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The clinical meaning of pre- and post-ablation thyroglobulin levels at first radioiodine therapy in patients with papillary thyroid cancer

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Background/Aims: This study was conducted to identify prognostic factors in patients with papillary thyroid cancer (PTC) at the time of first radioactive iodine (RAI) therapy, and to evaluate the clinical value of the thyroglobulin (Tg) increase after RAI.

Methods: Serum Tg was sampled prior to (pre-Tg) and 7 days after RAI (post-Tg) in 680 patients with PTC. Patients were classified into excellent response (ER), biochemical incomplete response (BCIR), structural incomplete response (SIR), and indeterminate response (IR) groups using dynamic risk stratification at 6 to 18 months after RAI therapy.

Results: After RAI therapy, 514 patients (75.6%) had an ER, 34 (5.0%) had a BCIR, 13 (2.0%) had an SIR, and 119 (17.5%) had an IR. Pre-Tg level was significantly different among the groups, with the highest level being in the SIR group, followed by the BCIR, IR, and ER groups. However, post-Tg levels were not different among the groups. Post-Tg level increased significantly after RAI therapy compared to the pre-Tg level (mean 13.8 ± 32.2 ng/mL vs. 2.5 ± 8.9 ng/mL). In 422 patients whose pre-Tg level was < 1 ng/mL, 205 had post-Tg levels < 1 ng/mL, while 167 had post-Tg levels of 1 to 10 ng/mL, and 50 had levels > 10 ng/mL. No difference was observed in the response to therapy. Differences in RAI dose and uptake pattern were observed among the three groups.

Conclusions: Pre-Tg was useful as a prognostic factor in patients with PTC. In patients with low pre-Tg, increased post-Tg may reflect remnant tissue and does not help predict the prognosis.

Keywords: Thyroid cancer, papillary; Radioactive iodine therapy; Thyroglobulin; Prognosis; Therapeutic response

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INTRODUCTION

Thyroidectomy and selective postoperative administration of radioactive iodine (RAI) are important treatment modalities in patients with papillary thyroid cancer (PTC) [1]. During follow-up, serum thyroglobulin (Tg) and anti-thyroglobulin antibody (ATAb) levels are useful markers for residual or recurrent disease, with a high degree of sensitivity and specificity in patients treated with RAI because the thyroid follicular cells are the only source of Tg [1]. However, the prognostic value of pre-ablative thyroid stimulating hormone (TSH)-stim-

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ulated Tg (pre-Tg) at the first ablative RAI a few weeks after total thyroidectomy has been controversial. Several studies have suggested that pre-Tg level is a useful marker for early therapeutic failure or metastatic disease [2-5]. It is considered that pre-Tg values should be < 1 ng/mL if the tumor removal is complete. However, the predictive value of pre-Tg level is undeniably diminished by interference from surgical residual tissue, because an increase in pre-Tg level may simply reflect Tg production by residual follicular cells [6]. In previous studies, serum Tg level immediately after RAI therapy was frequently elevated and reflects remnant thyroid tissue, which is significantly higher in patients with midline uptake on post-ablation whole-body scans [7]. Thus, we investigated the clinical value of pre-Tg as a prognostic marker in patients who had undergone clinically complete resection of the tumors. We also evaluated the clinical characteristics of patients with pre-Tg levels < 1 ng/dL according to the difference in serum Tg level measured immediately after RAI (post-Tg), to determine whether the post-Tg level reflects the prognosis or simply activity of the residual thyroid gland.

METHODS

Patients

We included 1,051 potentially eligible patients with differentiated thyroid cancer who underwent their first RAI therapy at 3 to 12 months after conventional open total thyroidectomy from April 2013 to January 2015. After excluding patients with follicular thyroid cancer, remnant cancer after surgery, confirmed distant metastasis, reoperation for recurrent cancer, and ATAb-positive patients, 680 patients with PTC were enrolled in this retrospective study. Disease stage and the risk assessment were based on the 7th American Joint Committee on Cancer/tumor, node, metastasis (AJCC/TNM) staging system [8] and the modified 2009 risk stratification system of the American Thyroid Association (ATA) [1]. The ATA risk stratification system was classified into low risk, intermediate risk, and high risk of recurrence.

Radioactive iodine ablation therapy and evaluation of therapeutic response and outcome

Doses of RAI ranged from 1.11 GBq (30 mCi) to 6.66 GBq (180 mCi) based on tumor size, extra-thyroidal invasion, and lymph node involvement. A total of 425 patients (62.5%) were prepared for RAI therapy by withdrawing thyroid hormone, and 255 patients (37.5%) received recombinant human TSH. Patients were asked to follow a low-iodine diet for 2 weeks. Serum TSH levels were > 30 mIU/L in all patients at the pre-Tg check point. Serum TSH, pre-Tg, and ATAb levels were measured prior to RAI administration on the day of RAI therapy, and TSH, post-Tg, and ATAb, as well as post-treatment whole-body RAI (RxWBS) scans, were performed 7 days after RAI therapy. Thyroid bed uptake on RxWBS was graded from I to III by visual assessment: I, overt remnant thyroid (star sign); II, focal uptake on the thyroid bed; and III, no uptake on the thyroid bed. All images were analyzed separately by two experienced nuclear medicine physicians who were blinded to the clinical findings. To verify the response to therapy, we reclassified the patients into four categories: excellent response (ER), biochemical incomplete response (BCIR), structural incomplete response (SIR), and indeterminate response (IR) according to suppressed or TSH-stimulated Tg and ultrasonography with or without a diagnostic whole-body scan (DxWBS), obtained 6 to 18 months after RAI therapy. This is known as dynamic risk stratification (DRS) [1]. Definitions for each category are as follows: ER, clinical, biochemical, or structural evidence of disease-free conditions; BCIR, abnormal Tg or rising ATAb levels in the absence of localizable disease; SIR, persistent or newly identified loco-regional or distant metastases; and IR, nonspecific biochemical or structural findings that cannot be confidently classified as either benign or malignant. The IR group included patients with stable or declining ATAb levels without definitive structural evidence of disease. Additionally, clinical outcomes were estimated as no evidence of disease (NED), recurrence, or persistence at the final follow-up visit, which took place a mean of 27.8 months after the surgery. NED status was defined as a negative Tg (suppressed Tg < 0.2 ng/mL or TSH-stimulated Tg < 1.0 ng/mL) with NED in the imaging study. Recurrence was defined as a disease that developed again after NED, and persistent disease refers to structural and/or biochemical evidence of disease until the final follow-up without NED status.

Biochemical measurements

Serum Tg and ATAb were measured with immunoradiometric assays (BRAHAMS AG, Hennigsdorf, Germany). The assays had measurement ranges of 0.1 to 1,000 ng/mL and 10 to 4,000 IU/mL, respectively. Serum TSH levels were measured using the TSH-CTK-3 immunoradiometric assay (DiaSorin SpA, Saluggia, Italy).

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Chonnam National University Hwasun Hospital, Hwasun, Korea (CNUHH-2017-059). Informed consent was waived due to the study's retrospective design.

Statistical analysis

All statistical analyses were performed using SPSS software version 23.0 (IBM Co., Armonk, NY, USA). Descriptive quantitative data are expressed as mean values and standard deviations, and qualitative data are expressed as percentages. A univariate analysis was performed prior to the multivariate analysis using the chi-square test for categorical variables and Student's *t* test for continuous variables. Multivariate analyses were performed to identify independently significant prognostic variables in DRS or recurrent/persistent disease; all variables (except DRS or outcome) with a *p* value below 0.05 in univariate analysis were included. A $p < 0.05$ was considered significant.

RESULTS

Patient characteristics

Of the 680 enrolled patients with PTC (168 males and 512 females), the mean age at diagnosis was 49.2 ± 11.6 years. Most of the patients had classical PTC (96.0%), and the mean tumor size was 1.1 ± 0.7 cm (range, 0.2 to 5.3). In total, 255 patients (37.5%) were in the ATA low risk group, and 292 (42.9%) and 133 (19.6%) were in the ATA intermediate and high risk groups, respectively, on the initial risk stratification. After a mean 108.2 mCi of RAI therapy, 514 patients (75.6%) had an ER, 34 (5.0%) had a BCIR, 13 had a (2.0%) SIR, and 119 (17.5%) had an IR.

Predictive factors for recurrent/persistent disease

In the final analysis, 572 out of 680 patients (84.1%) showed NED status; six patients showed recurrence during follow-up, and 102 had persistent disease. Univariate analysis suggested that sex, ATA risk, tumor size, AJCC stage (T and N status), RAI dosage, pre-Tg, post-Tg and DRS were significant predictors of recurrent/persistent disease. Sex, ATA risk, tumor size, N status and pre-Tg remained as statistically significant independent factors in multivariate analysis (Table 1). There was no difference in outcome between the overall patient cohort and the individual patient groups, regardless of whether they were receiving recombinant human thyrotropin (rhTSH).

Patient characteristics according to the dynamic risk stratification

Among the four groups, the SIR group had the largest tumor size and worst prognostic factors on the initial postoperative risk stratification (ATA initial risk stratification, T and N stage, and AJCC stage) followed, in order, by the BCIR, IR, and ER groups. Although RAI dose was lowest in the ER group and highest in the SIR group, the final outcome showed that NED was 99.4% in the ER group and zero in the SIR group. Pre-Tg levels were also significantly different between the groups, with the highest level being in the SIR, followed by the BCIR, IR, and ER groups. The size of the SIR group increased significantly with pre-Tg levels (0.5%, 2.6% and 17.2% of patients with pre-Tg < 1, 1 to 10, and > 10 ng/dL, respectively; $p < 0.001$). However, post-Tg levels were not different. Multivariate analysis revealed that sex, RAI dose, and pre-Tg affected the DRS (Table 2).

Differences according to the increase in post-ablative thyroglobulin in patients with pre-ablative thyroglobulin < 1 ng/mL

The mean post-Tg level (13.8 ± 32.2 ng/mL) increased significantly after RAI therapy in all 680 patients compared to the mean pre-Tg level (2.5 ± 8.9 ng/mL). Serum TSH levels decreased from 93.1 ± 33.9 mIU/dL at pre-ablation to 33.4 ± 16.7 mIU/dL at 7 days after RAI therapy. Pre-Tg levels were < 1 ng/mL (mean 0.3 ± 0.3 ng/mL) in 422 patients, which increased to 4.2 ± 10.3 ng/mL after ablation. A total of 205 patients with pre-Tg < 1 ng/mL had post-Tg levels < 1 ng/mL (group 1); the post-Tg level

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Table 1. Patients' clinical characteristics according to final outcome

Characteristic	Total (n = 680)	NED (n = 572)	Recurrence + persistence (n = 108)	Univariate *p* value	Multivariate *p* value
Age, yr	49.2 ± 11.6	49.3 ± 11.1	48.5 ± 14.0	0.553	
Male sex	168 (24.7)	129 (22.6)	39 (36.1)	0.003	0.014
ATA risk				< 0.001	< 0.001
Low	255 (37.5)	242 (42.3)	13 (12.0)		
Intermediate	292 (42.9)	226 (39.5)	66 (61.1)		
High	133 (19.6)	104 (18.2)	29 (26.9)		
Tumor size, cm	1.1 ± 0.7	1.1 ± 0.6	1.4 ± 0.8	0.001	0.014
T status				0.001	0.060
T1a	229 (33.7)	204 (35.7)	25 (23.1)		
T1b	121 (17.8)	103 (18.0)	18 (16.7)		
T2	25 (3.7)	21 (3.7)	4 (3.7)		
T3	260 (38.2)	215 (37.6)	45 (41.7)		
T4a	45 (6.6)	29 (5.1)	16 (14.8)		
N status				< 0.001	0.009
N0	164 (24.1)	154 (26.9)	10 (9.3)		
N1a	392 (57.6)	335 (58.6)	57 (52.8)		
N1b	99 (14.6)	60 (10.5)	39 (36.1)		
NX	25 (3.7)	23 (4.0)	2 (1.9)		
7th AJCC				< 0.001	0.395
I	274 (40.3)	232 (40.6)	42 (38.9)		
II	5 (0.7)	5 (0.9)	0		
III	322 (47.4)	282 (49.3)	40 (37.0)		
IVa	79 (11.6)	53 (9.3)	26 (24.1)		
RAI dosage, mCi	108.2 ± 51.8	105.2 ± 52.1	123.6 ± 48.1	0.001	0.098
rhTSH use	255 (37.5)	211 (36.9)	44 (40.7)	0.450	
RAI uptake				0.330	
Overt remnant thyroid (star sign)	122 (17.9)	105 (18.4)	17 (15.7)		
Focal uptake	539 (79.3)	449 (78.5)	90 (83.3)		
No uptake	19 (2.8)	18 (3.1)	1 (0.9)		
Pre-Tg, ng/mL	0.6 (0–117.9)	0.4 (0–16.6)	3.7 (0–117.9)	< 0.001	< 0.001
< 1	422 (62.1)	409 (71.5)	13 (12.0)		
1–10	229 (33.7)	159 (27.8)	70 (64.8)		
> 10	29 (4.3)	4 (0.7)	25 (23.1)		
Post-Tg, ng/mL	3.5 (0–378.0)	2.7(0–290.0)	10.7 (0–378.0)	0.029	0.936
< 1	210 (30.9)	203 (35.5)	7 (6.5)		
1–10	261 (38.4)	217 (37.9)	44 (40.7)		
> 10	209 (30.7)	152 (26.6)	57 (52.8)		
Follow-up, mon	27.7 ± 8.5	27.7 ± 8.5	28.2 ± 9.0	0.520	
Dynamic risk				< 0.001	
ER	514 (75.6)	511 (89.3)	3 (2.8)		
BCIR	34 (5.0)	1 (0.2)	33 (30.6)		
SIR	13 (1.9)	0	13 (12.0)		
IR	119 (17.5)	60 (10.5)	59 (54.6)		

Values are presented as mean ± SD, number (%), or median (range).
NED, no evidence of disease; ATA, American Thyroid Association; AJCC, American Joint Committee on Cancer; RAI, radioactive iodine; rhTSH, recombinant human thyroid stimulating hormone; Tg, thyroglobulin; ER, excellent response; BCIR, biochemically incomplete response; SIR, structurally incomplete response; IR, incomplete response.

Table 2. Patients' clinical characteristics, radioiodine therapy type, and outcomes according to dynamic risk stratification

Characteristic	ER (n = 514)	BCIR (n = 34)	SIR (n = 13)	IR (n = 119)	Univariate *p* value	Multivariate *p* value
Age, yr	49.7 ± 11.3	47.5 ± 11.9	53.6 ± 13.6	47.1 ± 12.4	0.063[a]	
Male sex	112 (21.8)	12 (35.3)	3 (23.1)	41 (34.5)	0.015	0.016
ATA risk					< 0.001	0.213
Low	216 (42.0)	1 (2.9)	0	38 (31.9)		
Intermediate	203 (39.5)	25 (73.5)	9 (69.2)	55 (46.2)		
High	95 (18.5)	8 (23.5)	4 (30.8)	26 (21.8)		
Tumor size, cm	1.1 ± 0.6	1.3 ± 0.7	1.5 ± 0.6	1.2 ± 0.8	0.001[a]	0.070
T status					0.003	0.935
T1a	187 (36.4)	6 (17.6)	2 (15.4)	34 (28.6)		
T1b	93 (18.1)	4 (11.8)	3 (23.1)	21 (17.6)		
T2	17 (3.3)	2 (5.9)	0	6 (5.0)		
T3	193 (37.5)	20 (58.8)	5 (38.5)	42 (35.3)		
T4a	24 (4.7)	2 (5.9)	3 (23.1)	16 (13.4)		
N status					< 0.001	0.073
No	139 (27.0)	4 (11.8)	0	21 (17.6)		
N1a	304 (59.1)	17 (50.0)	4 (30.8)	67 (56.3)		
N1b	53 (10.3)	12 (35.3)	8 (61.5)	26 (21.8)		
NX	18 (3.5)	1 (2.9)	1 (7.7)	5 (4.2)		
7th AJCC					0.002	0.684
I	204 (40.3)	12 (35.3)	3 (232.1)	52 (43.7)		
II	3 (0.6)	0	0	2 (1.7)		
III	259 (50.4)	15 (44.1)	5 (38.5)	43 (36.1)		
IVa	45 (8.8)	7 (20.6)	5 (38.5)	22 (18.5)		
RAI dosage, mCi	103.2 ± 50.5	126.8 ± 49.2	137.7 ± 51.0	121.3 ± 54.5	< 0.001[a]	0.004
rhTSH use	193 (37.5)	11 (32.4)	8 (61.5)	43 (36.1)	0.298	
RAI uptake on thyroid bed					0.410	
Overt remnant thyroid (star sign)	92 (17.9)	4 (11.8)	5 (38.5)	21 (17.6)		
Focal uptake	407 (79.2)	30 (88.2)	8 (61.5)	94 (79.0)		
No uptake	15 (2.9)	0	0	4 (3.4)		
Pre-Tg, ng/mL	0.9 (0–25.5)	15.2 (0–104.3)	26.4 (0.5–117.9)	3.1 (0–43.7)	< 0.001	< 0.001
< 1	373 (72.6)	5 (14.7)	2 (15.4)	42 (35.3)		
1–10	138 (26.8)	15 (44.1)	6 (46.2)	70 (58.8)		
> 10	3 (0.6)	14 (41.2)	5 (38.5)	7 (5.9)		
Post-Tg, ng/mL	11.9 (0–290)	23.1 (0–97.8)	31.9 (1.7–161.1)	17.4 (0–378.0)	0.145	
< 1	189 (36.8)	4 (11.8)	0	17 (14.3)		
1–10	192 (37.4)	9 (26.5)	4 (30.8)	56 (47.1)		
> 10	133 (25.9)	21 (61.8)	9 (69.2)	46 (38.7)		
Follow-up, mon	27.0 ± 8.4	29.4 ± 8.6	28.2 ± 10.5	30.4 ± 8.6	< 0.001[a]	
Outcome					< 0.001	
NED	511 (99.4)	1 (2.9)	0	60 (50.4)		
Recurrence	1 (0.2)	2 (5.9)	2 (15.4)	1 (0.8)		
Persistence	2 (0.4)	31 (91.2)	11 (84.6)	58 (48.7)		

Values are presented as mean ± SD, number (%), or median (range).
ER, excellent response; BCIR, biochemically incomplete response; SIR, structurally incomplete response; IR, incomplete response; ATA, American Thyroid Association; AJCC, American Joint Committee on Cancer; RAI, radioactive iodine; rhTSH, recombinant human thyroid stimulating hormone; Tg, thyroglobulin; NED, no evidence of disease.
[a]Statistical significance was tested by one-way analysis of variance.

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increased to 1 to 10 ng/mL in 167 patients (group 2) and to > 10 ng/mL in 50 patients (group 3). No differences in the postoperative risk stratification (ATA initial risk stratification, T and N stage, or AJCC stage), response to therapy (DRS), or clinical outcome were observed among the three groups. RAI doses and uptake patterns were different among the three groups. No uptake was seen in 8.3% of group 1 patients, and uptake with the star pattern was seen in only 3.8% of these patients. All group 2 and 3 patients showed some uptake, and the rate of star sign uptake was significantly higher compared to group 1 (Table 3). There was no significant difference between the 255 patients on rhTSH and the 425 patients with T4 withdrawal.

DISCUSSION

In this study, the most important factor for predicting the DRS was pre-Tg level. The post-Tg increase was not related to prognosis in patients with a low pre-Tg level and was confirmed as a factor reflecting remnant thyroid tissue, which in turn was related to the RxWBS uptake pattern at the first RAI therapy.

RAI therapy is selectively recommended after thyroidectomy based on the postoperative risk stratification [1]. The goal of RAI is to reduce recurrence risk by eliminating remnant thyroid tissue and to facilitate the use of Tg as a tumor marker during follow-up. Tg is only produced by normal and cancerous thyroid follicular cells. Tg is stored in the follicular lumen, and is a precursor of thyroid hormone that is released into the blood along with thyroid hormones. Serum Tg is cleared with a half-life of about 30 hours following thyroidectomy [9]. If all tumor tissue has been eliminated, the nadir should occur after total thyroidectomy and RAI therapy. Therefore, monitoring serum Tg during follow-up provides important information about the presence or absence of residual, recurrent, or metastatic disease in patients with differentiated thyroid cancer after thyroidectomy with or without RAI therapy [10,11]. However, the predictive value of pre-Tg level can be diminished by the surgical residual tissue, because the increase in the pre-Tg level may simply reflect Tg production by residual follicular cells [6,12]. Several studies have demonstrated that pre-Tg is a useful marker for predicting tumor recurrence [4,5,11,13-17]. Lee et al. [4] and Kim et al. [5] used a pre-Tg cut-off of 2 ng/mL and reported the usefulness of pre-Tg level to predict recurrence. Park et al. [2] reported that the pre-Tg level is the most powerful predictor of therapeutic failure and patients with pre-Tg levels > 10 ng/mL had a 26-fold greater chance of therapeutic failure than those with levels < 10 ng/mL. In our study, we confirmed that pre-Tg level was the best predictor of therapeutic failure according to the DRS recommended by the ATA 2015. When pre-Tg levels were divided into < 1, 1 to 10, and > 10 ng/mL categories, the DRS and clinical outcome also differed significantly by category.

Several studies have reported increased Tg levels immediately after RAI; however, reports on the significance of this finding have been rare [7,15,16,18]. In a study by Jeong et al. [7], although pre-Tg level was not different, post-Tg level and the Tg ratio (preTg/post-Tg) were significantly higher in patients with versus without midline uptake on RxWBS, regardless of initial tumor stage and size. They suggested that the post-Tg increase was caused by a large amount of remnant thyroid tissue, such as thyroglossal ductal remnants (TGDR), which show mid-line uptake. Several reports have investigated the prognostic value of the Tg ratio and showed that a higher Tg ratio was related to ablation success despite a higher pre-Tg level [15,16]. The post-Tg increase is linked to destruction of follicular cells after RAI therapy. In our study, post-Tg levels were higher in patients with high pre-Tg levels; therefore, we examined the post-Tg increase in patients with pre-Tg levels < 1 ng/mL. Post-Tg increased to 4.2 ± 10.3 ng/mL (range, 0 to 161.1) in patients with pre-Tg < 1 ng/mL, and increased to > 10 ng/mL in 50 patients. The DRS and clinical outcome were not different according to the post-Tg level (< 1, 1 to 10, and > 10 ng/mL groups). A significant difference was found only in the RxWBS uptake pattern, so this may be representative of the amount of remnant thyroid tissue. Normal thyroid follicular cells surround the Tg-containing colloid, whereas cancerous cells are devoid of colloid. Therefore, normal thyroid remnants rather than cancerous cells contributed to the increase in Tg after destruction of the follicular cells by RAI therapy. It has been proposed that elevated post-Tg levels may be a marker for successful ablation of remnant thyroid tissue. However, several studies have reported that the degree of the post-Tg increase could be a better (or

Table 3. Clinical characteristics, radioiodine therapy type, and outcomes of patients whose stimulated thyroglobulin level was less than 1 ng/mL according to the degree of thyroglobulin increase after radioiodine therapy

Characteristic	Tg < 1 ng/mL (n = 205)	Tg 1–10 ng/mL (n = 167)	Tg > 10 ng/mL (n = 50)	*p* value
Age, yr	50.2 ± 10.5	50.5 ± 12.5	53.0 ± 11.3	0.276[a]
Male sex	30 (14.6)	35 (21.0)	12 (24.0)	0.155
ATA risk				0.319
Low	78 (38.0)	78 (46.7)	24 (48.0)	
Intermediate	84 (41.0)	58 (34.7)	20 (40.0)	
High	43 (21.0)	31 (18.6)	6 (12.0)	
Tumor size, cm	1.1 ± 0.8	1.0 ± 0.6	1.1 ± 0.6	0.236[a]
T status				0.637
T1a	70 (34.1)	70 (41.9)	14 (28.0)	
T1b	35 (17.1)	26 (15.6)	13 (26.0)	
T2	8 (3.9)	5 (3.0)	2 (4.0)	
T3	79 (38.5)	58 (34.7)	18 (36.0)	
T4a	13 (6.3)	8 (4.8)	3 (6.0)	
N status				0.067
No	73 (35.6)	37 (22.2)	14 (28.0)	
N1a	104 (50.7)	106 (63.5)	33 (66.0)	
N1b	20 (9.8)	17 (10.2)	3 (6.0)	
NX	8 (3.9)	7 (4.2)	0	
7th AJCC				0.290
I	85 (41.5)	65 (38.9)	14 (28.0)	
II	2 (1.0)	0	1 (2.0)	
III	99 (48.3)	84 (50.3)	32 (64.0)	
IVa	19 (9.3)	18 (10.8)	3 (6.0)	
TSH, mIU/L	30.5 ± 36.5	32.4 ± 38.3	36.2 ± 45.1	0.624
RAI dosage, mCi	96.0 ± 54.0	110.1 ± 53.2	113.2 ± 45.4	0.015
rhTSH	88 (42.9)	66 (39.5)	20 (40.0)	0.788
RAI uptake on thyroid bed				< 0.001
Overt remnant thyroid (star sign)	7 (3.4)	38 (22.8)	20 (40.0)	
Focal uptake	181 (88.3)	129 (77.2)	30 (60.0)	
No uptake	17 (8.3)	0	0	
Response to therapy				0.072
ER	186 (90.7)	141 (84.4)	46 (92.0)	
BIR	4 (2.0)	1 (0.6)	0	
SIR	0	1 (0.6)	1 (2.0)	
Indeterminate	15 (7.3)	24 (14.4)	3 (6.0)	
Outcome				0.711
Remission	200 (97.6)	160 (95.8)	49 (98.0)	
Recurrence	0	1 (0.6)	0	
Persistent	5 (2.4)	6 (3.6)	1 (2.0)	

Values are presented as mean ± SD or number (%).
Tg, thyroglobulin; ATA, American thyroid association; AJCC, American Joint Committee on Cancer; TSH, thyroid stimulating hormone; RAI, radioactive iodine; rhTSH, recombinant human thyroid stimulating hormone; ER, excellent response; BIR, biochemically incomplete response; SIR, structurally incomplete response.
[a]Statistical significance was tested by one-way analysis of variance.

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equally valid) predictor of ablation failure than pre-Tg level [15,16,18]. This may be due to the surgeon's skill or to TGDR.

RAI accumulates in thyroid tissue, so RxWBS can be used to identify radioiodine uptake lesions, which do not distinguish between residual normal remnants and cancerous tissues. Star artifacts, which represent intense tracer uptake in the thyroid bed, are often observed after initial RAI and total thyroidectomy. Star artifacts are often seen in regions of high intensity radioiodine uptake because of septal penetration of the collimator holes, which are hexagonally shaped [19]. These artifacts reflect remnant thyroid tissue in the thyroid bed. In our study, we divided the thyroid bed uptake pattern of enrolled patients into three categories: no uptake, focal uptake (without star artifacts), and star artifacts. Star artifacts were observed in 122 patients (17.9%) and were significantly more frequent in the patient group with the highest post-Tg level. No significant difference was observed in the DRS or clinical outcome according to uptake pattern among all patients, or within the pre-Tg < 1 ng/mL patient group.

Several limitations of our study should be mentioned. First, there were no strict guidelines for determining RAI dose because this study was retrospective. However, because the dose of RAI was based on the TNM stage, it was increased according to patient risk, and the highest dose was applied in the SIR group. In the multivariate analysis, differences in pre-Tg and RAI dosage were observed in each group based on the DRS, but the difference according to the pre-Tg level was more significant than the RAI dose. Second, 361 patients (53.1%) were evaluated by stimulated Tg and neck ultrasonography, with or without a diagnostic RAI scan, when assessing the DRS, and the remaining 319 patients (46.9%) were evaluated by suppressed Tg and ultrasonography. The ATA guidelines [1] state that any of the Tg indices can be used, but there may be a difference in the evaluation results. However, the number of patients using suppressed Tg was not significantly different between groups, suggesting that suppressed Tg did not have a significant effect on the results. Third, we did not perform single photon emission computed tomography/computed tomography (SPECT/CT) to identify normal remnant tissue, such as TGDR, in all patients. TGDR uptake can be visualized on SPECT/CT images in 48% of patients and can induce an increase in Tg [20]. In a study by Jeong et al. [7] the pre-Tg level did not differ according to mid-line uptake (TGDR), regardless of thyroid bed uptake. According to our study, although thyroid bed uptake and intensity were analyzed, and midline uptake was not assessed separately, pre-Tg may be an important factor for predicting prognosis regardless of TGDR. In addition, differences in serum TSH levels before versus 7 days after the RAI therapy could have been a confounding factor. As TSH increases, the Tg level also increases. In our patients, the mean post-Tg level was significantly higher after RAI therapy compared to the mean pre-Tg level (2.5 ± 8.9 ng/mL), despite serum TSH levels decreasing from 93.1 ± 33.9 mIU/dL at pre-ablation to 33.4 ± 16.7 mIU/dL at 7 days after RAI therapy. TSH levels were not significantly different among the post-Tg < 1, 1 to 10, and > 10 ng/mL groups. This suggests that TSH levels did not affect post-Tg values in our study.

In conclusion, this study reaffirmed that pre-Tg level can be used as a prognostic factor in patients with PTC. Tg increased after RAI in most patients, but the clinical significance of the post-Tg level may reflect remnant thyroid tissue and does not help in predicting the prognosis.

KEY MESSAGE

1. Pre-ablative thyroid stimulating hormone-stimulated thyroglobulin level can be used as a prognostic factor in patients with papillary thyroid cancer.
2. Thyroglobulin increased after radioactive iodine therapy in most patients, but the clinical significance of the serum thyroglobulin level measured immediately after radioactive iodine may reflect remnant thyroid tissue and is not helpful for predicting the prognosis.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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