies are particularly problematic as they interfere with the assay and result in over- or underestimated Tg values (5,6). Only 25% of the study population was found to have such antibodies. In the low-risk, discordant group, a very low number of cases (13%) presented anti-TgAb. Thus in our group of patients, the low Tg values were not related to the presence of TgAb.

Tissue burden was also estimated in our patients, based on the intensity of radioiodine uptake on the WBS (Fig. 1). We found that the majority was evenly distributed in the mild- and high-uptake categories, which suggests that false-negative Tg findings may be independent of tissue volume. In addition, the pathology reports of our patient population showed all of those patients as having tumors indicative of WDTC. Thus, with regards to our study population, the theory of poorly differentiated tumors resulting in defective Tg production does not apply.

The results of our study showed a significantly high number of false-negative Tg values. A total of 47% of all patients presented discordant Tg values with positive WBS (i.e., positive WBS and normal Tg levels). This was particularly important in the low-risk patient group, in which group the discordant cases reached 55% (p value <0.5). These values are well above the 4 to 35% false-negative rate reported in the literature for thyroglobulin levels (6,7).

The high percentage of WBS+ and Tg- discordant cases is particularly worrisome, especially considering that the current ATA guidelines for the follow-up of low-risk WDTC patients suggest withholding radioiodine ablation and relying on Tg level for follow-up. However, in more than half of the cases, evidence of functional thyroid tissue in the neck (remnants of thyroid and/or local disease) was missed by the stimulated Tg assay. Two cases in the low-risk, discordant group developed recurrent disease after the initial radioiodine ablation therapy, and the patients required additional therapeutic doses. These cases were identified as a result of a follow-up diagnostic WBS.

A high Tg assay value is expected to alert the clinician to reevaluate the case and possible change in management, including the need for additional therapy; nevertheless, these cases with positive WBSs and negative Tg values present a worrisome scenario.

Several authors have addressed this problem. Phan et al. reported finding undetectable Tg levels in patients with positive WBSs. They found that such a result was not an independent predictor of a patient's being disease free. Other authors have found incongruencies in the results of both the Tg assays and WBS and have reported on the value of imaging studies, such as neck ultrasound and WBS, and have reported as well on the value of measuring stimulated Tg levels in the follow-up of WDTC patients with no apparent disease after surgery and ablation. Both ablation therapy and additional diagnostic studies are recommended; the first to ensure the complete eradication of the diseased tissue and the second to ensure that the diseased tissue has been completely eradicated (10,11).

Contrary to what is recommended in the current ATA guidelines, we believe that withholding initial radioiodine ablation therapy from low-risk patients should be done only with caution. Certain cases, such as those involving multifocal micro-carcinomas, otherwise classified as belonging in the low-risk group, have been shown by Ardito, et al., to consist of tumors that have a tendency to behave aggressively(12,13). This raises the possibility that other patients in the low-risk category could benefit from radioiodine treatment. The decision as to whether or not to treat low-risk patients using this strategy should be made on an individual basis, in particular because of the high false-negative rate of Tg reported. Tg assays should be complemented with imaging studies during the follow-up evaluations of patients in the low-risk group. Further studies are necessary to evaluate the clinical impact of the false-negative serum Tg values on the long-term management of these patients.

Conclusions

In the last 20 years, there has been an increasing trend in the incidence of thyroid tumors in the United States, Europe, and Puerto Rico. The evolution of imaging techniques and the use of ultrasound-guided fine-needle aspirations have probably contributed to the increase in diagnoses (5). New evaluation, treatment, and follow-up guidelines have been established in the last 10 years by the ATA. In the last 6 years, there have been important changes in their recommendations for the evaluation, management, and treatment of WDTC. Two of the major changes were the classification of recurrence risk and modifications to the evaluation and follow-up guidelines for low-risk tumors. In this group, conservative management is recommended limiting the extent of surgery and post-surgical ablation; follow-up evaluation is centered on the Tg assays. An important variability in the Tg values has been found by our group and others (6,8,10,11). This variability leads to questions with regard to the recommendation of conservative management and follow-up.

Because of the aforementioned Tg variability and the high frequency of discordant WBS and Tg values, we believe that the follow-up of thyroid cancer patients, including those classified as belonging in the low-risk group, should include a Tg assay, a neck ultrasound, and, in selected cases, ablation therapy and diagnostic WBS. This follow-up procedure is in accordance with what is recommended in the current 2015 ATA guidelines. Furthermore, the decision regarding whether to treat patients in the low-risk group using this strategy must be made on an individual basis.

Resumen

Objetivo: Evaluar la variabilidad de la tiroglobulina estimulada (Tg) en los pacientes con cáncer de tiroides bien diferenciado (CTBD) post tiroidectomía y determinar la frecuencia de Tg no detectable en pacientes con tejido tiroideo funcional en Estudios de Cuerpo Completo con I-131 (ECC). Métodos: Evaluación retrospectiva de los expedientes de pacientes referidos desde 1990-2010 con CTBD. Se recopilaron datos demográficos, histología, estadío, estudios de imágenes, valores de Tg estimulados y la presencia de anticuerpos (TgAb). Los ECC fueron revisados para evaluar la extensión del tejido residual. Resultados: Se evaluaron 142 casos con 417 ECC. La muestra incluía 112 mujeres y 30 hombres; edad media 47 años. La histología tumoral fue 97 papilares, 4 con células Hurthle, 33 papilar-variante folicular y 12 foliculares; 7 tumores multifocales. Utilizando la clasificación de ATA, los grupos se dividieron en riesgo bajo (55%), intermedio y alto (45%). El análisis se basó en 84 pacientes, 174 estudios con evidencia de los valores de Tg. El valor de corte de Tg fue 2.0 ng/ml, el de TgAb fue >20 IU/ml. Existía tejido tiroideo residual en 105 casos (62%). Los niveles de Tg discordantes se identificaron en 55% de los de bajo riesgo, 3 tenían TgAb. En el riesgo intermedio y alto, 47% eran discordantes, 2 tenían TgAb. Conclusión: La variabilidad de Tg y la alta frecuencia de ECC positivos y Tg negativos, plantea preguntas sobre la recomendación de manejo conservador de pacientes de bajo riesgo. El seguimiento debe incluir medidas de Tg y estudios de imagen.

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