Preablative Stimulated Thyroglobulin Correlates to New Therapy Response System in Differentiated Thyroid Cancer

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Context: Studies suggested a potential value of preablative stimulated thyroglobulin (ps-Tg) on predicting the recurrent and persistent diseases of differentiated thyroid cancer, whereas its correlations with therapeutic response remain uncertain.

Objective: To establish the correlation between ps-Tg and therapeutic response proposed in 2015 American Thyroid Association guidelines, and calculate a cutoff ps-Tg threshold for predicting a poor response.

Design/Setting: Patients who underwent total thyroidectomy and radioactive iodine therapy in a university hospital participated in this retrospective study.

Patients: Totally, 452 patients with differentiated thyroid cancer were followed for a median of 38 months and were divided into three groups in terms of ps-Tg level: group 1, less than 1 ng/ml (n = 82); group 2, 1–10 ng/ml (n = 173); and group 3, at least 10 ng/ml (n = 197).

Main Outcome Measure: Clinical outcomes were assessed based on response to therapy restaging system, dividing responses into excellent, indeterminate, biomedical incomplete, and structural incomplete (SIR).

Results: Therapeutic responses could be obviously distinguished by different ps-Tg strata. SIR was identified in none of group 1, 1.73% of group 2, and 42.74% of group 3, respectively ($\chi^2 = 123.037$, $P < .001$). A cutoff value of ps-Tg at 26.75 ng/ml was obtained by receiver operating characteristic curve for differentiating SIR from either excellent, indeterminate, or biomedical incomplete responses. The area under curve was 0.947 and negative predictive value was 96.99%. Ps-Tg was an independent predictive variable of SIR (odds ratio, 42.312; $P < .001$).

Conclusions: Ps-Tg has a great performance in predicting therapeutic response and providing incremental value for decision making of radioactive iodine therapy, especially for patients with high ps-Tg level. **(*J Clin Endocrinol Metab* 101: 1307–1313, 2016)**

Surgery and selective postoperative radioactive iodine (RAI) therapy are the primary initial treatment modalities for differentiated thyroid cancer (DTC). Although the overall outcome is exhilarating and the 10-year survival rate is approximately 90% (1, 2), persistent or recurrent cases can amount to 7 to 30% of DTC (3–6).

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Abbreviations: ATA, American Thyroid Association; BIR, biomedical incomplete response; CI, confidence interval; CT, computed tomography; DTC, differentiated thyroid cancer; ER, excellent response; FDG, ^{18}F-fluorodeoxyglucose; IDR, indeterminate response; NPV, negative predictive value; OR, odds ratio; PET, positron emission tomography; ps-Tg, preablative stimulated thyroglobulin; RAI, radioactive iodine; ROC, receiver operating characteristic; RxWBS, postradioiodine therapy whole-body scan; SD, standard deviation; SIR, structural incomplete response; TgAb, thyroglobulin antibody.

Therefore, it is important to choose a marker for prognosis prediction as well as postsurgical management. Stimulated thyroglobulin has been regarded as an important indicator for successful ablation, whose high negative predictive value (NPV) was 98% for predicting disease remission status (7–11). Our previous studies (12, 13) suggested that preablative stimulated thyroglobulin (ps-Tg) was associated with the three recurrence risk stratification raised by American Thyroid Association (ATA) guideline in 2009 (14), which suggested ps-Tg might be incorporated into radioiodine decision-making for tailoring management. Studies from Tuttle et al (15, 16) confirmed that this recurrence staging system could effectively predict the risk of recurrent and persistent disease by using a new response to therapy ongoing evaluation system, which was modified as a response to therapy restaging system in newly published 2015 ATA guidelines (17). This system reclassified the response into excellent response (ER), indeterminate response (IDR), biochemical incomplete response (BIR), and structural incomplete response (SIR) after initial treatment. And this reclassification system has been considered to be of great importance in ongoing clinical care of DTC patients after initial therapy (17). To date, no study has been reported regarding the relationships between ps-Tg and the new therapeutic response staging system.

The purpose of this study was to demonstrate the correlation between the ps-Tg level and the response to initial therapy in DTC patients, thereby evaluating whether ps-Tg could be used as a decision-making factor and predictive marker for RAI therapy response and clinical outcome.

Materials and Methods

This study was approved by ethics committee of Peking Union Medical College Hospital. Written informed consent was obtained from all participants.

Patients

We retrospectively reviewed our clinical database containing 963 consecutive records of patients with DTC. All patients came from the north of China and were referred for RAI therapy after total thyroidectomy between January 2006 and January 2013, of whom 511 patients were excluded. Among the excluded 511 cases, 95 missed data on ps-Tg or anti-Tg antibody (TgAb) level and 239 cases were followed for less than 24 months. Moreover, the concentration of TgAb could influence the Tg level and the association between TgAb and recurrence as well as prognosis is still indeterminate, thus 177 patients with positive anti-TgAb level were ruled out. Patients without total thyroidectomy or subsequent RAI therapy were excluded in this study.

Therefore, 452 patients were finally enrolled in this study, including 310 females and 142 males with an average age of 42.24 years (range, 4–77 years). Histologically, 432 patients had papillary thyroid cancer and 20 patients had follicular thyroid cancer. All patients underwent total thyroidectomy performed by experienced surgeons with no macroscopic thyroid remnants left, among whom seven patients with papillary thyroid microcarcinoma (tumor size $\leq$1 cm) did not undergo cervical lymph node dissection.

Radioiodine treatments

The decision to administer iodine-131 was based on risk factors including male, age greater than 45 years, tumor size larger than 1 cm, multiple lesions (more than one lesion), microscopic or macroscopic invasion of tumor into perithyroidal soft tissues at initial surgery, cervical lymph node metastasis, distant metastasis, and molecular characteristics such as $BRAF^{V600E}$ mutation. All patients received iodine-131 with the dosage varied from 30 mCi (1.1 GBq) to 200 mCi (7.4 GBq) according to different recurrence risk strata depicted in guidelines (14, 18) within 3 months after surgery, of which 26.33% (119/452) of patients experienced two or more rounds of RAI therapy owing to residual thyroid or persistent radioiodine-avid lesion. They all underwent levothyroxine withdrawal when serum TSH levels exceeded 30 μIU/ml, and they were assured of stringent low iodine–containing food and drugs intake for at least 2–6 weeks.

Initial assessment after initial therapy

Ps-Tg measurement was performed just before RAI therapy. Seven days after the first RAI therapy, all patients received postradioiodine therapy whole-body scan (RxWBS). Patients were regularly followed every 6 months in the first year. All patients experienced reassessment under levothyroxine withdrawal 6–12 months after the first RAI therapy. The reassessment was based on physical examination, serological examination (such as stimulated TSH, stimulated Tg, and TgAb), and imaging tests (such as neck ultrasound and radioiodine-131 whole-body scan).

Late follow-up

Assessment was conducted at each follow-up visit. Patients without apparent disease at the initial assessment were continued with TSH suppressive therapy. Chest computed tomography (CT) or ^{18}F-fluorodeoxyglucose positron-emission tomography/CT (FDG-PET/CT) was conducted if persistent or newly identified evidence was suspected. After the first year follow-up, the interval was extended to 6 to 12 months. The duration of follow-up was a minimum of 2 years, and in some patients the follow-up amounted to more than 9 years after the first RAI therapy.

According to the restaging system proposed by 2015 ATA guidelines, we evaluated clinical data obtained during follow-up and divided 452 patients into four kinds of result of ER, IDR, BIR, and SIR (17). Each patient who was classified as having an ER if he or she satisfied the following criteria: negative imaging and either suppressed Tg lower than 0.2 ng/ml or TSH-stimulated Tg greater than 1 ng/ml. IDR was defined to satisfy the following criteria: nonspecific findings on imaging studies with faint uptake in thyroid bed on RAI scanning, suppressed Tg lower than 1 ng/ml, stimulated Tg higher than 1 and lower than 10 ng/ml, or TgAb stable or declining in the absence of structural or functional disease. BIR was defined to satisfy the following criteria: negative imaging and suppressed Tg higher than 1 ng/ml,

stimulated Tg lower than 10 ng/ml, or rising TgAb values. SIR was defined as structural or functional evidence of disease with any Tg level and/or TgAb. According to 2015 ATA guidelines, functional evidence of disease was defined as disease detected by RAI scan and/or ^{18}FDG-PET.

Tg, TgAb, and TSH measurements

Levels of stimulated Tg were measured after thyroxine hormone withdrawal and the TSH level had risen to more than 30 μIU/ml. Tg and TgAb levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics GmbH); the TSH level was measured using a chemiluminescence immunoassay (Siemens Healthcare Diagnostics Inc.) in the same laboratory. Tg assay had a functional sensitivity of 0.1 ng/ml and a upper limit of 1000 ng/ml. Therefore, Tg level lower than 0.1 ng/ml was referred to as 0.1 ng/ml, and Tg level higher than 1000 ng/ml was regarded to as 1000 ng/ml.

Clinical data collection and grouping

Characteristics of all patients were compiled including age, sex, histology subtypes, tumor invasion, cervical lymph node metastasis, distant metastasis, remnant uptake on diagnostic radioiodine therapy whole-body scan or RxWBS, TSH levels, Tg levels, and TgAb levels. Patients with distant metastasis were further analyzed in terms of metastatic evidence obtained by imaging tests such as CT, FDG-PET/CT, bone scan, RxWBS, and diagnostic radioiodine therapy whole-body scan. By virtue of different ps-Tg levels measured just before the first RAI therapy, 452 patients were further divided into three groups: group 1, ps-Tg lower than 1 ng/ml (n = 82); group 2, 1 ng/ml lower than ps-Tg lower than 10 ng/ml (n = 173); and group 3, ps-Tg at least 10 ng/ml (n = 197).

Statistical analysis

Continuous data are denoted as mean ± standard deviation (SD) and median (range). Fisher exact tests and χ^2 tests were used to test the significance of categorical data. The nonparametric Kruskal-Wallis test was used to compare quantitative data when it was not normally distributed. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff level of ps-Tg for distinguishing SIR from the patients with ER, IDR, or BIR. Univariate and multivariate logistic regression analyses were performed to find independent prognostic factors for therapy response. P value $< .05$ was considered to be statistically significant. All of these statistical analyses were performed using R project (version 2.15.1).

Results

Description of cohort characteristics

The clinical characteristics of patients are summarized in Table 1. From the 452 included subjects, 79 with distant metastasis were involved, and all of them had ps-Tg values higher than 10 ng/ml. The ratio of female to male was 2.18:1, and the mean age was 42.24 years at the time of the first RAI therapy. Papillary thyroid cancer accounted for 95.58% of all patients, and the preablative TSH level was 90.63 ± 36.23 μIU/ml.

Table 1. Disease-Related Characteristics of Study Cohort

Characteristics	Total N (%)
Number	452
Sex	
Male	142 (31.42)
Female	310 (68.58)
Age	
Mean ± SD (y)	42.24 ± 13.12
Histologic subtype	
Papillary	432 (95.58%)
Follicular	20 (4.42%)
TSH stimulation method	
LT4 withdrawal	452 (100%)
rhTSH	0 (0%)
TSH	
Mean ± SD (μIU/ml)	90.63 ± 36.23
ps-Tg	
Median (25–75% quartile) (ng/ml)	6.44 (1.60–28.35)
Grouping by ps-Tg	
<1 ng/ml	82 (18.14%)
1–10 ng/ml	173 (38.28%)
≥10 ng/ml	197 (43.58%)
Surgery scope	
Total thyroidectomy + cervical lymph nodes dissection	447 (98.89%)
Total thyroidectomy only	5 (1.11%)
AJCC TNM stage	
I	248 (54.87%)
II	41 (9.07%)
III	52 (11.50%)
IV	111 (24.56%)
RAI therapy	
Yes	452 (100%)
Follow-up time	
Mean ± SD (mo)	43.01 ± 19.61
Median (range, mo)	38 (28–52)

Abbreviations: AJCC, American Joint Committee on Cancer; LT4, levothyroxine; rhTSH, recombinant human TSH.

Most patients (63.94%) were classified as American Joint Committee on Cancer pTNM stage I or II. The mean and median durations of follow-up were 43.01 and 38.00 months, respectively.

Therapeutic response correlates with ps-Tg level

The result of therapeutic response evaluation indicated that 92.68% (76/82) of group 1, 58.96% (102/173) of group 2, and 12.69% (25/197) of group 3 achieved ER ($\chi^2 = 172.102$, $P < .001$), whereas 7.32% (6/82) of group 1, 31.79% (55/173) of group 2, and 15.74% (31/197) of group 3 achieved IDR ($\chi^2 = 25.150$, $P < .001$). The proportions of the patients with either ER, IDR, or BIR amounted to 100% (82/82), 98.27%% (170/173), and 57.36% (113/197) in groups 1, 2, and 3, respectively ($\chi^2 = 123.037$, $P < .001$). Conversely, the proportion of the patients with SIR was identified in 0% (0/82) of group 1, 1.73% (3/173) of

Table 2. Clinical Outcomes in Terms of ps-Tg Level Stages (a Median of 38 Months After RAI Therapy)

	n = 452			
ps-Tg (ng/ml)	ER (n = 203)	IDR (n = 92)	BIR (n = 70)	SIR (n = 87)
<1 (n = 82)	76 (92.68%)	6 (7.32%)	0 (0.000%)	0 (0.000%)
1–10 (n = 173)	102 (58.96%)	55 (31.79%)	13 (7.52%)	3 (1.73%)
≥10 (n = 197)	25 (12.69%)	31 (15.74%)	57 (28.93%)	84 (42.64%)

group 2, and 42.64% (84/197) of group 3 (χ^2 = 123.037, $P < .001$) (Table 2).

During follow-up, all patients with ps-Tg lower than 1 ng/ml had suppressive Tg less than 1 ng/ml, of which only six patients had stimulated Tg level between 1 ng/ml and 10 ng/ml. Meanwhile, imaging continued to be negative for patients of group 1. In patients with ps-Tg lower than 10 ng/ml, it is noteworthy that only three (1.18%, 3/255) manifested SIR (one with local thyroid bed recurrence and two with cervical lymph node recurrence) (Table 2). They were all treated with repeated surgery and confirmed by pathological evidence. In addition, 178 patients (69.80%) presented ER in patients whose ps-Tg level was lower than 10 ng/ml.

The corresponding median ps-Tg and quartile values of four therapeutic response groups were 1.90 (0.40–4.80) ng/ml (ER), 6.44 (3.40–12.08) ng/ml (IDR), 24.55(15.24–46.85) ng/ml (BIR), and 226.50 (55.80–691.80) ng/ml (SIR), respectively (χ^2 = 275.231, $P <$ .001) (Figure 1).

ROC analysis for identifying structure incomplete response

In further ROC analysis, a cutoff value of ps-Tg at 26.75 ng/ml was obtained for differentiating the patients with SIR from those patients with either ER, IDR, or BIR, with corresponding specificity of 0.882, sensitivity of 0.885, and area under the ROC curve of 0.922 (Figure 2). NPV was 96.99% and positive predictive value was 64.17%. If ps-Tg level were lower than 26.75 ng/ml, the therapy response would be more likely to be better than ps-Tg above this limit.

Univariate and multivariate logistic regression analyses

The clinical characteristics, including ps-Tg (≥26.75 ng/ml or <26.75 ng/ml), sex (male or female), age (≥45 years or <45 years), tumor size (maximum diameter >1 cm or ≤1 cm), multifocality (multiple lesions or single lesion), cervical lymph node metastases (yes or no), and extrathyroidal invasion (yes or no), were analyzed as independent variables using logistic regression analyses (Table 3).

In univariate logistic regression analyses, the role of ps-Tg (odds ratio [OR], 57.660; 95% confidence interval [CI], 27.741–119.848; $P < .001$), sex (OR, 1.702; 95% CI, 1.051–2.758; $P = .031$), tumor size (OR, 8.248; 95% CI, 3.706–18.355; $P < .001$), cervical lymph node metastasis (OR, 4.616; 95% CI, 1.949–

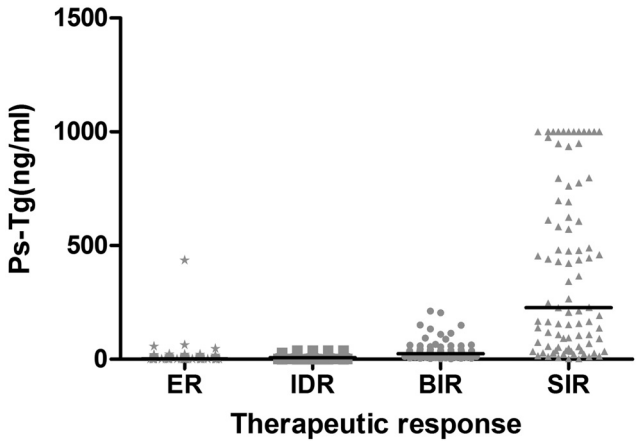

Figure 1. Corresponding ps-Tg level of four therapeutic response groups with a median follow-up duration of 38 months (n = 452 patients). The corresponding median ps-Tg and quartile values of the four therapeutic response groups were 1.90 (0.40–4.80), 6.44 (3.40–12.08), 24.55 (15.24–46.85), and 226.50 (55.80–691.80), respectively.

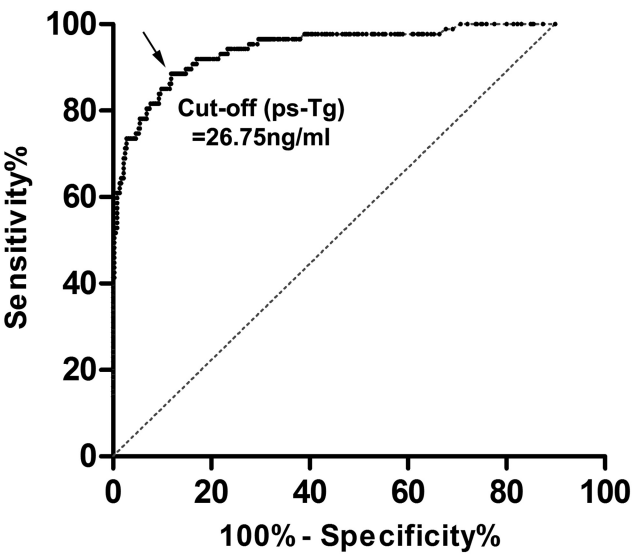

Figure 2. ROC curves for differentiating SIR from ER + IDR + BIR. Area under the ROC curve (ps-Tg), 0.947 (95% CI, 0.920–0.974); cutoff (ps-Tg), 26.75 ng/ml; specificity (ps-Tg), 0.882; sensitivity (ps-Tg), 0.885, NPV (ps-Tg); and 96.99%, positive predictive value (ps-Tg): 64.17%.

Table 3. Logistic Regression Analyses of Therapy Response Status According to Clinicopathologic Factors

	Univariate Logistic Regression		Multivariate Logistic Regression	
SIR/(ER + IDR + BIR)	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
ps-Tg (≥26.75/<26.75 ng/ml)	57.660 (27.741–119.848)	**<.001**	42.312 (19.837–90.254)	**<.001**
Sex (male/female)	1.702 (1.051–2.758)	**.031**	1.285 (0.641–2.578)	.480
Age (≥45/<45 y)	1.221 (0.764–1.953)	.404	—	—
Tumor size (≥1/<1 cm)	8.248 (3.706–18.355)	**<.001**	4.554 (1.743–11.898)	**.002**
Multifocality (>1/1 lesion)	1.416 (0.885–2.265)	.147	—	—
Cervical lymph node metastases (yes/no)	4.616 (1.949–10.930)	**<.001**	1.373 (0.453–4.157)	.575
Extrathyroidal invasion (yes/no)	2.738 (1.826–4.106)	**<.001**	1.987 (1.000–3.952)	.05

Bold numbers indicate statistical significance.

10.930; $P < .001$), and extrathyroidal invasion (OR, 2.738; 95% CI, 1.826–4.106; $P < .001$) was significant in distinguishing between the SIR and ER + IDR + BIR groups. In further multivariate logistic regression analyses, ps-Tg (OR, 42.312; 95% CI, 19.837–90.254; $P < .001$) and tumor size (OR, 4.554; 95% CI, 1.743–11.898; $P = .002$) were confirmed to be independent predictive factors for differentiating SIR from the ER + IDR + BIR group.

Discussion

In recent years, preablative Tg has been assigned considerable attention to pretreatment evaluation and brought informative guidance in clinical management. A recent meta-analysis implied that ps-Tg testing was a feasible tool with high NPV for future disease-free status, and a cutoff value of ps-Tg at 10 ng/ml was obtained by a summary ROC (19). Clinicians used to evaluate the recurrence by risk staging system proposed by 2009 ATA guidelines and mortality by American Joint Committee on Cancer TNM staging system. Response to therapy was first proposed in 2015 ATA guidelines, and took all clinical, biochemical, imaging findings obtained during follow-up under consideration to reassess the clinical status of patients, which correlated with clinical outcome (17). However, whether ps-Tg could indicate therapeutic response is still uncertain.

Results from this study showed that patients with ps-Tg level lower than 10 ng/ml presented an ER rate of 69.80%, which was much lower than the NPV of 94.2% obtained by Webb et al, who used 10 ng/ml as a cutoff ps-Tg level to predict no evidence of disease (19). What may contribute to the difference between the two studies? It is noteworthy that no evidence of disease was previously defined as stimulated Tg lower than 2 ng/ml with negative imaging (19). However, the ER we adopted in this study was more strictly defined as suppressed Tg lower than 0.2 ng/ml or stimulated Tg lower than 1 ng/ml according to 2015 ATA guidelines (17). These stringent cutoff levels may be derived from the study of Brassard et al (20), which showed a favorable prognosis with the recurrence rate as low as 1.55% (10/646) among the patients whose suppressed Tg was lower than 0.27 ng/ml or stimulated Tg was lower than 1.4 ng/ml during a median follow-up of 6.2 years. Several studies showed that the recurrence risk was less than 4% over 5–10 years and the disease specific death was less than 1% in patients who were reassessed as ER during 6–18 months after initial therapy (15, 21, 22). Although the patients with stimulated Tg ranged from 1 to 10 ng/ml without specific imaging findings were regarded as IDR in 2015 ATA guidelines, whose structural disease rate could reach up to 15–20% during follow-up (15, 23). Thus, it might be more appropriate and accurate using 1 ng/ml as stimulated Tg cutoff value to reflect good prognosis. In view of the evidence mentioned previously, together with the finding in this paper that more than 30% of patients with ps-Tg lower than 10 ng/ml could not achieve ER, it seemed that the cutoff value of 10 ng/ml was not eligible enough to have a beneficial impact on prognosis.

When we used 1 ng/ml as ps-Tg cutoff value, the rate of ER could be as high as 92.68% with no SIR identified during follow-up. Thus, ps-Tg lower than 1 ng/ml may allow for much more confident prediction of outcomes for individual patients. Generally, low ps-Tg level has been proven to indicate nearly complete dissection of total thyroid gland and predict low recurrence risk and good prognosis (10, 11, 19, 24, 25). Therefore, given the favorable prognosis for patients with ps-Tg lower than 1 ng/ml, which represents a status of low risk restratified by ongoing postsurgical assessment, is it indispensable for these patients to receive RAI therapy and experience radiation exposure? A study from Rosario et al (26) claimed that low-risk patients with postsurgical stimulated Tg level less than or equal to 1 ng/ml could avoid RAI therapy, because the recurrence rate was quite low (1.47%, 2/136) for these patients who did not receive RAI therapy with a mean follow-up period

of 3.7 years. Considering the better clinical outcome in terms of high disease-free rate and excellent response rates, it is worth considering that patients with stimulated Tg less than 1 ng/ml after cautious postsurgical assessment could be spared from RAI treatment.

On the contrary, our previous study demonstrated that high level of ps-Tg might be regarded as a predictive marker for distant metastases of DTC (12, 13, 27). In the current study, patients with a higher ps-Tg level also hold higher probability to suffer from a worse response to initial therapy. Moreover, a cutoff value of 26.75 ng/ml with high NPV (96.99%) was obtained for distinguishing the patients with SIR from those patients with either ER, IDR, or BIR 2 years after the first RAI therapy. Multivariate logistic regressions analysis corroborated ps-Tg of at least 26.75 ng/ml as an independent predictor of indicating structural disease. Evidences indicated poor prognosis in patients who had a SIR to initial therapy (ie, 50–85%) continued to have persistent disease despite additional therapy, 11% with locoregional metastases, and 50% with structural distant metastases would eventually die from this disease (16, 28–30). So our results for the first time imply that ps-Tg $\geq$ 26.75 ng/ml might indicate a poor therapeutic response even before subsequent RAI management, which might leave us adequate time for possible individualized intervention. It is reported that the efficacy of RAI therapy is related to the mean radiation dose delivered to neoplastic foci (31), reminding us of the probable feasibility to administrate higher dose of RAI for these patients with ps-Tg. Our previous study also demonstrated that more than 10% of patients with high ps-Tg level but no definite evidence of metastases would benefit from modified higher dose of RAI (13). So we suggest that high level of ps-Tg ($\geq$26.75 ng/ml) might predict poor therapeutic response, should be regarded as an ongoing high-risk postsurgical reassessment marker and allow the clinicians for a modified individualized RAI management, though further prolonged follow-up is needed.

In summary, our data demonstrated the clinical efficacy of ps-Tg in indicating response to initial therapy (total thyroidectomy and RAI therapy). The relative risk of probable structural incomplete response increases along with ps-Tg level. Postsurgical ongoing reassessment should not only be considered after the first RAI therapy but also before it. Ps-Tg might be used to guide early tailored administration of RAI and then modify management over time.

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