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Prognostic significance of changes in serum thyroglobulin antibody levels of pre- and post-total thyroidectomy in thyroglobulin antibody-positive papillary thyroid carcinoma patients

Yukiko Tsushima^{1), 2)}, Akira Miyauchi²⁾, Yasuhiro Ito²⁾, Takumi Kudo³⁾, Hiroo Masuoka²⁾, Tomonori Yabuta²⁾, Mitsuhiro Fukushima²⁾, Minoru Kihara²⁾, Takuya Higashiyama²⁾, Yuuki Takamura²⁾, Kaoru Kobayashi²⁾, Akihiro Miya²⁾, Toyone Kikumori¹⁾, Tsuneo Imai¹⁾ and Tetsuya Kiuchi⁴⁾

¹⁾Department of Breast and Endocrine Surgery, Nagoya University, Nagoya 466-8550, Japan

²⁾Department of Surgery, Kuma Hospital, Kobe 650-0011, Japan

³⁾Department of Internal Medicine, Kuma Hospital, Kobe 650-0011, Japan

⁴⁾Department of Transplantation, Nagoya University, Nagoya 466-8550, Japan

Abstract. Although postoperative serum thyroglobulin (Tg) is a prognostic indicator for papillary thyroid carcinoma (PTC), it is unreliable when Tg antibody (TgAb) is positive. We evaluated the prognostic significance of changes in serum TgAb levels of pre- and post-total thyroidectomy in TgAb-positive PTC patients. We reviewed our medical charts of 225 TgAb-positive PTC patients in whom TgAb levels were measured before and 1–2 years after total thyroidectomy, performed between April 2002 and March 2007. We divided them into 3 groups based on changes in TgAb levels. Postoperative serum TgAb levels decreased by $\geq 50\%$ in 181 patients (80.4%) (Group 1), by $< 50\%$ in 22 patients (9.8%) (Group 2), and increased in 22 patients (9.8%) (Group 3). During the follow-up, 3 patients died of the disease and 14 patients had recurrences. All 3 patients who died of PTC were seen only in Groups 2 and 3. Groups 2 and 3 showed similar prognostic outcomes, thus were analyzed together as Group 2+3. Group 1 had significantly better lymph node recurrence-free survival and distant recurrence-free survival than Group 2+3 (96.9% vs. 90.5%, $p < 0.001$, and 98.9% vs. 90.1%, $p = 0.004$, respectively at 5 years). Multivariate analyses on prognostic factors revealed that classification to Group 2+3 was the strongest indicator for poor prognosis. The present results suggest that changes in TgAb levels following total thyroidectomy can be an important dynamic prognostic factor of PTC patients. Prospective periodical measurements of TgAb are necessary to confirm these findings.

Key words: Thyroglobulin antibody, Papillary thyroid carcinoma, Prognostic factor

THE SERUM THYROGLOBULIN (Tg) level after total thyroidectomy for differentiated thyroid carcinoma (DTC) is very important whether carcinoma was biochemically cured or remains persistent. Recently, we reported that short serum Tg-doubling time after total thyroidectomy significantly predicted a poor cause-specific survival of patients with papillary thyroid carcinoma (PTC) [1], suggesting that elevation of Tg levels straightforwardly indicates the growth of

PTC recurrence. However, the presence of TgAb interferes with Tg immunometric assay and makes the Tg levels unreliable [2, 3]. The prevalence of TgAb in PTC patients is reported to be 25%, higher than that (10%) in the normal population [2, 3], and follow-up by Tg levels is not appropriate for these patients.

Recently, Chung *et al.* reported that DTC patients with detectable TgAb after total thyroidectomy and radioactive iodine (RAI) ablation showed a higher recurrence rate than those with undetectable TgAb [4]. Kim WG *et al.* studied a similar group of patients and reported that those with decreases in serum TgAb levels by more than 50% within 6–12 months after ablation had significantly lower recurrence rate than those who showed decreases by less than 50% or increases

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Correspondence to: Yukiko Tsushima, M.D., Department of Breast and Endocrine Surgery, Nagoya University, 65 Tsurumai-cho, Syowa-ku, Nagoya 466-8550, Japan.

E-mail: yukukotsushima@med.nagoya-u.ac.jp

in TgAb levels [5]. These studies suggest that persistently elevated TgAb is a marker of persistent disease or recurrence of DTC.

In Japan, RAI ablation is not widely adopted because the capacity of RAI facilities is limited because of legal restrictions as well as because most PTCs, except for high-risk cases, show an excellent prognosis, even without RAI ablation. In the current clinical practice, we need to differentiate between high-risk and low-risk patients for indication of RAI ablation. In TgAb-positive PTC patients, postoperative changes in serum TgAb levels might give prognostic information. In this retrospective study, we investigated the prognostic value of changes in pre- and postoperative TgAb levels in TgAb-positive PTC patients who underwent total thyroidectomy.

Patients and Methods

Patients

From our medical charts, we selected 225 TgAb-positive PTC patients who underwent total thyroidectomy between April 2002 and March 2007 in Kuma Hospital and whose TgAb level was measured before and 1–2 years after surgery. The patients with distant metastases at the time of surgery and those having thyroid carcinomas other than PTC were excluded from this series. They consisted of 204 females and 21 males with a mean age of 48.7 ± 13.9 years (range; 12–79 years).

Preoperative evaluation

All patients underwent ultrasonography to evaluate carcinoma size (T size) and lymph node metastasis (N). Tumors showing significant extrathyroid extension (Ex2) were classified as T4a or T4b in the TNM classification [6].

Surgery

All patients underwent total thyroidectomy with central compartment dissection. Prophylactic or therapeutic, unilateral or bilateral modified neck dissection was also performed in 146 patients. Mediastinal dissection was also performed in 2 patients.

Postoperative follow-up

Thyroid ablation with 30mCi or more of RAI was performed only in 7 patients. In all patients, serum TSH levels were suppressed or set at low normal. In all patients, the serum TgAb levels were measured before

and 1–2 years after surgery. For TgAb measurements, the TgAb radioimmunoassay (Roche Diagnostics GmbH) was employed. Imaging studies included once-a-year ultrasonography examinations of the neck and chest roentgenography or computed tomography as well as other studies if indicated. In this study, we regarded patients whose recurrent foci were detected on imaging studies as having recurrence. The mean follow-up periods were 5.4 ± 1.1 years (range, 1.45–8.53 years).

Statistical analyses

Data are presented as mean \pm SD. Fisher's exact test and χ^2 test was used to compare variables. The Kaplan-Meier method and log-rank test were adopted to analyze time-dependent variables. Cox-hazard regression model was employed on multivariate analysis. These analyses were performed with StatFlex Ver.6.0: Artech Co., Ltd., Osaka. A p -value <0.05 was regarded as significant. This study was approved by the Ethics Committee of Kuma Hospital.

Results

Postoperative serum TgAb levels decreased by $\geq 50\%$ in 181 patients (80.4%) and these patients were categorized as Group 1. Postoperative serum TgAb levels decreased by $<50\%$ in 22 patients (9.8%) (Group 2) and increased in 22 patients (9.8%) (Group 3). Table 1 summarizes the backgrounds and clinicopathological features of the patients. The incidence of $T \geq 4$ cm, clinically detectable lateral node metastasis (N1b), Stage IVA [6], and performance of RAI ablation were significantly higher in Group 2 and Group 3 than Group 1.

During the follow-up, 12 patients had lymph node recurrence, 8 had distant metastases, and 6 of them had both; 3 patients died of the disease and 14 patients had recurrence. Lymph node recurrence were noted in 5 (2.8%), 4 (18.2%), and 3 patients (13.6%) in these groups, respectively. Distant recurrences were observed in 3 (1.7%), 3 (13.6%), and 2 patients (9.1%) in Group 1, Group 2, and Group 3, respectively. No patients in Group 1 died of the disease, while 1 patient (4.5%) in Group 2 and 2 patients (9.1%) in Group 3 died of PTC (Table 2). Since there were no significant differences in the ratios of distant recurrence and lymph node recurrence in Groups 2 patients and Group 3 patients ($p = 0.63$, and $p = 0.68$, respectively), these 44 patients were analyzed together as Group 2+3.

Table 1 Backgrounds and clinicopathological features of patients

	Total	Group 1	Group 2	Group 3	<i>p</i> values
Number of Patients	225	181	22	22	
Age (years)	48.7 ± 11.8	48.7 ± 13.9	46.8 ± 15.5	51.0 ± 16.0	0.61
Follow-up period (years)	5.4 ± 1.1	5.4 ± 1.4	5.3 ± 1.8	5.3 ± 1.4	0.84
Male	21 (9.3%)	14 (7.7%)	6 (27.3%)	1 (4.5%)	0.17
Age ≥55 years	89 (39.6%)	70 (38.7%)	8 (36.4%)	11 (50.0%)	0.52
T ≥4 cm	31 (13.8%)	18 (9.9%)	8 (36.4%)	5 (22.7%)	<0.01
Ex2	38 (16.9%)	29 (16.0%)	5 (22.7%)	4 (18.2%)	0.51
N1b	96 (42.7%)	70 (38.7%)	11 (50.0%)	15 (68.2%)	0.01
Stage IVA	64 (28.4%)	47 (26.0%)	8 (36.4%)	9 (40.9%)	0.09
RAI ablation	7 (3.1%)	3 (1.7%)	2 (9.1%)	3 (13.6%)	<0.01

Group 1: Patients with TgAb that decreased more than 50% 1 to 2 years after surgery.

Group 2: Patients with TgAb that decreased less than 50% 1 to 2 years after surgery.

Group 3: Patients with TgAb that increased at 2 years after surgery.

T ≥4cm: tumor 4 cm or larger.

Ex2: significant extrathyroid extension.

N1b: clinically detectable lateral node metastasis.

Table 2 Clinical outcomes of patients in Groups 1, 2 and 3

	Group 1	Group 2	Group 3	<i>p</i> values
Number of patients	181 (80.4%)	22 (9.8%)	22 (9.8%)	
Lymph node recurrence	5 (2.7%)	4 (15.9%)	3 (13.6%)	<0.01
Distant metastases	3 (1.7%)	3 (11.4%)	2 (9.1%)	<0.01
Disease-specific death	0 (0.0%)	1 (6.8%)	2 (9.1%)	<0.01

Group 1: Patients with TgAb that decreased more than 50% 1 to 2 years after surgery.

Group 2: Patients with TgAb that decreased less than 50% 1 to 2 years after surgery.

Group 3: Patients with TgAb that increased at 2 years after surgery.

We then investigated the lymph node and distant recurrence-free survivals of patients in Groups 1 and 2+3. The 5-year lymph node recurrence-free survival rate of Group 2+3 patients was 90.5%, which was significantly lower ($p < 0.001$) than that of Group 1 patients (96.9%) (Fig. 1). Similarly, the 5-year distant recurrence-free survival rate of Group 2 patients (90.1%) was poorer ($p = 0.004$) than that of Group 1 patients (98.9%) (Fig. 2). Their mean lymph node and distant recurrence periods were 3.57 ± 1.63 years (range, 1.53–6.41 years) and 3.59 ± 2.31 years (range, 1.53–7.94 years), respectively.

Table 3 indicates the results of univariate and multivariate analyses on prognostic factors for lymph node recurrence. Being Group 2+3, cN1b, and Age ≥55 years were significant factors for nodal recurrence on univariate analysis and multivariate analysis. The hazard ratio was highest at 4.86 for Group 2+3.

Table 4 shows the results of univariate and multivariate analyses on prognostic factors for distant recurrence. Univariate analysis revealed that being in Group 2+3, Ex2, and T ≥4 cm were significant factors for distant recurrence. However, multivariate analysis revealed that the factors, including being in Group 2+3 and Ex2, remained significant. The hazard ratio was highest at 4.62 for Group 2+3.

Among the 64 patients in Stage IVA, 17 patients (26.6%) remained in the high-risk category Group 2+3, while the remaining 47 patients (73.4%) were moved to the low-risk category Group 1. Among the 161 patients in Stage I–III, 134 patients (83.2%) remained in Group 1, while the remaining 27 patients (16.8%) were moved to Group 2+3. These results indicate that risk stratification depending on the changes in serum TgAb values might be more appropriate compared with TNM Staging.

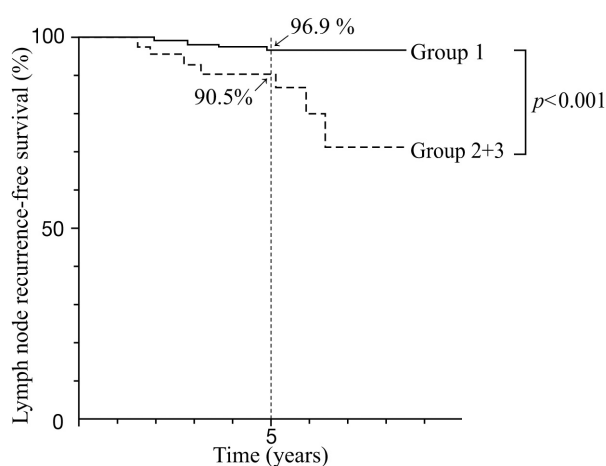


Fig. 1 Kaplan-Meier curves for lymph node recurrence in Groups 1 and 2+3 patients

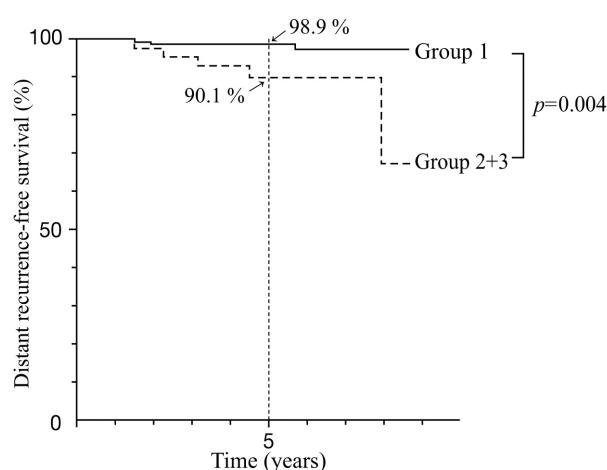


Fig. 2 Kaplan-Meier curves for distant recurrence in Groups 1 and 2+3 patients

Table 3 Univariate and multivariate analyses on prognostic factors for lymph node recurrence

	Univariate analysis		Multivariate analysis	
	Log-rank statistics	<i>p</i> values	HR (95% CI)	<i>p</i> values
Male	1.02	0.312	1.45 (0.31–6.77)	0.635
Age ≥ 55 years	4.71	0.030	3.45 (1.02–11.6)	0.045
T ≥ 4 cm	1.82	0.136	1.25 (0.31–4.89)	0.747
cN1b	5.45	0.019	3.46 (0.92–13.0)	0.065
Ex2	0.63	0.428	1.22 (0.26–5.64)	0.797
Group 2+3	12.90	<0.001	4.86 (1.47–16.0)	0.009

HR, hazard ratio; CI, confidence interval

Table 4 Univariate and multivariate analyses on prognostic factors for distant recurrence

	Univariate analysis		Multivariate analysis	
	Log-rank statistics	<i>p</i> values	HR (95% CI)	<i>p</i> values
Male	3.07	0.080	2.82 (0.51–15.4)	0.230
Age ≥ 55 years	2.68	0.102	2.85 (0.64–12.6)	0.166
T ≥ 4 cm	4.90	0.021	1.95 (0.41–9.18)	0.397
cN1b	5.32	0.060	2.88 (0.54–15.2)	0.212
Ex2	6.25	0.013	4.29 (0.94–19.5)	0.058
Group 2+3	8.01	<0.001	4.62 (1.02–20.9)	0.047

HR, hazard ratio; CI, confidence interval

Discussion

In this study, we demonstrated that in TgAb-positive PTC patients, 1) patients with postoperative TgAb values more than half of the preoperative values had poorer prognosis than those whose postoperative TgAb was less than half of the preoperative values, and 2) high postoperative TgAb was an independent prognostic factor on multivariate analysis.

Previous studies showed that detectable TgAb levels at the time of RAI ablation and persistent TgAb concentration 6–12 months after RAI ablation can predict DTC recurrence [4, 5]. Chiovato *et al.* reported that complete ablation of thyroid tissue by thyroidectomy and RAI treatment resulted in the disappearance of antibodies to thyroid peroxidase, thyroglobulin, and the TSH receptor [7]. They reported that the median disappearance time was 6.3 years for thyroid peroxi-

dase antibody and 3.0 years for TgAb. Gorges *et al.* showed that the median half-life of TgAb in treated DTC patients was 10 weeks [8]. These results suggest that the disappearance of antibodies indicates extinction of the antigen including carcinoma tissue by surgery and RAI ablation.

However, in our series, as many as 80.4% of patients showed that postoperative TgAb level was less than half of the preoperative TgAb level, despite that most patients did not undergo RAI ablation. We reported that serum TSH receptor antibody values in patients with Graves' disease decreased more rapidly after total thyroidectomy than after subtotal thyroidectomy [9], indicating that changes in thyroid antibodies concentration depend on the quantity of tissue containing their antigens. We also reported that serum Tg levels became undetectable in all 22 patients with medullary thyroid carcinoma after total thyroidectomy [10]. With our surgical technique, this indicates that residual normal thyroid tissue after total thyroidectomy is minimal. Furthermore, these findings may justify the significant decrease in TgAb level in a large proportion of patients after total thyroidectomy without RAI ablation.

In Western countries, most patients with DTC undergo RAI ablation after total thyroidectomy. However, recent papers reported that there was no significant improvement in mortality or disease-specific survival in patients with low-risk DTC treated with RAI [11, 12]. Therefore, we should appropriately select high risk patients for RAI treatment to whom it is beneficial. Tuttle *et al.* suggested risk-adapted selection of treatments, which reflect the balance between the aggressiveness of the disease and the effectiveness as well as possible complications of the treatments. They proposed ongoing risk stratification judged 2 years after initial therapy and reported that this may aid in more appropriate selection

of treatments and follow-up studies [13, 14]. Castagna *et al.* [15] also reported that delayed risk stratification judged 8–12 months after the initial treatment was more accurate than the risk classification of the guidelines by the American Thyroid Association [16].

Currently, high-risk patients are selected based on pathological findings and classical risk factors such as TNM stage. We reported that in patients with TgAb-negative PTC, Tg-doubling time after total thyroidectomy had a much stronger prognostic significance than classical risk factors [1]. In the present study, we demonstrated that persistent TgAb level after total thyroidectomy had a strong prognostic impact in TgAb-positive patients. The use of these dynamic seromarkers for analyses could be an alternative approach to efficiently discriminate high-risk patients from others.

In summary, we demonstrated that in TgAb-positive PTC patients, changes in pre- and postoperative TgAb levels significantly predicted patients' prognosis. Further studies on periodical measurements of TgAb are necessary to confirm the prognostic value of postoperative changes in TgAb values in TgAb-positive PTC patients.

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Disclosure

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