Limited Clinical Value of Periablative Changes of Serum Markers in the Prediction of Biochemical Remission in Patients with Papillary Thyroid Cancer

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Abstract

Purpose Remnant thyroid ablation and 1-year stimulated thyroglobulin (sTg) measurement are recommended for those who have undergone total thyroidectomy for differentiated thyroid cancer. The serum Tg kinetics in such patients are still unclear. This study was designed to evaluate whether the periablative change in serum markers can predict biochemical remission in papillary thyroid cancer (PTC) patients.

Methods We reviewed the medical records of 185 patients who were given high-dose radioactive iodine ablation therapy from January 2006 to December 2008. Serum Tg, TSH, and anti-Tg antibody (TgAb) were measured on the day and the following 10th day of radioactive iodine administration. We defined preablative sTg as Tg-1, postablative Tg measured on the 10th day of ablation as Tg-2, and the 1-year sTg as Tg-3. Δ Tg means Tg2-Tg1. The same definition was applied to TgAb.

Results A biochemical remission defined as Tg-3 < 2 ng/ml was achieved in 144 patients. Among the patients who achieved biochemical remission, PTC recurred in six during

a median follow-up of 54 months. Tg-1 < 3.3 ng/ml ($p < 0.0001$) predicted biochemical remission. Neither the Δ Tg nor Δ TgAb was useful for predicting biochemical remission. On the evaluation of recurrence after biochemical remission, Tg-1 > 5.32 ($p < 0.0001$) and Tg-3 > 2.9 ($p = 0.01$) were proven to be statistically significant cutoff values for predicting recurrence. The Δ Tg and Δ TgAb were not able to predict recurrence.

Conclusion For the prediction of biochemical remission or recurrence after biochemical remission, preablative sTg was demonstrated to be a statistically significant serum marker. However, short-term changes in biochemical markers including Tg and TgAb around the day of ablation could not provide useful clinical information about biochemical remission or disease recurrence. In conclusion, 1-year sTg measurement cannot be omitted with short-term change.

Keywords Papillary thyroid cancer · Thyroglobulin · Biochemical remission

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Introduction

When patients receive a diagnosis of differentiated thyroid cancer (DTC), total (or near total) thyroidectomy and subsequent remnant thyroid ablation with radioactive iodine are recommended. After ablation, measurement of serum thyroglobulin (Tg) levels is an important modality for monitoring the patients. Especially serum-stimulated thyroglobulin (sTg) measurement is the best means for detecting the presence of normal and/or malignant thyroid tissue, which is the only source of Tg [1].

The American Thyroid Association (ATA) guidelines suggest that 6–12 months after total thyroidectomy and radioactive iodine remnant ablation, patients with DTC should be reevaluated in order to assess the efficacy of initial treatment

and to guide subsequent follow-up [2]. To obtain sTg, patients have to use recombinant human thyrotropin (rhTSH), which is expensive, or undergo thyroid hormone withdrawal, suffering from significant morbidity. Serum Tg levels are dependent on circulating thyrotropin (TSH) concentrations, even if tumor tissue is the source of Tg [3]. However, the specific cutoff levels of serum Tg during TSH suppression or stimulation that optimally distinguish normal residual thyroid tissue from persistent cancer are not known [2].

There have been a few studies about the prognostic value of the serum Tg value measured at a single time point or the trend of Tg on serial measurement. The serum Tg value measured at a single time point did not correlate significantly with survival in the previous studies [4, 5]. Monitoring the Tg trend plays a particular role, but only limited evidence on the prognostic and predictive significance of postablation Tg kinetics has been reported [6, 7]. In our institution, the follow-up serum chemistry was evaluated with a post-therapy iodine scan. We hypothesized that short-term changes in serum markers around the day of radioactive iodine administration could provide prognostic information and replace 1-year sTg measurement, and patients can save their efforts. This study was designed to evaluate the clinical value of periablative changes in serum markers including Tg and anti-thyroglobulin antibody (TgAb) for the prediction of successful ablation.

Materials and Methods

Definitions

Biochemical remission (BR) was defined as sTg < 2 ng/ml without serum TgAb at 1 year. Remaining patients with 1-year sTg values over 2 ng/ml were considered to have persistent disease. No clinical evidence of disease (NCED) was defined as no evidence of disease based on physical examination, neck ultrasonography (US), or neck computed tomography (CT) and any other imaging performed as a part of the clinical evaluation, performed at the end of the follow-up. Recurrence was defined as cytological or histological evidence of disease that was detected following any period of NCED.

Patients

We reviewed the medical records of 536 consecutive patients with papillary thyroid cancer (PTC) evaluated at Pusan National University Hospital who had undergone total thyroidectomy and high-dose radioactive iodine ablation between January 2006 and December 2008. Of the 536 potentially eligible patients, 330 without a record of sTg throughout their follow-up, 19 patients with inadequate TSH (TSH < 30 mU/l) on the day of sTg measurement and 2 patients with inadequate follow-up information were excluded from the study. Finally,

a total of 185 patients were enrolled. All patients were risk stratified using the 7th edition of the American Joint Committee on Cancer/Union for International Cancer Control tumor-node-metastasis staging system (AJCC/UICC TNM; stages I, II, III, and IV) and ATA risk of recurrence stratification system (low, intermediate, or high risk of recurrence) [8, 9].

Patients were given 100–200 mCi of I-131 according to the pathological status of the PTC. All patients included in the study have been receiving TSH suppressive therapy, and thyroid hormone replacement therapy was restarted on the 4th day (the next day of discharge from the hospital) of radioactive iodine administration in every patient. Patients were followed every 3–6 months during the first year and at 6–12-month intervals thereafter based on the risk and the clinical course of the disease. During the first 2 years of follow-up, at least one neck US was performed, and two or more serum Tg and TgAb values were obtained on levothyroxine suppression. Serum sTg measurement with a diagnostic whole-body scan with 3 mCi of I-131 was usually carried out 12 months after the remnant ablation to verify the absence of disease.

Tg, TgAb, and TSH Measurement

Tg, TgAb, and TSH were obtained just before radioiodine administration (day 0) and the following 10th day of ablation. Serum Tg was measured with the Tg-S radioimmunoassay (RIA) kit (B.R.A.H.M.S Tg-S RIA, Brahms AG, Berlin, Germany) having a functional sensitivity of 0.3 ng/ml. Serum TgAb was measured with the anti-Tg RIA kit (B.R.A.H.M.S anti-Tgn, Brahms AG, Berlin, Germany) with a functional sensitivity of 20 U/ml. Serum TSH was measured with the TSH kit (Siemens Healthcare Diagnostics) with a sensitivity of 0.03 uIU/ml.

The sTg was defined as a Tg value measured when TSH was > 30 mU/l. The preablation sTg was defined as Tg-1, the postablation Tg measured on the 10th day of ablation was defined as Tg-2, and 1 year sTg was defined as Tg-3. Δ sTg means Tg2-Tg1. The same definitions were applied to antiTgAb.

Statistical Analyses

To evaluate the diagnostic performance of laboratory tests, receiver-operating characteristic (ROC) curve analysis was done. The Spearman correlation test was done to evaluate the correlation between Tg-1 and Δ Tg, and Δ TgAb. The equation $y=b+a \log(x)$ was used because Tg-1 did not follow normal distribution. Logistic regression was used to analyze the relationship between biochemical remission or recurrence of papillary thyroid cancer and the following factors: Tg and Δ TgAb. The statistical analyses were performed using MedCalc®

for Windows version 12.0.4.0, and a p value less than 0.05 was regarded as significant.

Results

Clinical Characteristics

The clinical and pathological characteristics of the 185 patients are shown in Table 1. In total there were 185 patients (36 men and 149 women); the median age was 46.0 years (range 16–69 years). Median follow-up was 54 months (range 8.2–77.5 months). The median operation time to remnant ablation was 3.2 months (range 0.7–8.8 months). Patients were given 100–200 mCi of I-131 according to the pathological status of the PTC; 17 patients were treated with 100 mCi, 164 patients with 150 mCi, and 4 patients with 200 mCi. To achieve appropriate TSH levels before ablation, 177 patients underwent thyroid hormone withdrawal, and 8 patients were injected with rhTSH. The sTg was measured with a whole body scan at a median of 13.5 months (range 5.1–45.5 months) after the day of ablation.

BR was achieved in 144 patients, and among the patients with biological remission, PTC recurred in 6.

Short-Term Changes in Biochemical Markers

Preablative sTg levels were measured from 0.01 to 347.1 ng/ml. Δ Tg ranged from -50.2 to 269.49 (median 3.47 ; 95 % CI 1.5594 – 5.7656). Increasing Tg levels were observed in 146 patients, and decreasing Tg levels were observed in 39 (21.08 %).

Preablative TgAb levels were measured from 0 to 53.4 ng/ml. Δ TgAb was calculated from -26.5 to 39.4 (median 0; 95 % CI -0.4379 – 0.2936). Increasing TgAb levels were observed in 81 patients. Among the remaining 104 (56.22 %) patients, 82 showed decreasing and the remaining 22 showed maintained TgAb levels.

On the correlation test, the Δ Tg level showed a positive correlation with Tg-1 (Spearman's coefficient 0.296; $p < 0.0001$; 95 % CI 0.159–0.422). Δ TgAb ($p = 0.94$) did not show a correlation with Tg-1.

On the 10th day of ablation, serum TSH (TSH-2) was measured from 0.02 to 60 uIU/ml. The TSH-2 levels were above 30 uIU/ml in 175 patients. Among the ten patients who showed serum TSH-2 levels less than 30 uIU/ml, seven received rhTSH injections. Only one patient who received rhTSH injections showed a TSH-2 concentration above 30 uIU/ml (33 uIU/ml). With Spearman's rank correlation test, the periablative change in serum TSH and Δ Tg was not statistically correlated, with a Spearman's rho of 0.137 and p value of 0.0654.

Table 1 Clinical characteristics

Clinical characteristics	N	%
Tumor size (cm)		
<4 cm	178	96.2
≥ 4 cm	7	3.8
Extrathyroidal extension		
Absent	59	31.9
Present	126 (T4 = 2)	68.1
Lymph node metastasis		
pN0/Nx	80	43.2
pN1a	70	37.8
pN1b	35	18.9
AJCC TNM staging		
Stage I	95	51.4
Stage II	5	2.7
Stage III	69	37.3
Stage IV	16	8.6
ATA initial risk classification		
Low	25	13.5
Intermediate	158	85.4
High	2	1.1
Clinical status after initial therapy		
No evidence of disease	130	70.3
Persistent disease	55	29.7
Status at final follow-up		
No evidence of disease	159	85.9
Persistent disease	13	7.0
Recurrence	13	7.0

N number; AJCC TNM American Joint Committee on Cancer tumor-node-metastasis; ATA American Thyroid Association

Fig. 1 The ROC analysis for the prediction of biochemical remission (a) and recurrence after biochemical remission (b)

Prediction of Biochemical Remission

In the prediction of biochemical remission, Tg-1 3.3 ng/ml was determined to be a cutoff value on the ROC analysis (AUC 0.841; $p < 0.0001$) (Fig. 1). On the logistic regression analysis, $Tg-1 \leq 3.3$ ng/ml was related to achieving biochemical remission (OR 13.84; 95 % CI 6.50–29.45; $p < 0.0001$). However, none of the parameters derived from peri-ablative changes in serum markers predicted biochemical remission.

Prediction of Recurrence of Disease

Tg-1 5.3 ng/ml was determined to be a cutoff value that can predict recurrence on ROC analysis (AUC 0.866; $p < 0.0001$) (Fig. 1). On the logistic regression analysis, $TG-1 > 5.3$ ng/ml was related to recurrence (OR 36.14; 95 % CI 7.48–174.60; $p < 0.0001$). Tg-3 values > 2.9 ng/ml were also statistically significant cutoff values that could predict recurrence (OR 11.2; 95 % CI 3.33–37.68; $p = 0.0002$). Like for the prediction of successful achievement of biochemical remission, ΔsTg and $\Delta TgAb$ were not able to predict recurrence.

Discussion

This study was the first to evaluate the predictive value of preablative sTg and periablative changes in the serum Tg and anti-Tg levels in papillary thyroid cancer patients.

This study supports the view that stimulated thyroglobulin measured at the time of ablation can act as a useful predictor of biochemical remission. A study conducted by Kim et al. showed that serum Tg levels measured at the time of I-131 remnant ablation in low-risk patients with differentiated thyroid carcinoma could be correlated with serum Tg measured 6–12 months later, during thyroid hormone withdrawal, and could reliably predict persistent or recurrent disease in the earliest postoperative time period [1]. Another study suggests that, in particular, an elevated stimulated Tg level just before ablative radioiodine treatment has been shown to have a high predictive value for persistent cervical disease of distant metastasis [10, 11]. Also, Kendler et al. found that preablation Tg was the only independent predictor of ablation success with an optimal cutoff value of 18 ng/ml [12]. In agreement with earlier studies, this study showed statistical significance of the preablative serum Tg level in the prediction of biochemical remission with a cutoff value of 3.3 ng/ml.

Antibodies to thyroid antigens are mainly produced by lymphocytes infiltrating the gland and, to a lesser extent, by immune cells in cervical lymph nodes and bone marrow [13]. Anti-Tg antibody was observed in approximately 25 % of thyroid cancer patients [14] and 10 % of the general population [15]. The presence of anti-thyroglobulin antibody will falsely lower serum Tg determinations in immunometric

assays [16]. Serial serum anti-Tg antibody quantification using the same methodology may serve as an imprecise surrogate marker of residual normal thyroid tissue or tumor [17, 18]. This is supported by a study conducted by Luca Chitova et al. that demonstrated that the disappearance of thyroglobulin antibodies was statistically significantly correlated with that of thyroid tissue [18]. However, the present study failed to demonstrate a correlation of Δ anti-Tg and the prediction of biochemical remission.

Periablative change in the Tg did not successfully predict biochemical remission and disease recurrence. There might be several explanations for this. First, on the day of measuring Tg-2, ten patients did not show a high enough TSH level to stimulate remnant thyroid gland and metastatic foci. However, there was no statistical correlation between the serum TSH level and ΔTg in the present study. Therefore, this explanation may not be enough. Second, thyroid hormone replacement therapy was restarted on day 4 (the next day after discharge from the hospital) of radioactive iodine administration in every patient. We think that the serum Tg level could be affected by thyroid hormone replacement therapy. However, every patient underwent the same treatment procedure, so we think there would be no significant effect on the results of the study. Third, the Tg kinetics after RAI treatment might be different between remnant thyroid tissue and metastatic thyroid cancer. In the present study, 16 patients were in stage IV. According to the AJCC cancer staging manual, stage IV papillary thyroid cancer can be subdivided into IVA, IVB, and IVC. In the present study, all 16 patients with stage IV were stage IVA because of the N staging (N1b), and there was no distant metastasis at the time of ablation. We carried out additional statistical analysis with a subgroup according to metastatic lymph node status. Among the total eligible 185 patients, lymph node metastases were found in 112 patients. Sixty-eight of 112 patients (60.71 %) showed biochemical remission after ablation. Among the patients with N0 stage, 62 of 73 (84.93 %) showed biochemical remission. Although there was significant difference between the biochemical remission frequencies of the N staging classification on the chi-square test ($p = 0.0008$), we did not include this information in the Results section, because this study was originally designed to focus on the changes in serum markers.

There are several study limitations. After radioactive iodine ablation, stimulated Tg was not measured in every patient, and even measured with a relatively wide range of intervals, because of the diagnostic workup process and the physician's clinical decisions. The ΔTg , calculated from the change in stimulated serum thyroglobulin from the day of radioactive iodine administration to the following 10th day, failed to predict biochemical remission in the study. Although authors used post-ablative serum markers obtained at 10 days after the therapeutic dose administration, published data supporting this time interval are lacking. The total ablation process is

not fully understood, and the serum Tg kinetics are still unclear [19]. One study compared the post-therapy whole-body scan conducted on day 3 and 7 of ablation in the detection of the lung and bone metastases [20]. However, it lacks laboratory data analysis. In another study about the kinetics of radioiodinated Tg, published in 1982, the maximum amount of Tg appeared in the circulation at between 2 and 8 days and disappeared at 3.1 ± 0.396 days of the half-life [21]. The study investigated a limited number of patients and showed a relatively wide range of the maximal serum Tg levels a day after the administration of radioactive iodine, so the results are insufficient for generalization. However, further study with intervals shorter or longer than 10 days, not affected by individual differences in the kinetics of serum thyroglobulin, is anticipated to have positive results.

Conclusion

In the prediction of biochemical remission or recurrence after biologic remission, sTg was demonstrated to be a statistically significant serum parameter. However, peri-ablative changes in serum markers including Tg and TgAb could not provide useful clinical information about biochemical remission or disease recurrence. In conclusion, 1-year sTg measurement cannot be omitted with peri-ablative changes of serum markers with 10-day intervals, especially in patients with high preablative Tg levels.

Disclosure Statement The authors declare that no conflicts of interest exist.

Conflict of Interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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