Correlation of Consecutive Serum Thyroglobulin Levels During Hormone Withdrawal and Failure of Initial Radioiodine Ablation in Thyroid Cancer Patients

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Abstract

Objective The aim of this study was to evaluate the value of thyroglobulin (Tg) kinetics during preparation of radioiodine ablation for prediction of initial radioiodine ablation failure in thyroid cancer patients.

Methods Thyroid cancer patients after total thyroidectomy who underwent radioiodine ablation with 3–4 weeks of hormone withdrawal between May 2011 and January 2012 were included. Consecutive serum Tg levels 5–10 days before ablation (Tg1) and on the day of ablation (Tg2) were obtained. The difference between Tg1 and Tg2 (Δ Tg), daily change rate of Tg (Δ Tg/day) and Tg doubling time (Tg-DT) were calculated. Success of initial ablation was determined by the results of the follow-up ultrasonography, diagnostic radioiodine scan and stimulated Tg level after 6 to 20 months.

Results A total of 143 patients were included. Failed ablation was reported in 52 patients. Tg2 higher than 5.6 ng/ml and Tg-DT shorter than 4.2 days were significantly related to a high risk of ablation failure. Δ Tg and Δ Tg/day did not show significant correlation with ablation failure.

Conclusions Thyroglobulin kinetics on consecutive blood sampling during hormone withdrawal may be helpful in

predicting patients with higher risk of treatment failure of initial radioiodine ablation therapy in thyroid cancer patients.

Keywords Papillary thyroid carcinoma · High-dose I-131 ablation therapy · Thyroglobulin doubling time · Therapeutic failure

Introduction

Radioiodine ablation with I-131 (RAI) after total thyroidectomy is widely used for patients with differentiated thyroid cancer (DTC) [1, 2]. RAI serves two purposes. First is to destroy microscopic residual tumor foci to reduce the recurrence and mortality rate [3, 4]. Second is to enable early detection of recurrence with serum thyroglobulin (Tg).

As the success of RAI is related to the prognosis of DTC [4], patients with RAI failure at the initial attempt may require repeated RAI or other treatments. Therefore, selection of patients with high risk of RAI failure may assist patient management.

Measurement of serum Tg after thyroid-stimulating hormone (TSH) stimulation is a well-known tumor marker in detecting remaining or recurrent tumor after RAI [1, 5]. Several studies have also suggested that high levels of serum Tg at the time of RAI could be a prognostic marker for prediction of ablation failure [6–9]. Also, several studies have reported the serum Tg doubling time under thyrotropin suppression as a prognostic predictor in patients with DTC [10].

Serum Tg is heavily dependent on TSH stimulation, and serum Tg may increase dramatically during TSH stimulation. There are reports of serum Tg elevation during prolonged exogenous hormone withdrawal [11]. Theoretically, the rate

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of Tg elevation during TSH stimulation may be related to the burden of remnant thyroid tissue, which in turn may be related to the risk of RAI failure. However, to our knowledge, no studies have investigated the relationship between Tg kinetics during TSH stimulation and the risk of ablation failure.

The aim of this study is to investigate the clinical importance of Tg kinetics under TSH stimulation for initial RAI after total thyroidectomy for predicting therapeutic failure. Other clinical, laboratory and pathologic factors were also investigated.

Methods

Subjects

This retrospective study was approved by our Institutional Review Board, and patient consent was not required. We

retrospectively reviewed the records of 508 differentiated papillary thyroid carcinoma patients who underwent first high-dose radioiodine therapy from May 2011 and January 2012 at Seoul Saint Mary's Hospital. Patients who had prepared radioiodine therapy by the thyroid hormone withdrawal method were included.

We excluded patients with: (1) prior history of RAI, (2) known distant metastasis, (3) incomplete blood chemistry, (4) no follow-up DxWBS, (4) inadequately elevated TSH (under ≥ 30 mIU/l) or elevated anti-Tg Ab (over 70 IU/ml) at the time of pretreatment DxWBS [12, 13]. Finally, a total of 143 patients were included in our study.

All patients were switched to triiodothyronine (T3) from levothyroxine (T4) for 2 weeks, followed by T3 withdrawal and a low iodine diet for 2 weeks. Blood chemistry including the thyroid function test was performed along with a pretreatment diagnostic radioiodine whole-body scan (DxWBS). TSH, Tg and anti-thyroglobulin antibody (anti-Tg Ab) were

Fig. 1 The process of RAI treatment and evaluation

included. A therapeutic dose of 3700–5550 MBq was administered 5–10 days after the date of first blood sampling. Serum levels of TSH, Tg and anti-Tg were again measured at the date of therapeutic radioiodine administration. The preparation process for RAI is described in Fig. 1. Table 1 shows the demographic data and TNM classification of the included patients.

Evaluation of RAI

Serum Tg and anti-Tg levels were measured at the time of the first follow-up whole-body scan (FuWBS), performed between 6–20 months after the initial RAI. The definition of successful ablation in this study was as follows: negative

FuWBS, stimulated serum Tg <2 ng/ml and no pathologic evidence of residual tumor. Failure to meet any one of the criteria was considered ablation failure.

Tg Kinetics

The elevation rate of Tg under TSH stimulation was calculated by several methods. The Tg difference (Δ Tg) was simply calculated by subtracting Tg1 from Tg2. The amount of Tg difference over time (Δ Tg/day) was calculated by dividing Δ Tg by d_t , where d_t is the time between the Tg assays. Thyroglobulin doubling time (Tg-DT) was computed by the following formula: $Tg-DT = (0.693 \times d_t) / \ln(Tg1/Tg2)$. In patients with $Tg2 \leq Tg1$, Tg-DT was considered infinite.

Statistical Analysis

The relationship between the variables and success of RAI was evaluated using the chi-square or Fisher exact test for categorical variables and Student t-test or Mann-Whitney U-test for continuous variables. The optimal cutoff for continuous variables was defined by receiver-operating characteristic (ROC) curve analysis. Logistic regression was used to identify prognostic factors with independent significance to predict RAI failure. A p-value < 0.05 was considered statistically significant. Analysis was performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA), R i386 version 2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria) and MedCalc version 15.6 (Medcalc Inc., Ostend, Belgium).

Results

Of 143 patients, ablation failure was reported in 52 (36.4 %). Of 52 patients with ablation failure, 19 had stimulated serum Tg elevated over 2 ng/ml, 37 had residual I-131 uptake on fuWBS, and 7 had both. Three patients were considered to have failed ablation because residual tumor was confirmed by ultrasonographic biopsy.

Tg1 levels ranged from 0.05 to 725.15 ng/ml (median 1.11 ng/ml, 75th percentile=4.28 ng/ml), and Tg2 levels ranged from 0.04 to 695.93 ng/ml. There were a total of 22 cases where Tg1 was measured below 0.2 ng/ml and 11 cases where Tg2 was measured below 0.2 ng/ml. Tg1 and Tg2 distribution was asymmetrical to the left.

A receiver-operating characteristic curve analysis showed that the optimal cutoff for the prediction of ablation failure was 5.6 ng/ml for Tg2 ($p < 0.001$) and 4.2 days for Tg-DT ($p = 0.020$) (Table 2).

By chi-square analysis, age <45 years ($p = 0.031$), Tg-DT shorter than 4.2 days ($p = 0.002$) and Tg2 higher

Table 1 Patient characteristics (n=143)

Characteristic	Number of patients (%)
Gender	
Male	24 (16.8 %)
Female	119 (83.2 %)
Age at diagnosis (years)	
Mean (range)	45.0 (15–78)
Time interval between blood sampling (days)	
Median (range)	8 (5–10)
Type of operation	
No lymph node dissection	6 (4.2 %)
Central lymph node dissection	106 (74.1 %)
Lateral neck dissection	31 (21.7 %)
Size of primary tumor (mm)	
Median (range)	10 (1–90)
T stage ^a	
T1	51 (35.7 %)
T2	5 (3.5 %)
T3	80 (55.9 %)
T4	7 (4.9 %)
N stage ^a	
Nx	6 (4.2 %)
N0	41 (28.7 %)
N1a	71 (49.7 %)
N1b	25 (17.5 %)
AJCC stage ^a	
I	71 (49.7 %)
II	2 (1.4 %)
III	56 (39.2 %)
IV	14 (9.5 %)
Dose of administered I-131 (MBq)	
3700	61
5550	76

^a According to the AJCC cancer staging manual, 7th edition

Table 2 ROC curve analysis of continuous parameters for prediction of failed ablation

Variables	AUC (95 % CI)	P value	Cutoff value	Sensitivity	Specificity
Tg1	0.615 (0.530–0.695)	0.024	>1.8	63.46	62.64
Tg2	0.788 (0.712–0.852)	<0.001	>5.6	75.00	83.52
Tg-DT	0.619 (0.534–0.698)	0.020	<4.2	42.31	83.52

5.6 ng/ml ($p<0.001$) were significant factors for prediction of ablation failure. Gender ($p=0.250$), T stage ($p=1.000$), N stage ($p=0.130$), AJCC stage ($p=0.082$) and dose of administered I-131 ($p=0.089$) did not reach statistical significance. There was no significant difference in ΔTg ($p=0.685$), $\Delta Tg/day$ ($p=0.586$) and largest tumor size ($p=0.923$) (Table 3). After multivariate analysis, Tg-DT <4.2 days ($p=0.002$) and Tg2 >5.6 ng/ml ($p<0.001$) remained significant factors predictive of ablation failure (Table 4).

Patients were divided into two groups according to Tg2. Eighty-eight patients had Tg2 lower than 5.6 ng/ml, and 55 patients had Tg2 higher than 5.6 ng/ml. In patients with high Tg2, Tg-DT failed to reach statistical significance ($p=0.54$). In patients with low Tg2, Tg-DT shorter than 4.2 days was a significant factor predicting ablation failure ($p=0.030$, odds ratio 4.09). Patients with low Tg2 and short Tg-DT showed an ablation failure rate of 31.5 % (6/19), while patients with low Tg2 and long Tg-DT showed an ablation failure rate of 10.1 % (7/69) (Fig. 2).

Table 3 Comparison of variables between successful and failed ablation

Variables	Successful ablation	Failed ablation	Odds ratio	P value
Age				
<45	40	32		
≥45	51	20	0.490 (0.245–0.983)	0.031
Gender				
Female	73	46		
Male	18	6	0.529 (0.196–1.431)	0.250
T stage				
T1+T2	36	20		
T3+T4	55	32	1.047 (0.521–2.107)	1.000
N stage				
Nx+N0	34	13		
N1	57	39	1.789 (0.839–3.818)	0.130
AJCC stage				
I+II	41	31		
III+IV	50	21	0.513 (0.256–1.027)	0.082
Dose of I-131 (MBq)				
3700	47	20		
5550	44	32	0.585 (0.292–1.171)	0.089
Tg1				
<1.8	70	22		
≥1.8	21	30	4.545 (2.179–9.481)	<0.001
Tg2				
<5.6	75	13		
≥5.6	16	39	14.063 (6.145–32.180)	<0.001
Tg-DT				
>4.2	76	21		
≤4.2	15	31	3.43 (1.568–7.512)	0.002
ΔTg	1.5±3	4.3±50		0.685
$\Delta Tg/day$	0.2±0.3	0.7±6.4		0.586
Largest tumor diameter	2.3±1.0	2.3±1.0		0.923

Table 4 Multivariate analysis of categorical variables and Tg-DT

Variables	Successful ablation	Failed ablation	Odds ratio (univariate)	P value (univariate)	Odds ratio (multivariate)	P value (multivariate)
Model 1: Tg-DT						
Age						
<45	40	32				
≥45	51	20	0.490 (0.245–0.983)	0.031	0.456 (0.115–1.803)	0.263
Gender						
Female	73	46				
Male	18	6	0.529 (0.196–1.431)	0.250	0.518 (0.174–1.540)	0.237
T stage						
TI+T2	36	20				
T3+T4	55	32	1.047 (0.521–2.107)	1.000	1.112 (0.501–2.468)	0.794
N stage						
Nx+N0	34	13				
N1	57	39	1.789 (0.839–3.818)	0.130	1.987	0.145
AJCC stage						
I+II	41	31				
III+ IV	50	21	0.513 (0.256–1.027)	0.082	0.930 (0.790–5.000)	0.918
Dose of I-131 (MBq)						
3700	47	20				
5550	44	32	0.585 (0.292–1.171)	0.089	0.638 (0.231–0.282)	0.280
Tg-DT						
>4.2	76	21				
≤4.2	15	31	3.43 (1.568–7.512)	0.002	3.809 (1.638–8.857)	0.002
Model 2: Tg2						
Age						
<45	40	32				
≥45	51	20	0.490 (0.245–0.983)	0.031	0.731 (0.163–3.276)	0.731
Gender						
Female	73	46				
Male	18	6	0.529 (0.196–1.431)	0.250	1.010 (0.300–3.395)	0.988
T stage						
TI+T2	36	20				
T3+T4	55	32	1.047 (0.521–2.107)	1.000	1.306 (0.530–3.215)	0.562
N stage						
Nx+N0	34	13				
N1	57	39	1.789 (0.839–3.818)	0.130	1.769 (0.640–4.889)	0.271
AJCC stage						
I+II	41	31				
III+ IV	50	21	0.513 (0.256–1.027)	0.082	0.937 (0.204–4.310)	0.933
Dose of I-131 (MBq)						
3700	47	20				
5550	44	32	0.585 (0.292–1.171)	0.089	0.849 (0.339–2.215)	0.726
Tg2						
<5.6	75	13				
≥5.6	16	39	14.063 (6.145–32.180)	<0.001	13.209 (5.442–32.056)	<0.001

Discussion

Several studies have proposed the relationship between preablation stimulated Tg and successful ablation. Higher

preablative Tg values were associated with treatment failure, although the optimum cutoff value has not been established [6–8].

Lim et al. showed that preablation Tg >5 ng/ml, presence of LN metastasis and >10 % quantified cervical uptake in the

Fig. 2 Ablation failure rate categorized by Tg2 and Tg-DT

RxWBS were significant predictors of ablation failure. Among these predictors, preablation Tg > 5 ng/ml was the most significant predictive factor for ablation failure [14]. A meta-analysis of 3,947 patients by Brassard et al. demonstrated that the preablation Tg level was a useful negative predictor of persistent and recurrent DTC, with a negative predictive value (NPV) of 94 % when the preablation Tg value was less than 10 ng/ml [15]. These findings were in line with the results of our study, where preablation Tg greater than 5.6 ng/ml was a significant predictive factor for ablation failure.

There are several studies on Tg kinetics used as a representative of progression in correlation with tumor burden. Miyauchi et al. studied serum Tg kinetics in patients under thyrotropin suppression and demonstrated that Tg-DT less than 1 year under thyrotropin suppression is a very strong predictor of locoregional recurrence [16, 17]. Giovannella et al. also reviewed Tg-DT under thyrotropin suppression and demonstrated that patients having Tg-DT less than 1 year under thyrotropin suppression significantly improves that chance of positive findings on F-18 FDG PET/CT [10]. Kelders et al. studied 57 patients and have suggested a mild correlation between Tg-DT under thyrotropin suppression and the presence of F-18 FDG-positive, I-131-negative metastases [18]. Wong et al. studied 507 patients treated with curative thyroidectomy and radioiodine ablation and found that having a Tg change of over 0.3 ng/ml per year predicted recurrence with a sensitivity of 83.3 % and specificity of 94.4 % [19].

There is little literature about the significance of Tg kinetics during RAI. Bernier et al. studied the Tg values in patients just before and 5 days after RAI and concluded that having a TgD5/TgD0 ratio higher than 20 was significantly related to

successful ablation [9]. Kim et al. also studied 152 patients treated with rh-TSH and found that high elevation of Tg 3 days after RAI compared with preablative stimulated Tg was significantly related to successful ablation [20]. Such results conflict with our study, where high elevation of Tg was predictive of ablation failure. The main reason for this difference may be the different timing of Tg elevation, as Bernier and Kim's study reviewed Tg elevation after RAI, which is thought to be related to good I-131 uptake and radiation-induced cellular damage, while our study reviewed Tg elevation before RAI, which may be related to the activity, remnant thyroid tissue or tumor.

In this retrospective study, we reviewed the correlation between the TG elevation rates during hormone withdrawal and showed that the logarithmic growth rate of Tg, demonstrated as Tg-DT, is a good predictor of therapeutic response after RAI therapy. Tg-DT shorter than 4.2 days was associated with increased risk of therapeutic failure.

To our knowledge, this is the first study that has investigated the clinical significance of Tg kinetics under TSH stimulation before RAI. This study has shown that patients with Tg-DT less than 4.2 days under TSH stimulation are more likely to experience ablation failure. As our subgroup analysis suggests, Tg-DT has the potential to further differentiate patients with higher rates of ablation failure in addition to preablation Tg. Even among patients with low preablation Tg, those with shorter Tg-DT had significantly high ablation failure of 31.5 %. A combination of low serum preablation Tg (<5.6 ng/ml) and long Tg-DT showed an ablation success rate of 89.9 %.

There are several limitations to our study. First, this study was retrospective in nature, and the time interval between Tg1

and Tg2 was not uniform. Second, while Tg-DT was calculated under the assumption that Tg shows exponential growth under TSH stimulation, most tumor markers correlate with the tumor burden and thus show exponential growth. This is also true for Tg in patients with recurrent thyroid cancer. However, before RAI, Tg is produced by both remnant normal thyroid tissue and thyroid cancer cells and may not necessarily show exponential growth. Therefore, we analyzed both Tg-DT to represent exponential growth and $\Delta\text{Tg}/\text{day}$ to represent linear growth. Tg-DT appeared to show better correlation with ablation failure than $\Delta\text{Tg}/\text{day}$. The Tg kinetics under TSH stimulation need to be further validated by further studies. Third, this study only included patients who have stimulated TSH because of thyroid hormone withdrawal and did not include those who have stimulated TSH because of rh-TSH. Rh-TSH is increasingly used for preparation of RAI because of its simplicity and reduction of side effects related to hormone withdrawal [21, 22]. A separate study for the Tg kinetics under rh-TSH administration would provide more information on such patients.

Conclusion

In conclusion, shorter Tg-DT under TSH stimulation performed before initial radioiodine ablation is a significant predictive factor for ablation failure.

Conflict of Interest Hyukjin Yoon, Sung Hoon Kim, Joo Hyun O, Ye Young Seo, Yeongjoo Lee, Hyoungwoo Kim and Jiyoung Ryu declare that they have no conflict of interest.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As a retrospective study, the study was approved by the Seoul Saint Mary's Hospital IRB, and informed consent was waived.

This manuscript has not been published before, is not under consideration for publication anywhere else and has been approved by all coauthors.

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