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Research Article

Does Unstimulated Thyroglobulin Performs as well as Stimulated Thyroglobulin in the Follow-Up of Patients with Papillary Thyroid Carcinoma

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Abstract

Purpose According to the American Thyroid Association guidelines in 2015, both an unstimulated thyroglobulin (u-Tg) below 0.2ng/ml and a stimulated thyroglobulin (s-Tg) below 1.0ng/ml were required along with negative imaging findings to define an excellent response. This study aimed to investigate whether a u-Tg below 0.2ng/ml coincides with a s-Tg below 1ng/ml. Patients and methods A total of 61 patients with nonmetastatic Papillary Thyroid Carcinoma were retrospectively evaluated with a median follow-up of 12 months. The levels of s-Tg were observed in patients whose u-Tg levels were below 0.2ng/ml after radioiodine therapy, and risk factors associated with the increase of s-Tg to above 1 ng/ml from below 0.2ng/ml were analyzed. Results In total, 59% (36/61) of the patients achieved a u-Tg below 0.2ng/ml 3 months after remnant ablation, most of whom (86.11%, 31/36) also achieved a s-Tg below 1ng/ml. A total of 5 (13.89%) patients had an increased s-Tg above 1ng/ml. A comparative analysis showed no significant difference between patients who showed an increase in thyroglobulin from below 0.2ng/ml to above 1ng/ml and those who did not. Conclusion Assessment of the level of u-Tg might be a better parameter to use for defining excellent response as u-Tg is more stable, convenient, economical, and is not associated with hypothyroidism as a side effect.

Keywords: Papillary thyroid carcinoma; Stimulated thyroglobulin; Unstimulated thyroglobulin

Introduction

Thyroid cancer is an epidemic increasing (>5% in every year) in incidence worldwide and has become the most common endocrine carcinoma [1]. Despite a favorable response in Differentiated Thyroid Cancer (DTC), active surveillance remains necessary as the recurrence rate of DTC is up to 30% [1,2]. Serum thyroglobulin (Tg), produced by thyroid follicular epithelial cells or well- differentiated DTC cells plays a vital role in the surveillance of DTC, especially associated with cervical ultrasound [3-5]. If necessary, a diagnostic radioiodine (RAI) whole-body scan, chest Computed Tomography (CT), and PET/CT can be used to evaluate the persistence or recurrence of disease [4,5]. Previously, undetectable stimulated thyroglobulin (s-Tg) was considered to have an improved Negative Predictive Value (NPV) compared with unstimulated-thyroglobulin (u-Tg) in predicting how thyrotropin [Thyroxin-Stimulating Hormone (TSH)] could promote the synthesis of Tg [6,7]. Many studies showed that s-Tg less than 1ng/ml could be used to predict an Excellent Response (ER) even without imaging or clinical evidence of disease [8-10]. In 2015, American Thyroid Association (ATA) guidelines suggested that both u-Tg below 0.2ng/ml and s-Tg below 1ng/ml were recommended to define ER as part of the therapy stratification system [4-11]. However, the correlation between the two exact cut-off values was rarely addressed, and there is uncertainty whether a u-Tg level of less than 0.2ng/ml corresponds to a s-Tg level of less than 1 ng/ml. In addition, it has been shown that the level of s-Tg could be affected by TSH stimulation. In this study, we retrospectively assessed the consistency between these two ER criteria. We also investigated the factors that may influence the correlation between u-Tg and s-Tg.

Patients and methods: A total of 73 consecutive patients with DTC were retrospectively accessed. All patients were treated with total/near-total thyroidectomy, RAI remnant ablation, and TSH-suppressive therapy. Sixty-one patients were finally enrolled, after excluding patients with incomplete medical information, positive Tg antibody (Tg-Ab > 115 IU/ml) and distant metastasis. Patients were classified into different stages (I, II, III, IVA and IVB) according to American Joint Committee on Cancer (AJCC) TNM staging. All patients were treated with total or near-total thyroidectomy, RAI remnant ablation, and TSH-suppressive therapy. Next, post-treatment RAI whole-body scans were obtained after RAI therapy to treat the distant metastasis. TSH suppressive therapy was started one day after performing the radioiodine whole body. Initial post-treatment evaluation (ultrasound and u-Tg) was performed 3 months after remnant ablation and s-Tg was measured 6 months after RAI therapy. Based on the dynamic risk stratification patients were reclassified, one year after initial therapy, using Thyroglobulin (Tg) and thyroglobulin antibodies (anti-Tg) levels, Ultrasonography (USG) and other imaging methods as parameters. Patients were reclassified as having excellent, indeterminate, incomplete response to treatment. Chemiluminescence immunoassay was used to measure the TSH, with a sensitivity ranging from 0.08 to 150 μIU/ml. Electrochemiluminescence immunoassay was used to measure Tg with a sensitivity ranging from 0.04 to 500ng/ml. Tg-Ab was

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measured in the same laboratory with a functional sensitivity of 10 IU/ml.

Statistical analysis: Continuous data were expressed as mean ± SD. Comparisons between groups were evaluated using Student's t-test, the Mann-Whitney U-test, χ^2, or Fisher's exact test, Mac Nemar test. All statistics were analyzed using SPSS 22.0, and a P value below 0.05 was considered to have statistical significance.

Result

Patient characteristics: A total of 61 patients with DTC were enrolled in the study, the male to female ratio was 1:5.8, and the average age at diagnosis was 43,85 years. Table 1 shows the detailed clinical and histological features of the 61 patients at diagnosis. In the first evaluation, 3 months after RAI therapy, 36 (59%) patients had a u-Tg level of less than 0.2ng/ml. Comparing, patients with a u-Tg level of above 0.2ng/ml we did not find a statistically significant difference for sex (p=0.286), T stage (p=0.603), N stage (0.333), Pronostic stage (p= 0.130) and the mean of TSH (p=0.873) (Table 2). In the second evaluation 6 months after RAI therapy, 39 (63.9%) patients had a s-Tg level of less than 1ng/ml. In comparison, patients with a s-Tg level of above 1 ng/ml we did not find a statistically significant difference for mean of age (p=0.518), sex (p=0.585), T stage (p=0.742), N stage (p=0.144), Pronostic stage According to American Joint Committee on Cancer (AJCC) TNM staging (p= 0.131) and the mean of TSH (p=0.408) (Table 2). For patients with an initial u-Tg level less than 0.2ng/ml 3 months after RAI remnant ablation, 86.1% (31 of 36) had a s-Tg level below 1ng/ml 6 months after RAI therapy (table 3). To assess the clinical and pathological factors associated with the increase in Tg from u-Tg below 0.2 to s-Tg 1 ng/ml, patients with a u-Tg level below 0.2ng/ml were further divided into two groups according to their s-Tg levels. Group 1 had a s-Tg level of below 1ng/ml and group 2 had a level of s-Tg above 1ng/ml. However, multivariate analysis showed no significant association with clinicopathologic features (such as sex (p=0.508), age (p=0.909), T stage (p=0.453), N stage (p=0.689), pronostic stage (p=0.727), TSH mean (p=0.058). We studied the values of uTg and sTg in the different stage of the Dynamic risk stratification one year after RIT (Table 4) and we noted a significant statistical difference between patients with u-Tg level of less than 0.2ng/ml (p=0.021) and patients with s-Tg level of less than 1ng/ml (p=0.039).

Table 1: Clinical features at diagnosis Outcome.

Clinical features at diagnosis	Outcome
Sex (female/male)	190/100 (65.5%/35.5%)
Age (mean ±SD)	43.85±13.369 years
Pathological pattern (papillary/follicular)	61/0 (100%/0%)
T stage	
1a	21 (34,4%)
1b	21 (34,4%)
2	16 (26,2%)
3a	12 (19,7%)
N stage	
Nx	43 (70.5%)
N0	7 (11.5%)
N1a	8 (13.1%)
N1b	3 (4.9%)
TSH	68,0462±21,20
Dose of 131I (mCi)	98.85±8,96

In the first evaluation, 3 months after RAI therapy, 36 (59%) patients had a u-Tg level of less than 0.2 ng/ml. Comparing, patients with a u-Tg level of above 0.2 ng/ml we did not find a statistically significant difference for sex (p=0.286), T stage (p=0.603), N stage (0.333), Pronostic stage (p= 0.130) and the mean of TSH (p=0.873).

Table 2: Clinical and histological features at the 3 and 6 months evaluations.

Sex (female/male)	23-Feb	29-Jul	19-Mar	23-Jun
Age	41,12±13,91	45,75±12,82	42,363±14,489	44,692±12,812
T stage				
1a	10	11	10	11
1b	2	10	1	11
2	8	8	6	10
3a	5	7	5	7
N stage				
Nx	17	26	13	30
N0	2	5	3	4
N1a	4	4	4	4
N1b	2	1	2	1
Pronostic stage				
I	8	19	7	20
II	8	11	7	12
III	6	5	5	6
IVA	3	1	3	1
TSH	0.68±1.08	0.72±0.99	61.638±29.244	55.996±22.981

In the second evaluation 6 months after RAI therapy, 39 (63.9%) patients had a s-Tg level of less than 1 ng/ml. In comparison, patients with a s-Tg level of above 1 ng/ml we did not find a statistically significant difference for mean of age (p=0.518), sex (p=0.585), T stage (p=0.742), N stage (p=0.144), Pronostic stage According to American Joint Committee on Cancer (AJCC) TNM staging (p= 0.131) and the mean of TSH (p=0.408).

Table 3: Distribution of patients according to uTg and sTg.

		sTg
	≥ 1	<1
uTg		
≥ 0.2	17	8
<0.2	5	31

To assess the clinical and pathological factors associated with the increase in Tg from u-Tg below 0.2 to s-Tg 1 ng/ml, patients with a u-Tg level below 0.2ng/ml were further divided into two groups according to their s-Tg levels. Group 1 had a s-Tg level of below 1ng/ml and group 2 had a level of s-Tg above 1 ng/ml. However, multivariate analysis showed no significant association with clinicopathologic features (such as sex (p=0.508), age (p=0.909), T stage (p=0.453), N stage (p=0.689), pronostic stage (p=0.727), TSH mean (p=0.058).

Discussion

The gold standard in DTC follow up has for years been the determination of the concentration of s-Tg which, together with neck Ultra Sound (US), enables correct diagnosis in nearly all cases of the active disease [12,13,14]. In fact, for most low-risk patients, remission

Table 4: Patients distribution according to Dynamic risk stratification one year after RIT, uTg and sTg.

		uTg	sTg	
	≥ 0.2	<0.2	≥ 1	<1
Excellent response	13	32	8	37
Indeterminate response	4	2	5	1
Incomplete response	8	1	9	0
	25	35	22	38

we noted a significant statistical difference between patients with u-Tg level of less than 0.2ng/ml (p=0.021) and patients with s-Tg level of less than 1ng/ml (p=0.039).

is confirmed by just evaluating the s-Tg and US of the neck, as s-Tg is the most sensitive biological indicator of local recurrence or distant metastases [12,13,15,16].

However, the level of serum thyroglobulin can be affected by Tg-Ab, circulating Tg heterogeneity, and the method and equipment used in the laboratory for the measurement [17]. In this study, patients with positive Tg-Ab were excluded and all samples were measured using a single method in the same laboratory. In recent decades, s-Tg has been recommended as a serum biomarker in the surveillance of patients with DTC because it can increase in production because of thyroxin withdrawal [8]. Robbins et al. [18] reported that 2 ng/ml of s-Tg was not a reliable cut-off point in predicting DFS because the rate of recurrence could reach 13.7% in the following 2 years after RAI therapy. In previous studies, a lower cut-off of s-Tg of 1 ng/ml was shown to have an NPV ranging from 98 to 99% to predict recurrence-free survival, with a follow-up of more than 5 years [8-10]. Therefore, it can be concluded that 1 ng/ml of s-Tg could be used as a reliable serum marker for ER, but it also has some disadvantages. For example, patients may experience hypothyroidism several weeks after thyroxin withdraw and the risk of stimulating disease with a high TSH (>30μIU/ml); this can be reduced with the help of recombinant human TSH in some developed countries, but this is not economical and convenient.

With improvements in measuring methods and by implementing more advanced laboratory techniques, u-Tg has been studied to predict the response in patients DTC. In this study of Giovanella L only 1.6% (3/188) of the patients with DTC experienced recurrence over 6.8 years of follow-up with an undetectable u-Tg level (< 0.2 ng/ml) [19]. In addition, some other cut-off points have been studied to predict DFS: 0.1 and 0.27 ng/ml of u-Tg were proven to have 100, and 99% NPV, respectively, all with follow-up durations more than 5 years [3,20]. In sum, it could be concluded that 0.2ng/ml of u-Tg was a reliable cut-off point in predicting DFS; a lower cut-off point was unnecessary. Both 0.2ng/ml of u-Tg and 1 ng/ml of s-Tg were recommended in the 2015 ATA guideline. To assess which is the better choice in predicting ER, we observed the s-Tg in patients with a u-Tg below 0.2ng/ml to observe whether their s-Tg would satisfy below 1ng/ml. The result indicated that only 86.1 % of the patients had a s-Tg below 1ng/ml, which means that 0.2ng/ml of u-Tg did not exactly correspond to 1ng/ml of s-Tg. Thus, it would be irrational to use the above two definite cut-off criteria to define ER as contradictory evaluation results of response might occur. In addition, it would inevitably lead to confusion about which criterion is the better choice to evaluate ER. Our results first indicated that 0.2ng/ml of u-Tg could be used to classify patients into ER without any recurrence in the one year following radioiodine therapy. Using s-Tg to predict the response, u-Tg could simplify procedures during follow- up, avoid iatrogenic hypothyroidism after thyroxin withdrawal, and would be more economically feasible. We also attempted to identify the factors that increased s-Tg to above 1ng/ml in patients with u-Tg below 0.2ng/ml. However, there was no difference in the clinical and pathological features. We might believe there was no difference in the risk of recurrence between the two groups. Therefore, u-Tg below 0.2ng/ml is enough to define ER even if some patients experience an increase in u-Tg to above 1ng/ml after thyroxine withdrawal. In previous studies, the level of s-Tg showed instability because it could be influenced by the magnitude of TSH [21-23]. In this study, we carried out a subgroup analysis on the influence of TSH on s-Tg. We propose that u-Tg is the optimal choice for predicting ER. The u-Tg is a stable, convenient, and economical choice to facilitate the management of patients with DTC. In addition, it could prevent patients from experiencing iatrogenic hypothyroidism during the period of thyroxin withdrawal.

Conclusion

Most of patients with a u-Tg below 0.2ng/ml could reach a favorable response, but the s-Tg of them might do not satisfy below 1ng/ml. Compared with s-Tg, u-Tg is the better choice in predicting ER as it is more stable, convenient, economical, and not associated with hypothyroidism.

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