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ORIGINAL ARTICLE

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

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Abstract
Purpose To investigate the clinical importance of serum thyroglobulin (Tg) levels just before high-dose I-131 ablation therapy (preablation Tg) for predicting therapeutic failure in patients with papillary thyroid carcinoma (PTC).
Methods Patients with PTC (n=132) undergoing total thyroidectomy followed by the first high-dose I-131 ablation therapy (HI-Rx) were included in this retrospective review. Just before HI-Rx, preablation Tg, anti-Tg antibody, and TSH were measured. The patients were followed up for a mean period of 7 months (range 6–23 months) by I-123 whole-body scans (f/u IWBS) and stimulated Tg (f/u Tg). Therapeutic failure was defined by positive f/u IWBS or f/u Tg >2 ng/ml. We classified patients into three groups according to the value of preablation Tg (group 1, <1 ng/ml; group 2, ≥1 and <10 ng/ml; group 3, ≥10 ng/ml) and compared clinical variables to therapeutic response.
Results Therapeutic failure was noted in 39 patients (29.5 %). On univariate analysis, T stage, tumor size, and preablation Tg were the statistically significant factors that could predict therapeutic failure. After multivariate analysis, preablation Tg was the only independent predictor of therapeutic failure ($P<0.001$). The therapeutic failure rate was significantly increased as the preablation Tg level increased (11.3 %, 33.3 %, and 87.5 % in groups 1, 2, and 3, respectively; $P<0.001$). Individuals with preablation Tg levels ≥10 ng/ml had 25.5 times greater chance of therapeutic failure than those with levels <10 ng/ml (95 % CI=5.43–119.60; $P<0.001$).
Conclusions A high preablation Tg level is the most significant predictor of therapeutic failure at the time of first HI-Rx in patients with PTC.

Keywords Papillary thyroid carcinoma · High-dose I-131 ablation therapy · Predictive factor · Thyroglobulin · Therapeutic failure

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Introduction

Total thyroidectomy followed by high-dose I-131 ablation therapy (HI-Rx) is a widely used treatment strategy for most patients with differentiated thyroid carcinoma (DTC) [1, 2]. HI-Rx is thought to reduce the recurrence and mortality rate in DTC by destroying microscopic residual tumor foci [3–5], and it enables early detection of recurrence by enhancing the reliability of serum thyroglobulin (Tg) and post-therapy radioiodine whole-body scans (WBSs).

Although DTC shows a relatively good response to HI-Rx, the ablation failure rate is reported from 2.3 % to 49 % [6–9]. As the result of ablation is associated with the prognosis of DTC [10], understanding of the prognostic factors that predict therapeutic response is an important clinical issue.

Measurement of serum Tg after thyroid-stimulating hormone (TSH) stimulation, i.e., stimulated Tg, is recommended to monitor the possible persistence or recurrence of tumors during follow-up [4, 11, 12]. The serum Tg level is a reliable tumor marker for DTC and has high sensitivity in detecting tumor persistence and recurrence after eliminating all noncancerous thyroid tissues [1, 13, 14]. Several studies have suggested that a high serum Tg level measured after thyroidectomy and just before HI-Rx (preablation Tg) could be a prognostic marker for predicting the recurrence or metastasis of a tumor [15–20]. However, the clinical usefulness of preablation Tg for predicting disease severity or therapeutic response is not clear because postsurgical remnants contribute to Tg production [16, 17].

We studied early clinical outcomes for papillary thyroid carcinoma (PTC) patients who received total thyroidectomy and the first HI-Rx to investigate the clinical importance of preablation Tg for predicting therapeutic failure. We also investigated potential clinical and laboratory factors such as age, gender, pathologic type, primary tumor size, bilaterality and multiplicity of tumor, dose of administered I-131, and stages of tumors and lymph nodes (LN).

Subjects and Methods

Patients

We retrospectively investigated 132 patients with PTC who were treated at our institution between June 2009 and December 2011. We included patients who met all of the following criteria: (1) total thyroidectomy and central compartment LN dissection (CND) with or without laterocervical compartment LN dissection (LND), (2) initial HI-Rx at least 2 months after operation, (3) no evidence of distant metastasis, (4) no history of other primary malignancies at the time of HI-Rx, and (5) serum anti-Tg antibody (TgAb) <100 IU/ml [21].

I-131 Ablation Therapy and Tg Measurement

Patients underwent the postoperative HI-Rx 2 to 10 months after total thyroidectomy (mean 5 months). For HI-Rx, all patients were replaced with triiodothyronine for the first 2 weeks of the treatment period, prepared by levothyroxine withdrawal for 4 weeks. According to the instructions regarding limiting exposure to environmental iodine, patients followed a low-iodine diet for 2 weeks prior to HI-Rx. On the first day of admission, serum Tg, TgAb and TSH levels were measured. Serum TSH levels were >30 μIU/ml prior to I-131 administration in all subjects. The dose for the HI-Rx was chosen according to the status of patients and the guideline of the American Thyroid Association [2]: 3.7 GBq for low-risk patients, 5.6 GBq for most intermediate-risk patients, and 6.7 GBq for patients with some intermediate- and high-risk patients. The intermediate-risk patients showing cervical LN metastases were treated with a dose of 5.6 GBq between 2008 and 2010, and the dose was raised to 6.7 GBq between 2010 and 2011 as we previously reported [22]. A post-therapy I-131 whole-body scan (RxWBS) was performed 7 to 8 days after a therapeutic dose of I-131 administration and reviewed for exclusion of those with distant metastasis.

Serum Tg and TSH levels were measured by an immunoradiometric assay (CISBio, France) with a lower detection limit of 0.2 ng/ml for serum Tg. Levels of TgAb were measured by radioimmunoassay (Brahms, Berlin, Germany).

Follow-up and Evaluation of Therapeutic Response

Serum Tg and TgAb levels were measured at the time of the follow-up diagnostic whole-body scan with 185 MBq of I-123 (f/u IWBS) to evaluate the status of ablation. Therapeutic failure was defined by positive f/u IWBS or follow-up TSH-stimulated Tg (f/u Tg) >2 ng/ml.

Data Analyses

We stratified the patients by their preablation Tg levels: <1 ng/ml (group 1), ≥1 ng/ml and <10 ng/ml (group 2), and ≥10 ng/ml (group 3) [23]. The therapeutic response was investigated against each clinical and laboratory variable, including age, gender, pathological type, stages of tumors and LN, primary tumor size, multiplicity and bilaterality of tumora, dose of administered I-131, and preablation Tg levels using chi-square or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U-test for continuous variables. Tumor and LN metastasis classifications were based on the classification system of the International Union Against Cancer and the 7th edition of the American Joint Committee on Cancer.

Multivariate analyses were done to identify significant prognostic variables of independent statistical significance in therapeutic failure. It included all variables with a P value below 0.05 in univariate analysis. Values are given as mean ± standard deviation. $P<0.05$ was considered statistically significant. All the analyses were performed using SPSS version 19.0 for Windows® (SPSS Inc., Chicago, IL, USA).

Results

Patient Characteristics

Table 1 shows the characteristics of enrolled patients. Among the 132 patients reviewed, almost 80 % of the patients were women, and almost all of the patients (97.7 %) had the

Table 1 Patients characteristics

Parameters	No. of patients
Age (years)	
Mean (range)	50±12 (22–82)
≥45	84 (63.6 %)
Male/female	27 (20.5 %)/105 (79.5 %)
Size of primary tumor (mm)	
Median (range)	10.0 (3.0–35.0)
>10 mm	54 (40.9 %)
Histology	
PTC, classical type	129 (97.7 %)
PTC, follicular variant	3 (2.3 %)
Presence of extrathyroidal extension	51 (38.7 %)
Multiplicity	
Solitary/multiple	78 (59.1 %)/54 (40.9 %)
Bilaterality	
Unilateral/bilateral	109 (82.6 %)/23 (17.4 %)
T stage	
T1	77 (58.3 %)
T2	4 (3.0 %)
T3	41 (31.1 %)
T4	10 (7.6 %)
N stage	
N0	41 (31.1 %)
N1a	73 (55.3 %)
N1b	18 (13.6 %)
Dose of administered I-131 (GBq)	
3.7	33 (25.0 %)
5.6	60 (45.5 %)
6.7	39 (29.5 %)

PTC, papillary thyroid carcinoma

classical type of PTC. The mean age of subjects was 50± 12 years (range, 22-82 years). The frequencies of tumor size greater than 10 mm, presence of multiplicity, bilaterality, extrathyroidal extension, and LN metastases were 40.9 %, 40.9 %, 17.4 %, 38.7 %, and 68.9 %, respectively. Doses of 3.7 GBq I-131 were administered to 33 patients, 5.6 GBq to 60 patients, and 6.7 GBq to 39 patients.

Therapeutic Response

RxWBS showed radioactivities in the thyroid bed in all patients. The mean time interval from the initial HI-Rx to first follow-up study was 7 months (range, 6 to 23 months). The mean value of preablation Tg and f/u Tg level were 6.3± 17.5 ng/ml (range, 0.2–136.0 ng/ml) and 2.9±10.5 ng/ml (range, 0.2–101.0 ng/ml), respectively. According to the criteria used in this study, 39 out of 132 patients (29.5 %) showed therapeutic failure. Among them, 18 showed f/u Tg >2 ng/ml with negative f/u IWBS; 15 showed f/u Tg ≤2 ng/ml and positive f/u IWBS; and 6 patients showed f/u Tg >2 ng/ml and positive f/u IWBS. Among 39 patients of therapeutic failure, 8 underwent reoperation, and the histopathology of the surgical specimens was revealed as metastases in all.

Predictive Factors for Therapeutic Failure

Univariate analyses showed that T stage, tumor size, and the preablation Tg were significantly associated with a therapeutic failure. Preablation Tg remained as the only independent factor with statistically significant impact after multivariate analysis (Table 2). Preablation Tg levels of therapeutic success and failure groups were 1.9±3.9 ng/ml and 16.9±29.3 ng/ml, respectively (mean ± SD, $P<0.001$).

Therapeutic response was significantly different according to the level of preablation Tg as presented in Fig. 1. The therapeutic failure rate was significantly increased as the preablation Tg level increased (11.3 %, 33.3 %, and 87.5 % in groups 1, 2, and 3, respectively; $P<0.001$). The therapeutic failure rate was about 55-fold higher in group 3 than in group 1 (95 % CI=10.3–294.4, $P=0.001$). When we compared therapeutic failure rates according to the preablation Tg levels below and above 10 ng/ml, patients with preablation Tg ≥10 ng/ml had 25.5 times greater chance of therapeutic failure than those with values <10 ng/ml (95 % CI=5.43–119.60; $P<0.001$).

Discussion

This retrospective study demonstrated that the serum Tg measured just before the first HI-Rx is the most predictive factor for therapeutic response. An increase in preablation Tg level in patients with PTC was associated with increased risk for therapeutic failure.

Many studies have proposed that preablation Tg has a high predictive value for tumor recurrence or metastasis [15–20]. Ruiz-Garci et al. reported that the probability of disease-free survival was 100 % in patients with TSH-stimulated preablation Tg below 23 ng/ml, whereas the probability was only 68.3 % in the patients with preablation Tg above this limit [19]. Kim et al. showed the correlation between the serum Tg levels measured at the time of immediate postoperative I-131 ablation therapy and clinical outcome. Clinical recurrence was observed in 23.1 % of patients with preablation Tg greater than 2 ng/ml, whereas recurrence was observed in 2 % of patients with preablation Tg equal to or less than 2 ng/ml [9]. However, the suggested preablation Tg level for predicting recurrence varied from 2 to 69.7 ng/ml in the previous studies [9, 15–20].

Some studies have shown the relationship between preablation Tg and successful ablation. Rosário et al. showed

Table 2 Univariate and multivariate analyses of factors predicting therapeutic failure

Variables	Therapeutic success (%) (n=93)	Therapeutic failure (%) (n=39)	Univariate	Multivariate	
			P value	*P* value	OR (95 % CI)
Age (years)					
< 45	33 (68.8)	15 (31.3)	0.843		
≥ 45	60 (71.4)	24 (28.6)			
Gender					
female	73 (69.5)	32(30.5)			
male	20 (74.1)	7 (25.9)	0.814		
T stage					
T1 + T2	64 (79.0)	17 (21.0)			
T3 + T4	29 (56.9)	22 (43.1)	0.01*	0.121	
Multiplicity					
solitary	51 (65.4)	27 (34.6)	0.174		
multiple	42 (77.8)	12 (22.2)			
Bilaterality					
unilateral	74 (69.2)	33 (30.8)			
bilateral	19 (76.0)	6 (24.0)	0.629		
N stage					
N0	31 (75.6)	10 (24.4)			
N1	62 (68.1)	29 (31.9)	0.418		
Tumor size (cm)					
≤ 1	61 (78.2)	17 (21.8)	0.021*	0.106	
>1	32 (59.3)	22 (40.7)			
Dose of administered					
I-131 (GBq)					
3.7	22 (66.7)	11 (33.3)			
5.6	42 (70.0)	18 (30.0)			
6.7	29 (74.4)	10 (25.6)	0.771		
Preablation Tg (ng/ml)					
<1	55 (88.7)	7 (11.3)	<0.001*	Reference	
1 ≤ and <10	36 (66.7)	18 (33.3)		<0.001	3.93 (1.49–10.35)
≥ 10	2 (12.5)	14 (87.5)	<0.001*	0.001	55.0 (10.28–294.35)

Preablation Tg, thyroglobulin measured just before I-131 ablation therapy; OR, odds ratio; CI, confidence interval

*$P<0.05$

a relationship between Tg level and f/u IWBS performed 6 to 12 months after ablation. A negative f/u IWBS was shown in 95 % of patients with TSH-stimulated preablation Tg levels less than 1 ng/ml, 71.8 % with preablation Tg between 1 and 10 ng/ml, and 52.6 % with preablation Tg greater than 10 ng/ml. Half of the patients with preablation Tg greater than 10 ng/ml eventually had lymph node and/or distant metastasis. In this study, ablation success was defined using f/u IWBS only [24].

Lim et al. assessed predictive factors for successful ablation using univariate and multivariate analyses. Multivariate analysis showed that preablation Tg greater than 5 ng/ml, presence of LN metastasis, and greater than 10 % of quantified cervical uptake in the RxWBS were significant predictors for ablation failure. Among these predictors, preablation Tg greater than 5 ng/ml was the most significant predictive factor for ablation failure [6]. In our retrospective study, the preablation Tg level was the only predictive factor for persistence or recurrence of PTC after the first HI-Rx (termed "therapeutic failure"), and patients with preablation Tg greater than 10 ng/ml experienced higher rates of therapeutic failure (87.5 %, $P<0.001$).

A recent meta-analysis of 3,947 patients across a broad spectrum of disease demonstrated that the preablation Tg level is a useful negative predictor of persistent and recurrent DTC. Especially the negative predictive value (NPV) was 94 % when the preablation Tg value was less than 10 ng/ml [25]. In other words, a patient with a preablation Tg level less than 10 ng/ml has only 6 % likelihood of having persistent disease. Our retrospective study also showed a relatively high NPV of preablation Tg. In the patients with less than 1 ng/ml level of preablation Tg, the therapeutic success rate was 88.7 %, and with the preablation Tg levels less than 10 ng/mLl, the

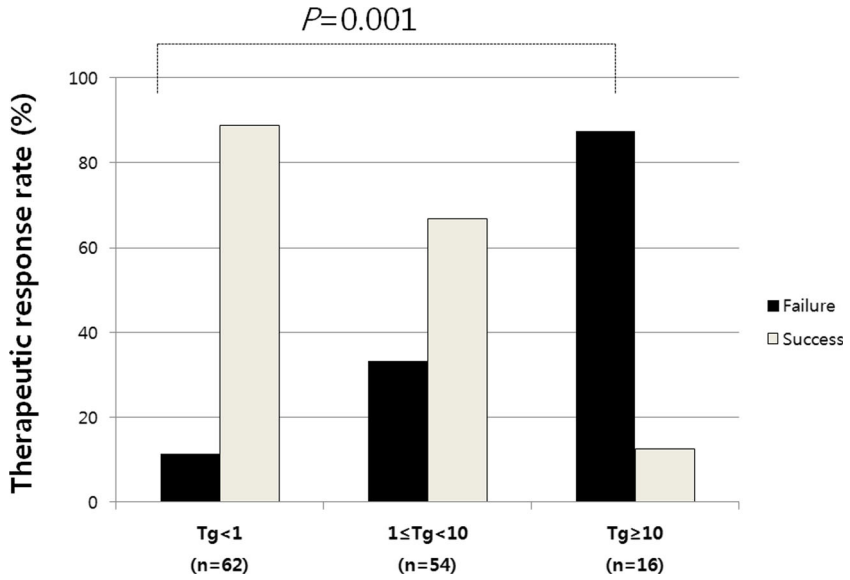

Fig. 1 Therapeutic responses according to the preablation stimulated thyroglobulin (Tg) levels. Therapeutic failure rates were significantly increased as the value of preablation Tg increased ($P<0.001$)

therapeutic success rate was 78.4 %. The positive predictive value (PPV) of the preablation Tg level was poor in the meta-analysis. It was reported to be 47 % with preablation Tg levels above 10 ng/ml. In the present study, however, the preablation Tg levels above 10 ng/ml had a relatively high PPV of 87.5 %.

This study was conducted at an institution located in the southwestern part of South Korea, where the dietary iodine content is known to be high [26, 27]. The high dietary iodine content could be associated with the high rate of therapeutic failure in this study. Some studies revealed the association between a low iodine diet and ablation therapy. Choi et al. showed that 24-h urine iodine excretion was significantly lowered after a stringent low iodine diet in Korean patients with thyroid cancer [28], and Dobrenic et al. reported that a more stringent low iodine diet might result in higher radioiodine avidity in patients undergoing I-131 ablation therapy [29]. Maurice et al. showed the percentage of patients with successful ablation was significantly high in the low iodine diet group compared with the normal diet group [30]. Hence, the success rate of I-131 ablation therapy has been shown to be less in patients with a high plasma inorganic iodide pool, although this was not statistically significant [31].

We classified patients into subgroups according to disease status based on the ATA guideline and treated them with three different doses of I-131 (3.7 GBq, 5.6 GBq, and 6.7 GBq). The discussion regarding the optimal dose for ablation is controversial. Some studies have emphasized higher ablation success rates corresponding to higher doses of radioiodine administered [21, 32, 33]. Several other studies have suggested that there were no differences in the ablation success rate between low and high dose among low-risk patients [34, 35]. There was no statistical difference in the preablation Tg level and clinical outcome among the three I-131 dose groups in our study. A prospective study with a large number of patients could help to determine the optimal dose of I-131 ablation therapy.

The definition of therapeutic failure was variable according to the authors. Lee et al. defined therapeutic failure as a detectable level of Tg >1 ng/ml with thyroid hormone suppression [8]. Kendler et al. and several other published studies defined therapeutic failure as positive f/u IWBS or f/u Tg levels more than 2 ng/ml [7, 15, 35–37]. Verburg et al. defined it as positive f/u IWBS or f/u Tg levels more than 1 ng/ml [10]. Lim et al. defined it as positive f/u IWBS or f/u Tg levels more than 1 ng/ml or additional therapy needed for thyroid cancer within the follow-up period [6]. Sawka et al. defined it as positive-stimulated Tg at follow-up by a value of more than 2 ng/ml in the absence of TgAb [38]. In this study, therapeutic failure was defined as a f/u Tg level more than 2 ng/ml or positive f/u IWBS during the follow-up period of 6 to 23 months after HI-Rx.

This study has several limitations. First, the total number of subjects was relatively small for a detailed analysis. Some of the factors that were revealed to have no significance in our study might have been underestimated. Further large-scale studies are needed. Second, the follow-up period was short. It is possible that patients who were considered to have no evidence of disease might have experienced recurrence later on. Third, iodine concentrations in serum or urine with their association with therapeutic failure were not evaluated in this study. Fourth, the definition of therapeutic failure in this article is not clear. It includes both ablation and treatment failure. Usually ablation indicates removal of remnant thyroid tissue, while treatment indicates removal of residual or recurrent tumor tissue. Although we excluded patients who had distant metastasis at the time of HI-Rx, we did not differentiate patients with remnant thyroid tissue or tumor tissue. Presence of residual tumor or regional metastasis at the time of Hi-Rx

might have an effect of increasing preablation Tg and therapeutic failure. However, differentiation of remnant thyroid tissue or tumor is not easy in practice. Therefore, we used the term 'therapeutic failure,' which includes both ablation and treatment failure. Finally, this study was retrospective in nature.

Conclusion

This study reveals that preablation Tg is an early predictor of therapeutic failure in patients with PTC who received HI-Rx after total thyroidectomy. Patients with preablation Tg levels equal to or greater than 10 ng/ml require close follow-up surveillance.

Conflict of Interest Hee Jeong Park, Geum-Cheol Jeong, Seong Young Kwon, Jung-Joon Min, Hee-Seung Bom, Ki Seong Park, Sang-Geon Cho, Sae-Ryung Kang, Jahae Kim, Ho-Chun Song, Ari Chong, and Su Woong Yoo declare that they have no conflict of interest.

Ethics Statement This study protocol was approved by the ethics committee at our hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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