Changes in serum thyroglobulin antibody levels as a dynamic prognostic factor for early-phase recurrence of thyroglobulin antibody-positive papillary thyroid carcinoma after total thyroidectomy

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Abstract. We demonstrated previously that dynamic prognostic markers such as the thyroglobulin (Tg)-doubling time in thyroglobulin antibody (TgAb)-negative papillary thyroid carcinoma (PTC) and changes in pre- and postoperative TgAb levels in TgAb-positive PTC patients more keenly reflect patients' prognosis than conventional static prognostic factors. Here we investigated periodic changes in TgAb levels in 513 TgAb-positive PTC patients who underwent total thyroidectomy. The TgAb levels at 1 year after surgery decreased to < 50% of the preoperative values in 407 (79%) patients, and the remaining 106 (21%) patients showed no decrease in TgAb. In 426 patients, TgAb was also measured more than 1 year after surgery. Compared with their TgAb levels 1 year after surgery, 59 patients (14%) showed an increase in TgAb levels of > 20% during the follow-up. The postoperative Tg levels at 1 year after surgery remained positive in 44 (9%) patients despite their TgAb positivity. To date (median follow-up period 35 months), 12 of the 426 patients (3%) showed PTC recurrence, and 11 of these patients showed either or both a TgAb elevation later than 1 year after surgery and postoperative Tg positivity. Although further studies with longer follow-ups are necessary, we can conclude that changes in postoperative TgAb levels may be usable as a surrogate tumor marker for TgAb-positive PTC patients after total thyroidectomy.

Key words: TgAb, Papillary thyroid carcinoma, Prognosis

PAPILLARY THYROID CARCINOMA (PTC) is the most common malignancy arising from normal follicular cells. To date, several prognostic factors of PTC evaluated pre-, intra-, or postoperatively have been identified: old age, large tumor size, significant extrathyroid extension, node metastasis, and distant metastasis at the diagnosis [1]. All of these are static factors evaluated at a certain time preoperatively, surgically or pathologically. In contrast, Miyauchi et al. showed that a dynamic prognostic factor—the change in serum thyroglobulin (Tg) levels after total thyroidectomy for thyroglobulin antibody (TgAb)-negative PTC—more significantly predicted the prognosis of patients than did conventional static prognostic factors. They reported that a Tg-doubling time (Tg-DT) shorter than 2 years was the strongest predictor of carcinoma-related death [2]. However, the Tg-DT is not usable for TgAb-positive patients, because Tg values are not reliable in these patients.

To date, a few groups including ours studied whether TgAb in TgAb-positive patients was usable as a surrogate marker of carcinoma recurrence [3–5]. We found that a decrease by < 50% or an increase in serum TgAb levels 2 years after surgery compared with the preoperative levels independently affected the disease-free survival (DFS) of PTC patients [3]. However, TgAb levels were measured with an old method in our previous study. In the present study, as a next step, we investigated whether the postoperative changes in TgAb levels...
measured with a new technique also serve as a dynamic prognostic factor in TgAb-positive PTC patients.

**Patients and Methods**

**Patients**

Between April 2008 and December 2012, 3234 patients underwent at least a total thyroidectomy with central compartment dissection for initial treatment of PTC. Of these patients, 513 (16%) were TgAb-positive, who enrolled in our study. The cutoff value between TgAb-positive and -negative was 28.0 U/mL. The patients were 29 males and 484 females, and their median age was 51 years (13 to 89 years). Of 513 patients, 173 underwent also uni- or bilateral modified radical neck dissection prophylactically or therapeutically. Three patients also underwent an upper mediastinal compartment dissection. Patients who had other thyroid malignancies such as follicular, medullary, or anaplastic carcinoma, those who had distant metastasis at surgery, and those whose postoperative follow-up periods were less than 1 year were excluded from the series.

**Evaluation of changes in TgAb and Tg**

Serum Tg and TgAb were measured by the electrochemiluminescent immunoassay (ECLIA) method (Roche Diagnostic, Mannheim, Germany). In our evaluation of TgAb and Tg levels, we determined whether each patient’s postoperative TgAb level decreased compared with his or her pre-operative TgAb level, whether the TgAb level increased later than 1 year compared with the TgAb level at 1 year after surgery, and whether the postoperative Tg level became negative (less than 0.5 ng/mL) at 1 year after surgery.

We defined a postoperative TgAb decrease as when the level had decreased by ≥50% compared with the pre-operative TgAb level. The TgAb level at later than 1 year was classified as a TgAb increase when it increased by >20% compared with the TgAb level at 1 year after surgery. The TgAb values of one particular patient (patient No. 1 in Tables 4 and 5) were always higher than the upper limit both pre- and post-operatively, and we regarded her TgAb as not decreased after surgery and as increased at later than 1 year after surgery.

**Postoperative follow-up**

Only 19 patients underwent radioactive iodine (RAI) ablation (30 mCi) within 1 year after surgery. As previously described [3], we followed the patients by conducting imaging studies such as ultrasonography, chest roentgenography or computed tomography (CT) as well as others if indicated. We regarded patients as having a recurrence only when recurrent foci were detected on imaging studies, and suspicious foci were evaluated cytologically or histopathologically whenever appropriate. The median follow-up period was 35 months (12–72 months).

**Statistical analysis**

The chi-square test and Student’s t-test were used to compare valuables. *P*-values < 0.05 were considered significant. All analyses were performed using StatFlex ver. 6.0 software.

**Results**

**Change in pre- and postoperative TgAb levels**

The postoperative TgAb levels of 407 patients (79%) decreased by ≥50% compared with their preoperative TgAb levels. Table 1 summarizes the relationship between the changes in pre- and postoperative TgAb levels and the patients’ clinicopathological features. The patients with clinical node metastasis (*p*=0.0003)

| Table 1 Relationship between change in pre-and postoperative TgAb levels and clinicopathological features |
|-------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Change in pre-and postoperative TgAb | p-value |
| Gender (F/M) | Not decreased (n=106) | Decreased (n=407) |
| Age (years) | 50.8 ±16.0 (13–89) | 49.9 ±15.5 (13–86) |
| Tumor size (mm) | 18.6 ±12.3 (3–85) | 18.3 ±10.3 (3–80) |
| Clinical node metastasis (1/0) | 52 (49%) | 123 (30%) |
| Extrathyroid extension (+/-) | 79 (75%) | 314 (77%) |
| Recurrence (y/n) | 6 (6%) | 401 (98%) |

N.S., not significant
TgAb in papillary thyroid cancer

and those showing carcinoma recurrence ($p=0.0213$) were significantly less likely to show a postoperative decrease of TgAb.

**Tg levels 1 year after surgery**

Although all of the patients were positive for TgAb, the Tg levels of 44 patients (9%) remained positive even at 1 year after surgery. Table 2 shows the relationship between Tg values 1 year after surgery and carcinoma recurrence. Patients with positive Tg at 1 year after surgery were more significantly likely to show carcinoma recurrence ($p=0.0019$).

**Change in postoperative TgAb levels**

TgAb was also measured later than 1 year after surgery in 426 patients. Forty-one (10%) of these patients were Tg-positive at 1 year after surgery, and 59 patients (14%) showed an increase in TgAb levels later than 1 year compared to their TgAb levels at 1 year after surgery. Table 3 summarizes the relationship between postoperative TgAb increases later than 1 year and other TgAb and Tg variables. A TgAb increase later than 1 year was significantly inversely related to decreased postoperative TgAb ($p<0.0001$), but was not linked to postoperative Tg positivity.

**Tg and TgAb profiles of patients showing carcinoma recurrence**

To date, 12 of the 426 patients (3%) showed carcinoma recurrence. Table 4 indicates the TgAb levels (pre-, postoperative and later than 1 year after surgery) and Tg levels 1 year after surgery, and Table 5 provides the profiles of these patients. Nine of these 12 patients showed a TgAb increase later than 1 year after surgery. More specifically, 9 of these 12 patients showed a TgAb increase later than 1 year after surgery. More specifically, 9 of these 12 patients showed a TgAb increase later than 1 year after surgery.
after surgery, and the postoperative Tg remained positive in 4 of the 12 patients. Eleven of these patients (all patients except for case No. 6) had either or both of these two characteristics. None of the patients have died of PTC to date.

**Discussion**

In this study, we showed that in TgAb-positive PTC, (1) patients with a postoperative TgAb level that was decreased by <50% compared to their preoperative level were less likely to show recurrence, and (2) all except for one patient who showed recurrence in the early postoperative phase showed either or both a TgAb increase later than 1 year after surgery and postoperative Tg positivity.

Tsushima et al. demonstrated that the lack of a decrease or increase of postoperative TgAb was an independent and stronger prognostic factor for DFS than conventional static prognostic factors such as tumor size, extrathyroid extension, large tumor size, and patient age [3]. Similar to the Tg-DT findings reported by Miyauchi et al. [2], this result suggested that dynamic markers more intensely reflect patient prognosis than static factors regardless of TgAb positivity. In 2008, the assay technique for TgAb changed from radioimmunoassay to ECLIA, and although the TgAb assay used for our patient series differed from that used by Tsushima et al., our findings are consistent with theirs.

Changes in the quantity of the tissues with antigens should bring changes in the serum levels of antibodies. We showed that TSH-receptor antibodies decreased more rapidly in patients with Graves’ disease who underwent total thyroidectomy than in those who underwent a subtotal thyroidectomy [7]. Thus, changes in serum TgAb levels in TgAb-positive patients following total thyroidectomy may reflect the changes in the antigen volume in residual thyroid tissue or metastatic PTC tissue. In our present patient series, RAI to ablate possible residual thyroid tissue was performed in only 19 patients. However, we previously showed that serum Tg was undetectable in all 22 patients who underwent total thyroidectomy for medullary thyroid carcinoma [8]. Therefore, with our surgical technique, the remnant thyroid tissue of patients who undergo total thyroidectomy is minimal, although most of the patients in the present study did not undergo RAI ablation. As a result, the TgAb value decreased by ≥50% in 79% of the patients, and we therefore tentatively set the cutoff at 50% as in our previous study [3].

We observed that TgAb later than 1 year after surgery was increased in eight of the 12 patients (67%) showing recurrence, but the increase was not always large, and we set the tentative cutoff at 20% to determine the TgAb increase at least at present. Based on these data, we suggest that, although the periodic changes in TgAb should be less sensitive than those in the Tg of TgAb-negative PTC patients, careful periodic examinations can be helpful to predict carcinoma recurrence in the early phase, and we propose that postoperative changes in TgAb can be used as a surrogate tumor marker. In our series, Tg was detected in 44 patients 1 year after surgery despite their TgAb-

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**Table 5** Profiles of the 12 patients with recurrence

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Initial tumor stagea</th>
<th>Pre-and postoperative TgAb</th>
<th>Later than 1 year</th>
<th>Post-operative Tg</th>
<th>Time and lesions of initial recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>F</td>
<td>IVA</td>
<td>Not decreased</td>
<td>Increasedb</td>
<td>Positive</td>
<td>20M Lymph node</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>II</td>
<td>Not decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>32M Lymph node</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>F</td>
<td>II</td>
<td>Not decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>34M Lymph node</td>
</tr>
<tr>
<td>4</td>
<td>89</td>
<td>F</td>
<td>II</td>
<td>Not decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>17M Lymph node</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>F</td>
<td>IVA</td>
<td>Not decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>22M Lung</td>
</tr>
<tr>
<td>6</td>
<td>79</td>
<td>F</td>
<td>IVA</td>
<td>Not decreased</td>
<td>Not increased</td>
<td>Negative</td>
<td>16M Lymph node</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>F</td>
<td>IVA</td>
<td>Decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>23M Subcutaneous tissue</td>
</tr>
<tr>
<td>8</td>
<td>73</td>
<td>F</td>
<td>IVA</td>
<td>Decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>44M Lymph node</td>
</tr>
<tr>
<td>9</td>
<td>69</td>
<td>F</td>
<td>IVA</td>
<td>Decreased</td>
<td>Increased</td>
<td>Negative</td>
<td>20M Lung</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>F</td>
<td>I</td>
<td>Decreased</td>
<td>Not increased</td>
<td>Positive</td>
<td>37M Lymph node</td>
</tr>
<tr>
<td>11</td>
<td>26</td>
<td>F</td>
<td>I</td>
<td>Decreased</td>
<td>Not increased</td>
<td>Positive</td>
<td>28M Lymph node</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>F</td>
<td>I</td>
<td>Decreased</td>
<td>Not increased</td>
<td>Positive</td>
<td>38M Lymph node</td>
</tr>
</tbody>
</table>

aBased on the UICC classification, 7th ed. [6]. bTgAb values were always higher than the upper limit.
positive status, indicating that these patients had persistent disease. It is thus reasonable that recurrences would be detected at high incidence in such patients on imaging studies during follow-up.

The TgAb level might be influenced by the quantity, antigenicity, and viability of remnant carcinoma lesions. Therefore, TgAb levels would be expected to vary among individuals. It might thus be better to use the change rate in the TgAb level than specific TgAb levels to evaluate the disease condition of TgAb-positive PTC patients and to predict patient prognosis. In this regard, our study design is in sharp contrast to that of another study regarding the same issue, by Hsieh et al. [9].

Our study has some limitations. Since our hospital used the ECLIA method to measure TgAb levels in 2008, we had to enroll patients who underwent surgery after that time. The follow-up periods were thus generally short (median about 3 years). In addition, this was a retrospective study and not all patients who showed TgAb elevation or Tg positivity underwent timely testing for carcinoma recurrence. If immediate examinations at the time of TgAb elevation had been performed, recurrences may have been found in more patients.

In summary, we demonstrated that postoperative changes in TgAb can be a surrogate tumor marker for TgAb-positive PTC patients after total thyroidectomy, and we observed that periodic TgAb and Tg measurements are helpful to understand the disease conditions of these patients. Further studies are necessary with longer follow-ups to expand our knowledge about the significance of changes in TgAb and Tg levels in TgAb-positive PTC patients.

References