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Optimization of serum thyroglobulin measured at different time points for prognostic evaluation in differentiated thyroid carcinoma patients

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Abstract

Although serum thyroglobulin (Tg) is a reliable differentiated thyroid carcinoma (DTC) prognostic marker, its cutoff values can be affected by TSH stimulation status. Serum Tg prognostic values measured at different time points before and after radioactive iodine (RAI) therapy prepared with recombinant human TSH (rhTSH) in DTC patients, were investigated.

This study included 160 DTC patients who underwent surgery followed by rhTSH-aided RAI therapy. Their serum Tg levels were measured 7 days before (D-7Tg), on the day of (D0Tg), and 2 days after (D2Tg) the RAI therapy. For response evaluation, the patients were classified into 2 groups: acceptable response and non-acceptable response (non-AR). Optimal Tg level cutoff values measured at different time points were evaluated for persistent or recurrent disease (PRD) prediction, as well as therapeutic response.

Multivariate analysis showed that D-7Tg, D0Tg, and D2Tg significantly predicted non-AR ($P < .05$, for all). Optimal Tg level cutoff values for non-AR prediction were 0.6, 2.6, and 3.7 ng/mL for D-7Tg, D0Tg, and D2Tg, respectively. Cox regression analysis showed that Tg levels were significantly associated with PRD free survival with D-7Tg, D0Tg, and D2Tg cutoff values of 0.8, 4.0, and 6.0 ng/mL, respectively (D-7Tg, $P = .010$; D0Tg, $P = .005$; D2Tg, $P = .011$).

Serum Tg levels measured at the different time points could predict PRD free survival as well as therapeutic response with different cutoff values in DTC patients who underwent rhTSH-aided RAI therapy.

Abbreviations: AR = acceptable response, AS = analytical sensitivity, ATA = American Thyroid Association, AUC = area under the curve, CI = confidence interval, DTC = differentiated thyroid carcinoma, FS = functional sensitivity, IRMA = immunoradiometric assay, NPV = negative predictive value, OR = odds ratio, PPV = positive predictive value, PRD = persistent or recurrent disease, RAI = radioactive iodine, rhTSH = recombinant human TSH, ROC = receiver-operating characteristic, SD = standard deviation, Tg = thyroglobulin, TgAbs = anti-Tg antibodies, THW = thyroid hormone withdrawal, US = ultrasound, WBS = whole body scan.

Keywords: differentiated thyroid carcinoma, radioactive iodine therapy, recombinant human TSH, therapeutic response, thyroglobulin

1. Introduction

Serum thyroglobulin (Tg) is one of most sensitive biomarkers for differentiated thyroid carcinoma (DTC) recurrence evaluation. In the body, serum Tg level is proportional to thyroid tissue volume at a rate of 1 ng/mL per gram of thyroid tissue in the euthyroid state.[1] During the postoperative and post-ablative period, serum Tg level acts as a workhorse for the evaluation of residual disease and treatment outcome, and lifelong monitoring. Several studies have stated that stimulated Tg level measured just before radioactive iodine (RAI) therapy has prognostic significance.[2–5]

Recombinant human TSH (rhTSH) is a safe and effective alternative of thyroid hormone withdrawal (THW) for TSH stimulation given that it avoids hypothyroidism symptoms, maintains quality of life, and lowers whole body radiation burden

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compared with THW.[6,7] In rhTSH stimulated patients, I-131 is conventionally administered 24 hours after the 2nd rhTSH dose. Serum Tg level reaches a peak value 72 hours after the final injection[8]; however, rhTSH-stimulated Tg, before or after RAI therapy, can be affected by many factors such as proliferation time, injury effect due to radioiodine-induced damage of normal thyrocytes, and residual cancerous cells.[5,9] These factors suggest that serum Tg levels measured at different time points might have different cutoff values for therapeutic response or prognosis prediction.

Serum Tg has been studied as one of the significant factors in RAI dose selection.[10] However, rhTSH-stimulated Tg, measured just before RAI therapy, is limited as a practical tool in the selection of an appropriate RAI dose, and serum Tg evaluated at an earlier time point is necessary, considering the time interval between ordering RAI after dose selection and arrival at the hospital.

In this study, prognostic values of serum Tg in DTC patients who underwent rhTSH-aided RAI therapy, measured at the different time points, were investigated.

2. Methods

2.1. Patients

Initially, 232 DTC patients who had received total or near total thyroidectomy, and rhTSH-aided RAI therapy between January 2011 and December 2017 were recruited. However, patients with missing Tg measurements (n = 32), insufficient follow-up (n = 18), serum anti-Tg antibodies (TgAbs) >100 IU/mL (n = 13), intermittent thyroid hormone withdrawal (n = 7), lung metastasis (n = 1), and cervical lymph node metastasis from colon carcinoma (n = 1) were excluded. Finally, 160 patients were enrolled in this retrospective study, which was approved by the institutional review board of our hospital, and the need for informed patient consent was waived owed to the study type.

2.2. Radioactive iodine therapy

RAI therapy was performed 2 to 8 months (mean, 3 months) after surgery. After ensuring that the patients were on a low iodine diet for 2 weeks, they were all administered 2 consecutive 0.9 mg rhTSH intramuscular injections daily (Thyrogen, Genzyme Transgenics Corp., Cambridge, MA). Twenty-four hours after the 2nd injection, a therapeutic dose of RAI varying between 1.11 GBq (30 mCi) and 6.66 GBq (180 mCi) was administered, after which a post-therapeutic whole body scan (WBS) was performed.

2.3. Thyroglobulin, anti-thyroglobulin antibodies and TSH measurements

Blood samples were collected at 3 different time points, and serum Tg levels were measured using an immunoradiometric assay (IRMA) (RIA Tg-plus, BRAHMS GmbH, Henningsdorf, Germany) with an analytical sensitivity (AS) and a functional sensitivity (FS) of 0.08 and 0.2 ng/mL, respectively. Serum Tg measurements were performed 7 days before (D-7Tg), on the day of (D0Tg), and 2 days after (D2Tg) rhTSH-aided RAI therapy. On the same day, serum TgAbs level was determined using a radioimmunoassay method (RIA anti-Tgn, BRAHMS GmbH, Hennigsdorf, Germany) with an AS and a FS of 5.5 and 20 U/mL, respectively, and serum TSH level was determined using an IRMA (TSH-CTK-3, DiaSorin, Saluggia, Italy) with an AS and FS of 0.04 and 0.07 mIU/L, respectively.

2.4. Assessment of therapeutic response

Serum Tg measurement (with/without TSH stimulation), neck ultrasound (US), and I-123 diagnostic WBS were evaluated for response assessment in 4 ways:

(1) neck US, THW-aided stimulated Tg, and diagnostic WBS (n = 76);
(2) neck US and suppressed Tg (n = 55);
(3) neck US and THW-aided stimulated Tg (n = 26);
(4) rhTSH-aided stimulated Tg and diagnostic WBS (n = 3).

The mean follow up period was 12.4 months (range, 7–19 months).

Therapeutic responses were defined mainly by emphasizing on Tg level based on previous studies, including the 2015 American Thyroid Association (ATA) guidelines, categorizing the patients in 2 groups. Patients with negative or non-specific findings on US and/or follow-up WBS and either non-stimulated Tg < 1 ng/mL or stimulated Tg < 10 ng/mL were categorized as the acceptable response (AR) group, while those with evidence of persistent or newly developed lesions on imaging studies or non-stimulated Tg level ≥1 ng/mL or stimulated Tg level ≥10 ng/mL or rising TgAbs level were considered as the non-acceptable response (non-AR) group.[11–13]

2.5. Assessment of persistent or recurrent disease

After therapeutic response assessment, the patients were further followed-up for persistent or recurrent disease (PRD) assessment, which was defined by evidence of malignant lesions, confirmed by histology or imaging study within a range of 3.4 to 84.7 months (mean, 23.8 months).

2.6. Statistical analyses

Continuous data are presented as mean ± standard deviation (SD), and categorical data are presented as percentage. Spearman coefficient of rank correlation test was used to determine the correlation between D-7Tg and D0Tg or D-7Tg and D2Tg. Differences in variables between the 2 groups were assessed using the Student *t* test and the Chi-square test for continuous, and categorical or ordinal variables, respectively. Binary multivariate logistic regression analysis was further performed on variables with $P \leq .2$ in univariate analysis. $P < .05$ was considered statistically significant. A receiver-operating characteristic (ROC) curve was constructed to define the best cutoff value for the 3 different Tg levels (D-7Tg, D0Tg, and D2Tg). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC) were reported for the established cutoff values. Kaplan Meier survival curve was constructed for PRD-free survival with optimal cutoff values for the 3 different Tg values. Multivariate Cox proportional hazard models were used to examine the association between PRD and Tg levels. All statistical analyses were performed using SPSS v21.0 (IBM Corp., Armonk, NY).

3. Results

Clinicopathologic variables are summarized in Table 1. A majority of the patients were women (75.6%) with an age ranged between 17 and 77 years (mean 49.2) at the time of surgery. Most of the primary tumors were papillary thyroid carcinoma (99.4%). The ranges of D-7Tg, D0Tg, and D2Tg were

between 0 and 27.4 ng/mL, 0 and 66.4 ng/mL, and 0 and 192.0 ng/mL, respectively. All the patients had elevated TSH levels (>30 μIU/mL) just before RAI therapy (range, 45.0–198.5 μIU/mL). A strong positive correlation was observed between D-7Tg and D0Tg (R = 0.81, $P < .0001$) and D-7Tg and D2Tg (R = 0.83, $P < .0001$).

For response evaluation, AR was observed in 147 (91.9%) patients, while 13 (8.1%) patients showed non-AR. Univariate analysis of the variables: patients' age ($P = .035$), N stage ($P = .001$), tumor multiplicity ($P = .005$), I-131 dose groups (low dose vs high dose; $P = .007$), D-7Tg (AR vs non-AR; 0.3 ± 0.9 ng/mL vs 5.4 ± 7.6 ng/mL; $P < .0001$), D0Tg (AR vs non-AR; 1.0 ± 2.3 ng/mL vs 19.5 ± 22.5 ng/mL; $P < .0001$), and D2Tg (AR vs non-AR; 2.9 ± 10.9 ng/mL vs 36.6 ± 52.2 ng/mL; $P < .0001$) showed statistically significant differences between the AR and non-AR groups (Table 2). Whereas tumor size (AR vs non-AR; 1.3 ± 0.8 cm vs 1.6 ± 0.7 cm; $P = .171$) showed a statistical trend between the 2 groups. Multivariate logistic regression analysis showed that only Tg levels measured at each time point significantly predicted non-AR as follows: D-7Tg (odds ratio [OR] = 1.897; 95% confidence interval [CI] = 1.141–3.154; $P = 0.014$), D0Tg (OR = 1.296; 95% CI = 1.071–1.570; $P = .008$), and D2Tg (OR = 1.035; 95% CI = 1.004–1.066, $P = .024$) (Table 3). Receiver-operating characteristic curve analysis showed that D-7Tg optimal cutoff value was 0.6 ng/mL (AUC = 0.879, $P < .0001$) with 76.9% sensitivity, 90.5% specificity, 41.7% PPV, 97.8% NPV, and 89.4% accuracy (Fig. 1A). That of D0Tg and D2Tg were 2.6 ng/mL (AUC = 0.896, $P < .0001$), and 3.7 ng/mL (AUC = 0.905, $P < .0001$), respectively, with the sensitivity, specificity, PPV, NPV, accuracy at 76.9%, 91.2%, 43.5%, 97.8%, 90.0%, and 84.6%, 85.7%, 34.4%, 98.4%, 85.6%, respectively (Fig. 1B and C).

Among the 160 patients, 6 had PRD (1/147 AR patients, 0.7%; 5/13 non-AR patients, 38.5%). The Kaplan Meier curve for survival analysis showed a significant difference in PRD with a cutoff value of 0.8, 4.0, and 6.0 ng/mL for D-7Tg, D0Tg, and D2Tg, respectively ($P < .0001$, for all) (Fig. 2). Multivariate Cox regression analysis of the 3 different Tg levels, after adjusting for age, sex and tumor multiplicity, showed a significant association with PRD free survival (D-7Tg, $P = .010$; D0Tg, $P = .005$ and D2Tg, $P = .011$) (Table 4).

Table 1

Patients' characteristics (n = 160).

Variables	No. (% or range)
Age (years)	49.2 ± 12.8 (17–77)
Sex	
Male	39 (24.4%)
Female	121 (75.6%)
T stage*	
T1	65 (40.6%)
T2	7 (4.4%)
T3	83 (51.9%)
T4	5 (3.1%)
N stage*	
N0/Nx	33 (20.6%)
N1a	87 (54.4%)
N1b	40 (25.0%)
Tumor size (cm)	1.3 ± 0.8 (0.1–4.5)
Multiplicity	
No	72 (45.0%)
Yes	88 (55.0%)
Thyroid capsular invasion	
No	105 (65.6%)
Yes	55 (34.4%)
Extrathyroidal extension	
No	71 (44.4%)
Yes	89 (55.6%)
Tumor pathology	
Papillary	159 (99.4%)
Follicular	1 (0.6%)
Patient preparation	
Recombinant human TSH	160 (100%)
I-131 dose	
1.11GBq (30 mCi)	1 (0.6%)
1.29 GBq (35 mCi)	100 (62.5%)
1.85 GBq (50 mCi)	3 (1.9%)
3.70 GBq (100 mCi)	52 (32.5%)
6.66 GBq (180 mCi)	4 (2.5%)
D-7Tg (ng/mL)	0.7 ± 2.7 (0–27.4)
D0Tg (ng/mL)	2.5 ± 8.3 (0–66.4)
D2Tg (ng/mL)	5.6 ± 20.0 (0–192.0)

Tg thyroglobulin, *D-7Tg* Tg measured 7 days before I-131 therapy, *D0Tg* Tg measured on the day of I-131 therapy, *D2Tg* Tg measured 2 days after I-131 therapy.

* Staging according to the American Joint Committee on Cancer: the 7th Edition.

Table 2

Univariate analysis of the clinicopathologic variables for the prediction of therapeutic response.

Variables	Acceptable response, n (%)	Non-acceptable response, n (%)	*P* value
Age			.035
<45 years	54 (36.7%)	9 (69.2%)	
≥45 years	93 (63.3%)	4 (30.8%)	
Sex			.217
Male	34 (23.1%)	5 (38.5%)	
Female	113 (76.9%)	8 (61.5%)	
T stage			.436
T1	61 (41.5%)	4 (30.8%)	
T2	7 (4.8%)	0 (0%)	
T3	74 (50.3%)	9 (69.2%)	
T4	5 (3.4%)	0 (0%)	
N stage			.001
N0/Nx	32 (21.8%)	1 (7.7%)	
N1a	84 (57.1%)	3 (23.1%)	
N1b	31 (21.1%)	9 (69.2%)	
Tumor size (cm)	1.3 ± 0.8	1.6 ± 0.7	.171
Multiplicity			.007
Solitary	71 (48.3%)	1 (7.7%)	
Multiple	76 (51.7%)	12 (92.3%)	
Thyroid capsular invasion			.746
No	97 (66.0%)	8 (61.5%)	
Yes	50 (34.0%)	5 (38.5%)	
Extrathyroidal extension			.389
No	67 (45.6%)	4 (30.8%)	
Yes	80 (54.4%)	9 (69.2%)	
I-131 dose			.012
Low dose (1.11–1.85 GBq)	100 (68.0%)	4 (30.8%)	
High dose (3.70–6.66 GBq)	47 (32.0%)	9 (69.2%)	
D-7Tg (ng/mL)	0.3 ± 0.9	5.4 ± 7.6	<.0001
D0Tg (ng/mL)	1.0 ± 2.3	19.5 ± 22.5	<.0001
D2Tg (ng/mL)	2.9 ± 10.9	36.6 ± 52.2	<.0001

Tg thyroglobulin, *D-7Tg* Tg measured 7 days before I-131 therapy, *D0Tg* Tg measured on the day of I-131 therapy, *D2Tg* Tg measured 2 days after I-131 therapy.

Table 3

Multivariate analysis of the clinicopathologic variables for the prediction of therapeutic response.

Variables	Odds ratio (95% CI)	*P* value
Model 1		
Age	0.482 (0.100–2.326)	.363
Tumor size	0.861 (0.295–2.516)	.784
Multiplicity	7.793 (0.845–71.907)	.070
N stage		.259
N0/Nx	–	
N1a	0.419 (0.030–5.758)	.515
N1b	2.015 (0.157–25.856)	.590
I-131 dose	0.329 (0.050–2.174)	.248
D-7Tg	1.897 (1.141–3.154)	.014
Model 2		
Age	0.915 (0.142–5.889)	.925
Tumor size	1.065 (0.361–3.138)	.909
Multiplicity	6.368 (0.634–63.965)	.116
N stage		.676
N0/Nx	–	
N1a	0.552 (0.041–7.391)	.654
N1b	1.315 (0.096–17.972)	.837
I-131 dose	0.367 (0.055–2.460)	.302
D0Tg	1.296 (1.071–1.570)	.008
Model 3		
Age	0.277 (0.063–1.223)	.090
Tumor size	1.263 (0.489–3.263)	.630
Multiplicity	8.090 (0.897–72.967)	.062
N stage		.094
N0/Nx	–	
N1a	0.584 (0.047–7.227)	.676
N1b	3.609 (0.325–40.035)	.296
I-131 dose	0.559 (0.106–2.953)	.494
D2Tg	1.035 (1.004–1.066)	.024

Tg thyroglobulin, *D-7Tg* Tg measured 7 days before I-131 therapy, *D0Tg* Tg measured on the day of I-131 therapy, *D2Tg* Tg measured 2 days after I-131 therapy.

4. Discussion

Serum Tg, anti-TgAb, and neck US have been used for postoperative evaluation in DTC patients. Tg has a half-life of 65 hours, which means theoretically, its serum level should become undetectable approximately 1 month after total thyroidectomy, without local residual disease or metastasis.[1,14] Several studies have suggested that postoperative stimulated Tg is related to the risk of DTC recurrence inpatients after RAI therapy. Pelttari et al reported that without a levothyroxine supplement, detectable serum Tg levels 4 to 6 weeks after surgery could be a prediction of further disease recurrence.[15] According to Park et al, pre-ablation stimulated Tg levels ≥10 ng/mL with THW had a 25.5 times greater chance of therapeutic failure than those with Tg levels <10 ng/mL.[4] In a subgroup analysis by Zhang et al, a higher success rate after RAI therapy was recorded in patients with pre-ablation Tg <1 ng/mL than those with 1≤ pre-ablation Tg < 2 ng/mL.[16]

Pre-ablation rhTSH-stimulated Tg has been reported as a prognostic marker in DTC patients. Melo et al. demonstrated that rhTSH-stimulated Tg measured 3 days after RAI therapy had a PRD predictive value with an optimal Tg cutoff value of 7.2 ng/mL.[17] Ciappuccini et al showed that there was a significant correlation between rhTSH-stimulated Tg (cutoff value for PRD prediction = 2.8 ng/mL) measured just before RAI therapy, and PRD.[18] In this study, PRD prediction cutoff values for D0Tg and D2Tg were 4.0 and 6.0 ng/mL, respectively, which had ranges that agreed with previous studies.

Tg cutoff values for prognosis evaluation can be different based on the stimulation method. Kowalska et al reported that rhTSH-stimulated Tg level was significantly lower than that obtained using THW in the same patients and the same cut-off thresholds should not be used for different stimulation methods.[19] They showed that rhTSH-stimulated Tg cutoff levels of 0.6 ng/mL for patients who remained free of disease and 2.3 ng/mL for patients with PRD corresponded to THW-stimulated Tg cutoff levels of 2.0 and 10.0 ng/mL, respectively, an observation that could be a reason why rhTSH-stimulated Tg cutoff value for PRD prediction was lower than that of THW-stimulated Tg.

Measurement time influenced rhTSH-stimulated Tg. A Tg measurement 72 hours after the 2nd rhTSH injection is usually recommended because the serum Tg level thus obtained usually corresponds to the peak level.[8,20] In this study, D0Tg level, which was not fully stimulated compared with D2Tg, was

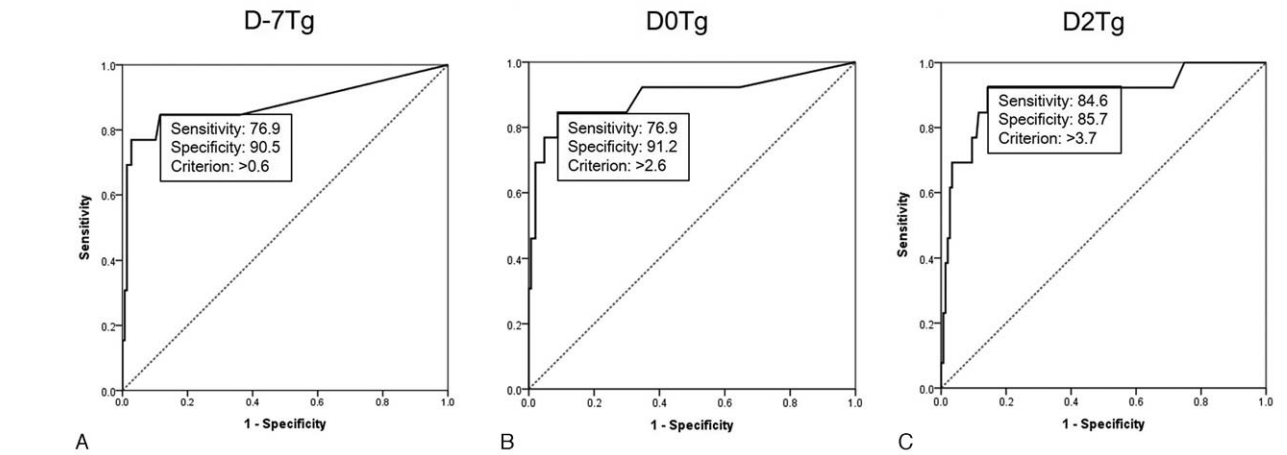

Figure 1. Receiver-operating characteristic curve analysis of Tg measured at each time point for the prediction of response after recombinant human TSH-aided radioactive iodine therapy. The optimal Tg cutoff value varied according to measurement time: 0.6 ng/mL in D-7Tg (AUC = 0.879, *P* < .0001) (A), 2.6 ng/mL in D0Tg (AUC = 0.896, *P* < .0001) (B), and 3.7 ng/mL in D2Tg (AUC = 0.905, *P* < .0001) (C). AUC = area under the curve, Tg = thyroglobulin

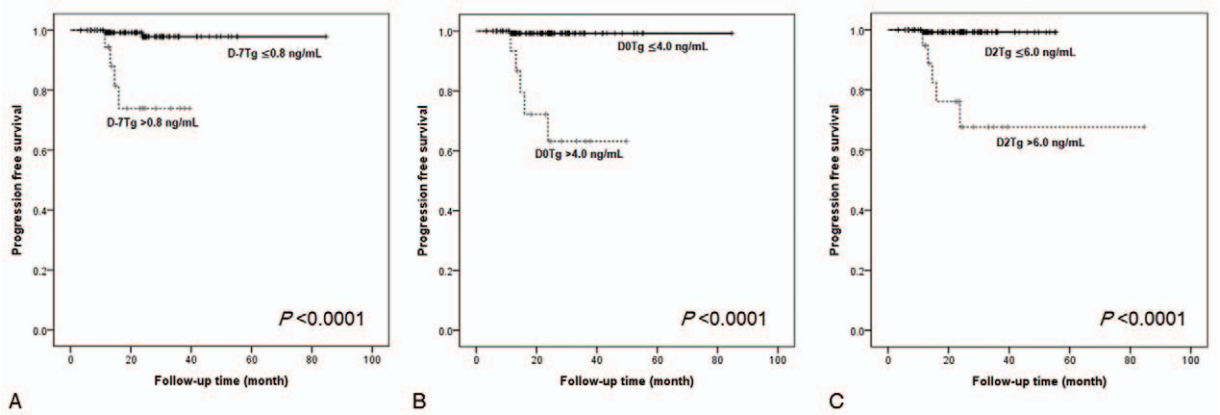

Figure 2. Kaplan Meier survival curve of progression (persistent or recurrent disease)-free survival according to each cutoff value of thyroglobulin. Difference in survival was significant in D-7Tg with 0.8 ng/mL (A), D0Tg with 4.0 ng/mL (B), and D2Tg with 6.0 ng/mL (C). $P < .0001$, for all.

measured 24 hours after the 2nd rhTSH injection. This could explain why Tg cutoff values for response or PRD prediction were different between D0Tg and D2Tg.

Remnant thyroid or residual malignant tissue might not be truly reflected by rhTSH-stimulated D2Tg because D2Tg measured after RAI therapy could contain Tg released as a result of injury to thyrocytes in some extent.[9] Park et al showed that post-ablation stimulated Tg did not have a significant value for response prediction, implying that it included Tg released by thyrocytes, as well as proliferative Tg.[21] On the other hand, post-ablation stimulated Tg, after rhTSH injection was found to be an independent prognostic indicator of disease persistence.[17] Response criteria were one reason that explained these controversial results. If response criteria were classified into excellent response (simulated Tg <1 ng/mL) and non-excellent response, only patients with a very low Tg level could be included in the excellent response group. Based on this classification, Tg released by damaged thyroid tissues could lower D2Tg predictive power because it comprised both stimulated and released Tg. However, the proportion of released Tg in D2Tg could be minor in AR or PRD prediction. In this study, patients were classified into 2 groups (AR vs. non-AR) for the purpose of investigating the correlation between response and PRD prediction, for which D2Tg as well as D0Tg might have also been significant predictors.

Table 4

Multivariate Cox regression analysis for the prediction of persistent or recurrent disease-free survival.

Variables	Odds ratio (95% CI)	*P* value
Model 1		
Age	0.472 (0.081–2.763)	.405
Sex	2.448 (0.482–12.420)	.280
Multiplicity	1.432×10^5 (0–1.927×10^{173})	.952
D-7Tg (≤0.8, >0.8 ng/mL)	10.416 (1.757–61.739)	.010
Model 2		
Age	0.766 (0.128–4.604)	.771
Sex	1.585 (0.306–8.194)	.583
Multiplicity	1.066×10^5 (0–3.718×10^{160})	.949
D0Tg (≤4.0, >4.0 ng/mL)	26.497 (2.687–261.318)	.005
Model 3		
Age	0.603 (0.101–3.581)	.578
Sex	2.170 (0.419–11.234)	.356
Multiplicity	8.997×10^5 (0–4.948×10^{192})	.959
D2Tg (≤6.0, >6.0 ng/mL)	17.903 (1.930–166.054)	.011

Tg thyroglobulin, *D-7Tg* Tg measured 7 days before I-131 therapy, *D0Tg* Tg measured on the day of I-131 therapy, *D2Tg* Tg measured 2 days after I-131 therapy.

Many experts have recommended serum Tg for RAI dose selection.[10] To fix a RAI dose group, Jin et al compared the adjusted dose group with respect to iodine uptake and serum Tg level.[22] They demonstrated that the successful response rate was significantly higher in the adjusted group, although the administered dose and side effects such as xerostomia, were significantly lower compared with the fixed dose group. D0Tg as well as D2Tg have a limitation in dose selection because a RAI dose could not be ordered after checking patient levels. D-7Tg could be used as a potential biomarker for RAI dose selection if it has clinical impact as a prognostic marker. Specifically, TSH level at measurement time was relatively stable because patients with rhTSH stimulation continued to receive thyroid hormone replacement. In this study, Tg measured 7 days before RAI (D-7Tg) could have reliable response and PRD prediction cutoff values of 0.6 and 0.8 ng/mL, respectively. In addition, D-7Tg has a strong correlation with rhTSH stimulated D0Tg and D2Tg. Further studies are therefore mandatory, to investigate whether D-7Tg could further increase the risk of stratification in RAI dose selection for DTC patients with rhTSH stimulation.

There are several limitations in this study. First, selection bias was inevitable due to the retrospective nature of the study. Specifically, it seemed to have significant influence on response prediction in low and high RAI dose groups, although therapeutic response was not different in multivariate logistic regression analysis. Second, the follow-up protocols for response assessment were not similar. Follow-up periods might not have been long enough to determine PRD. A long-term cohort study is needed to describe the actual recurrence or persistence status.

In conclusions, serum Tg levels measured at the different time points can independently predict therapeutic response as well as PRD-free survival with different cutoff values in DTC patients who underwent rhTSH-aided RAI therapy. For dose optimization and further risk stratification, special consideration should be taken in patients with low D-7Tg levels. Further studies are necessary to evaluate whether D-7Tg could be a potential biomarker that guides clinicians in the selection of an appropriate RAI dose.

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References

[1] Indrasena BS. Use of thyroglobulin as a tumour marker. World J Biol Chem 2017;8:81–5.
[2] Bernier MO, Morel O, Rodien P, et al. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. Eur J Nucl Med Mol Imaging 2005;32:1418–21.
[3] Kim TY, Kim WB, Kim ES, 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.
[4] Park HJ, Jeong GC, Kwon SY, et al. Stimulated serum thyroglobulin level at the time of first dose of radioactive iodine therapy is the most predictive factor for therapeutic failure in patients with papillary thyroid carcinoma. Nucl Med Mol Imaging 2014;48:255–61.
[5] Kim YI, Im HJ, Paeng JC, et al. Serum thyroglobulin level after radioiodine therapy (Day 3) to predict successful ablation of thyroid remnant in postoperative thyroid cancer. Ann Nucl Med 2015;29: 184–9.
[6] Hanscheid H, Lassmann M, Luster M, et al. Iodine biokinetics and dosimetry in radioiodine therapy of thyroid cancer: procedures and results of a prospective international controlled study of ablation after rhTSH or hormone withdrawal. J Nucl Med 2006;47:648–54.
[7] Pacini F, Ladenson PW, Schlumberger M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91: 926–32.
[8] Weiss R, Magner J. Serial measurements of serum thyroglobulin in response to recombinant human thyrotropin stimulation. Thyroid 2015;25:708–10.
[9] Taieb D, Lussato D, Guedj E, et al. Early sequential changes in serum thyroglobulin after radioiodine ablation for thyroid cancer: possible clinical implications for recombinant human thyrotropin-aided therapy. Thyroid 2006;16:177–9.
[10] Jabin Z, Kwon SY, Bom HS, et al. Clinico-social factors to choose radioactive iodine dose in differentiated thyroid cancer patients: an Asian survey. Nucl Med Commun 2018;39:283–9.
[11] Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 2010;20:1341–9.
[12] Haugen BR, Alexander EK, Bible KC, 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;26:1–33.
[13] Song M, Jeon S, Kang SR, et al. Response prediction of altered thyroglobulin levels after radioactive iodine therapy aided by recombinant human thyrotropin in patients with differentiated thyroid cancer. Nucl Med Mol Imaging 2018;52:287–92.
[14] Hocevar M, Auersperg M, Stanovnik L. The dynamics of serum thyroglobulin elimination from the body after thyroid surgery. Eur J Surg Oncol 1997;23:208–10.
[15] Pelttari H, Valimaki MJ, Loyttyniemi E, et al. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. Eur J Endocrinol 2010;163:757–63.
[16] Zhang Y, Hua W, Zhang X, et al. The predictive value for excellent response to initial therapy in differentiated thyroid cancer: preablation-stimulated thyroglobulin better than the TNM stage. Nucl Med Commun 2018;39:405–10.
[17] Melo M, Costa G, Ribeiro C, et al. Stimulated thyroglobulin at recombinant human TSH-aided ablation predicts disease-free status one year later. J Clin Endocrinol Metab 2013;98:4364–72.
[18] Ciappuccini R, Hardouin J, Heutte N, et al. Stimulated thyroglobulin level at ablation in differentiated thyroid cancer: the impact of treatment preparation modalities and tumor burden. Eur J Endocrinol 2014; 171:247–52.
[19] Kowalska A, Palyga I, Gasior-Perczak D, et al. The cut-off level of recombinant human TSH-stimulated thyroglobulin in the follow-up of patients with differentiated thyroid cancer. PLoS One 2015;10:e0133852.
[20] Rosario PW, Borges MA, Purisch S. Preparation with recombinant human thyroid-stimulating hormone for thyroid remnant ablation with 131I is associated with lowered radiotoxicity. J Nucl Med 2008;49: 1776–82.
[21] Park HJ, Min JJ, Bom HS, et al. Early stimulated thyroglobulin for response prediction after recombinant human thyrotropin-aided radioiodine therapy. Ann Nucl Med 2017;31:616–22.
[22] Jin Y, Ruan M, Cheng L, et al. Radioiodine uptake and thyroglobulin-guided radioiodine remnant ablation in patients with differentiated thyroid cancer: a prospective, randomized, open-label. Controlled Trial Thyroid 2019;29:101–10.