

Longitudinal Change of Postoperative Serum Anti-thyroglobulin Antibody Levels in Patients Without Total Thyroidectomy and Remnant Ablation

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Abstract

Background: There is little information regarding postoperative thyroglobulin antibody (TgAb) changes in patients without a total thyroidectomy and ablation. This study aimed to analyze the longitudinal change of TgAb levels in patients with remnant thyroid.

Methods: The study group were patients who had undergone a non-total thyroidectomy for a thyroid tumor from 1996 to 2018. The median follow-up period was 3.5 years (1–7.5 years). Eligible patients had a combined serum Tg and TgAb measurement at least three times biannually. We excluded patients with thyroid dysfunction at the initial diagnosis or with papillary carcinoma who had persistent or any recurrence of disease.

Results: A total of 222 patients were enrolled. In the preoperative analysis, 42 (30%) patients had positive TgAb values, and 98 were negative (70%). Seventeen years after the operation, a TgAb value over 1000 IU/ml was not seen. The positive TgAb ratio was stable for 12 years (20%–30%); however, its positivity gradually increased from 13 years onward to 53.8%. The number of patients with consistently negative and positive TgAb values was 151 (68.0%) and 48 (21.6%), respectively. The number of patients with a mixture of positive and negative TgAb values was 10 (4.5%). The number of patients who changed from positive to negative values was six (2.7%) and, inversely, seven (3.2%).

Conclusions: We found positivity of TgAb after surgery gradually increases over about 10 years in patients with normal remnant thyroid. We should measure both serum Tg and TgAb values concurrently for the patients with remnant thyroid tissue throughout.

Introduction

Papillary thyroid carcinoma is the most common thyroid and endocrine carcinoma, and it has a generally favorable prognosis. Surgical resection has been strongly recommended as first-line treatment; however, the recommended surgical procedure has suffered changes. In the 2009 version of the American Thyroid Association (ATA) guideline for thyroid nodule, total or nearly total thyroidectomy including postoperative radioiodine therapy was recommended for all differentiated thyroid carcinomas except those with a tumor size < 1 cm. In the latest ATA guideline (2), total or nearly total thyroidectomy with postoperative radioiodine is strongly recommended to patients classified as high risk (tumor size > 4 cm, extrathyroidal infiltration, or clinical lymph node involvement (cN1) or (M1)). For patients with thyroid cancer > 1 cm and < 4 cm without extrathyroidal extension and clinical evidence of lymph node metastases (cN0), the initial surgical procedure can be a bilateral (nearly total or total thyroidectomy) or unilateral procedure (lobectomy). For patients with thyroid cancer < 1 cm without extrathyroidal extension and cN0, the initial surgical procedure should be a thyroid lobectomy. Thus, total thyroidectomy becomes a less frequent procedure.

In active surveillance, serum thyroglobulin (Tg) and anti-thyroglobulin antibody (TgAb) are strongly recommended for patients with total thyroidectomy and radioiodine therapy (2). Surgical resection and

isotopic ablation eliminate almost all thyroid tissue; therefore, TgAb should spontaneously disappear within 3 years after treatment in non-recurrent thyroid cancer (3). However, it remains unclear how TgAb fluctuates after surgical treatment without radioiodine therapy in patients with remnant thyroid. This study determined the change in TgAb levels after surgical treatment in patients with thyroid disease. Furthermore, we elucidated the relationship between TgAb and clinical characteristics.

Materials And Methods

The study group consisted of patients who had undergone non-total thyroidectomy for thyroid tumor and were followed in our hospital from 1996 to 2018. Eligible patients had a combined measurement of serum Tg and TgAb at least three times biannually. We excluded patients with thyroid dysfunction and/or thyroid medical treatment (anti-thyroid drug or thyroid hormone) at the initial diagnosis. Furthermore, patients with papillary carcinoma who had residual tumor burden during the operation and any disease recurrence during follow-up were excluded.

Our surgical strategy for papillary thyroid carcinoma is lobectomy for a tumor smaller than 2 cm without infiltration to adjacent organs such as the trachea or esophagus and distant metastasis. Modified radical neck dissection, including central neck dissection (perithyroidal and paratracheal), was performed, except in patients with incidentally small papillary carcinoma. We do not routinely provide radioiodine as adjuvant therapy for patients without total thyroidectomy; however, thyrotropin (TSH) suppression therapy was given with thyroxine (T4) during the disease as adjuvant therapy after surgery. Surveillance included serum FT4, TSH, Tg, and TgAb values for all patients every 6 months. Neck palpation every 6 months and chest X-rays and cervical sonography once a year were performed after the operation for cancer patients. Serum TSH and FT4 levels were measured by chemiluminescent enzyme immunoassay (Fuji Rebio, Tokyo, JAPAN) with a normal range of 0.4–6.0 IU/ml and 0.8–1.6 ng/dl, respectively. Tg and TgAb were measured by electrochemiluminescent immunoassay (SRL, Tokyo, Japan). Values below 33.7 ng/ml and 28 IU/ml, respectively, were considered normal.

The Mann–Whitney U test, Spearman’s rank-order correlation, the Kaplan–Meier method, and Cox’s proportional hazard model were used. A *P*-value < 0.05 was considered significant. All statistical analyses were performed with EZR statistical software (Saitama Medical Center and Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0) (3).

Results

Patient characteristics

The characteristics of the patients enrolled in this study are shown in Table 1. A total of 222 patients were enrolled: 175 were women (78.8%) and 47 were men (21.2%). The median age was 52 years, with a range of 23 to 91. The histological findings for the resected specimens were 209 papillary carcinomas (94.1%), 5 adenomas, 5 multinodular goiters, and 3 follicular carcinomas. All papillary carcinoma patients had

lymph node dissection and thyroxin administration for postoperative TSH suppression during follow-up. The median follow-up period was 3.5 years (1–7.5 years).

Table 1
Characteristics of enrolled patients

Characteristic	Value
Gender ^b	
Male	47 (21.2)
Female	175 (78.8)
Age ^a (year)	52 (23–91)
Histology	
Papillary carcinoma ^b	209 (94.1)
Adenoma	5
Multinodular goiter	5
Follicular carcinoma	3
Measurement follow-up period ^a (Years)	3.5 (1–7.5)
Operation year ^a	2011 (1996–2018)
^a Parenthesis indicates range. ^b n(%).	

TgAb analysis during surveillance

1) Positive perioperative TgAb levels (Fig. 1a and 1b)

The perioperative Tg levels combined with TgAb were obtained from 140 of 222 eligible patients. A total of 82 patients had combined Tg and TgAb measurement values from the middle of the surveillance period. A total of 42 (30%) patients had positive TgAb values, and 98 were negative (70%). The distribution of TgAb values is shown in Fig. 1b. The maximum perioperative TgAb value was 3681 IU/ml.

2) The plot of the TgAb value in surveillance (Fig. 2)

The highest TgAb value was under 600 IU/ml during the entire surveillance period. Seventeen years after the operation, a TgAb value over 1000 IU/ml was not seen. However, the approximation straight line showed an extremely moderate increase in the long term after the operation ($R^2 = 0.0019$).

3) The change in the positivity of the TgAb and Tg ratio during surveillance (Fig. 3a and 3b)

The positivity ratio of Tg was almost stable during surveillance after the removal of the thyroid tumors. The positivity ratio of TgAb was almost stable within 12 years (20–30%); however, its positivity gradually increased from 13 years onward. The positivity rate of TgAb was 53.8% in 20 years after the operation. Regardless of serum TgAb changes, the postoperative serum Tg was almost stable in analyzed patients (Fig. 3b).

4) Pattern changes of the TgAb value during surveillance (Table 2)

The number of patients with consistently negative TgAb values during the course was 151 (68.0%), and this was the majority. The number of patients with consistently positive TgAb was 48 (21.6%), the second majority. Of 199 patients (89.6%), there were no cross-changes between positive and negative TgAb values during course surveillance.

The number of patients with a mixture of positive and negative TgAb values was 10 (4.5%). The number of patients turning to positive from negative was six (2.7%), and those turning to negative value were seven (3.2%). There was no significant difference in age at operation, gender, and the period from operation between groups according to TgAb pattern changes.

Table 2
The patterns of changes of serum TgAb during course

Pattern of changes in anti-TgAb	n (%)	Age at operation*	Male/female ratio	Period from operation (years)*
Consistently positive	48 (21.6)	48 (18–84)	1:5	8.25 (1–24.5)
Turning to positive	6 (2.7)	32 (16–32)	1:5	11.25 (2.5–14)
Mixture of negative or positive	10 (4.5)	47 (25–60)	1:4	9 (3–20)
Turning to negative	7 (3.2)	51 (18–57)	2:5	7 (2–16.5)
Consistently negative	151 (68.0)	53.5 (23–54)	32:119	8 (1–23.5)
TgAb, thyroglobulin antibody				
* The parenthesis indicates the range.				

Discussion

Thyroglobulin is synthesized and secreted into the lumen of the thyroid follicle and is bound to iodine and maintained as a thyroid hormone precursor. The production of Tg possesses pathological status, as benign, hyperplasia, and malignant tumors (4). Tg is the sole protein produced by thyrocytes; therefore, measurement of serum Tg is commonly performed for differentiated thyroid cancer (DTC). Valuable and reliable monitoring of serum Tg is performed for post-total-thyroidectomy cases of differentiated thyroid cancer with radioiodine ablation. Based on a meta-analysis on the utility of measuring Tg before 2013, it

was determined that Tg measurement has a very high negative predictive value but a low positive predictive value for monitoring DTC patients (5).

The timing of serum Tg measurements is very important in clinical cases. Routine preoperative measurement of serum Tg and/or TgAb is not recommended in the ATA guideline for the management of thyroid nodules (2). In a cross-sectional analysis of 1770 patients with perioperative anti-Tg antibody status data in the National Thyroid Cancer Treatment Cooperative Study, serum anti-Tg antibody status was not significantly associated with the stage of the disease or with disease-free or overall survival on multivariate analyses (6). After a median follow-up of 5 years (2.5–22 years), serum Tg levels were undetectable (1 ng/ml) in 274 of 290 patients without radioiodine ablation (RAI) (95%) and 492 of 495 controls with RAI (99%). In the subset of 78 patients without RAI, undetectable Tg levels (0.2 ng/ml) were found in 79% after 5 years (7). During 6.5 years of observation (78 ± 43.5 months) of 167 patients with lobectomy, serum Tg was 12.1 ± 14.8 ng/mL. Of 52 patients with Hashimoto's thyroiditis, 38% had positive TgAb with titers of 438 ± 528 IU/mL. During the first 2 years of follow-up, Tg declined ≥ 1 ng/mL in 42% of patients (by 5.1 ± 3.7 ng/mL), remained stable in 22%, and increased in 36% (by 4.9 ± 5.7 ng/mL). In patients with recurrence followed for more than 2 years, there was a rise in Tg in three cases, Tg was stable in two cases, and in one, TgAb decreased despite metastatic lymph nodes. Basal Tg and Tg dynamics did not predict disease recurrence (8). Park et al. reported that in 208 patients with low-risk PTC who underwent lobectomy without hormone replacement, serum Tg levels gradually increased after lobectomy in patients with and without recurrences, with no significant differences (9). Thus, measurement of serum Tg after lobectomy with a thyroid residue remains controversial. The ATA guideline recommends periodic serum Tg measurements with thyroid hormone therapy during the follow-up of patients with DTC who have undergone less than total thyroidectomy and patients who have had a total thyroidectomy but not RAI ablation (2).

Tg measurements are severely limited by the presence of Tg antibodies (TgAb), which can result in underestimation of Tg concentrations by commonly used non-equilibrium immunometric assays (IMA) (10). False-negative results are a significant problem since persistent or recurrent disease is treatable by surgery and/or radioiodine therapy. The comparison of measuring serum Tg with radioimmunoassay and an immunometric assay revealed discordance in Tg values under conditions of TgAb.

Radioimmunoassay had little TgAb interference compared to that of immunometric assay (11). TgAb and/or thyroid peroxidase (TPO)Ab is found in autoimmune thyroid disease. In 16,533 healthy volunteers, TgAb were positive in 10.4% and TPOAb in 11.3%; positive antibodies were more prevalent in women than men and increased with age. TPOAb were significantly associated with hypo- or hyperthyroidism, but TgAb were not (12). Of the 4,046 patients with goiter, 671 had TgAb, while 3,375 were negative. There were 535 (79.7%) patients with PTC in the TgAb-positive group and 2,154 (63.8%) with PTC in the TgAb-negative group. The prevalence of PTC was significantly higher in TgAb-positive patients than in TgAb-negative patients (13). Our result of consistently positive TgAb values of 21.6% and consistently negative TgAb values of 68% was similar to other reports.

TgAb has been reported to disappear within 3 years in DTC patients with RAI ablation after total thyroidectomy during 10.1 years of follow-up (14, 15). However, postoperative patients with residual normal thyroid as an antigen might have TgAb after operation even in the absence of TgAb in the preoperative and early after surgery. In our results, the number of patients with a mixture of positive and negative TgAb values was 10 (4.5%). The number of patients turning to positive from negative was six (2.7%) and those turning to negative were seven (3.2%). We found that the transition of TgAb after surgery occurred in 10.4% of patients with remnant normal thyroid. Nevertheless, there are few reports about transitions of TgAb after surgery. In our results, the ratio of positivity of TgAb was almost stable for 12 years (70–80%); however, positivity gradually increased from 13 years onward. The positivity rate of TgAb was 53.8% at 20 years after surgery.

Conclusion

We found the transit of TgAb after operation occur in 10.4% of patients with remnant normal thyroid. Furthermore, its positivity of TgAb after surgery gradually increased up to 53.8% over about 10 years. Continuingly, we should measure both serum Tg and TgAb values concurrently for the patients with remnant thyroid tissue.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from the enrolled patients. This study protocol was reviewed and approved by the Kawasaki Medical School Ethics Committee (No. 3169-1).

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

Authors' contributions

KT was a major contributor in writing the manuscript. The other authors as TM, SK, AS, MS, RO, WS, EK, YK and YY contributed to the collection and analysis of data. All authors read and approved the final manuscript.

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Disclosure of Conflict of Interest

All authors declare no conflict of interest.

References

1. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009; 19: 1167-1214.
2. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2016; 26: 1-133.
3. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 2013; 48: 452-458. doi: 10.1038/bmt.2012.244. Epub 2012 Dec 3.
4. Tanaka K, Sonoo H, Yamamoto Y, Udagawa K, Kunisue H, Arime I, Yamamoto S, Kurebayashi J, Shimozuma K. Changes of expression level of the differentiation markers in papillary thyroid carcinoma under thyrotropin suppression therapy in vivo immunohistochemical detection of thyroglobulin, thyroid peroxidase, and thyrotropin receptor. *J Surg Oncol*. 2000; 75: 108-116.
5. Giovanella L, Treglia G, Sadeghi R, Trimboli P, Ceriani L, Verburg FA. Unstimulated highly sensitive thyroglobulin in follow-up of differentiated thyroid cancer patients; a meta-analysis. *J Clin Endocrinol Metab* 2014; 99: 440-447.
6. McLeod DS, Cooper DS, Ladenson PW, Ain KB, Brierley JD, Fein HG, Haugen BR, Jonklaas J, Magner J, Ross DS, Skarulis MC, Steward DL, Maxon HR, Sherman SI, The National Thyroid Cancer Treatment Cooperative Study Group; for the National Thyroid Cancer Treatment Cooperative Study Group. Prognosis of differentiated thyroid cancer in relation to serum thyrotropin and thyroglobulin antibody status at time of diagnosis. *Thyroid*. 2014; 24: 35-42.
7. Durante C, Montesano T, Attard M, Torlontano M, Monzani F, Costante G, Meringolo D, Ferdeghini M, Tumino S, Lamartina L, Paciaroni A, Massa M, Giacomelli L, Ronga G, Filetti S, PTC Study Group. Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: Is there a role for serum thyroglobulin measurement? *J Clin Endocrinol Metab*. 2012; 97: 2748-2753.

8. Ritter A, Mizrachi A, Bachar G, Vainer I, Shimon I, Hirsch D, Diker-Cohen T, Duskin-Bitan H, Robenshtok E. Detecting recurrence following lobectomy for thyroid cancer: Role of thyroglobulin and thyroglobulin antibodies. *J Clin Endocrinol Metab.* 2020; 105: e2145-e2151.
9. Park S, Jeon MJ, Oh HS, Lee YM, Sung TY, Han M, Han JM, Kim TY, Chung KW, Kim WB, Shong YK, Kim WG. Changes in serum thyroglobulin levels after lobectomy in patients with low-risk papillary thyroid cancer. *Thyroid.* 2018; 28: 997-1003.
10. Spencer CA. Challenges of serum thyroglobulin (Tg) measurement in the presence of Tg autoantibodies. *J Clin Endocrinol Metab.* 2004; 89: 3702-3704.
11. Crane MS, Strachan MW, Toft AD, Beckett GJ. Discordance in thyroglobulin measurements by radioimmunoassay and immunometric assay: A useful means of identifying thyroglobulin assay interference. *Ann Clin Biochem.* 2013; 50: 421-432.
12. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE, Serum TSH, T4, and thyroid antibodies in the united states population (1988-1994): National health and nutrition examination survey (Nhanes III). *J Clin Endocrinol Metab.* 2002; 87: 489-499.
13. Jia X, Pang P, Wang L, Zhao L, Jiang L, Song Y, Fan X, Wang Y, Zhao S, Ba J, Yang G, Wang X, Gu W, Zang L, Pei Y, Du J, Mu Y, Lyu Z. Clinical analysis of preoperative anti-thyroglobulin antibody in papillary thyroid cancer between 2011 and 2015 in Beijing, China: A retrospective study. *Front Endocrinol.* 2020; 11: article 452.
14. G6rges R, Maniecki M, Jentzen W, Sheu SN, Mann K, Bockisch A, Janssen OE. Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy. *Eur J Endocrinol.* 2005; 153: 49-55.
15. Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, Grasso L, Pinchera A. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med.* 2003; 139: 346-351.

Figures

Fig. 1a

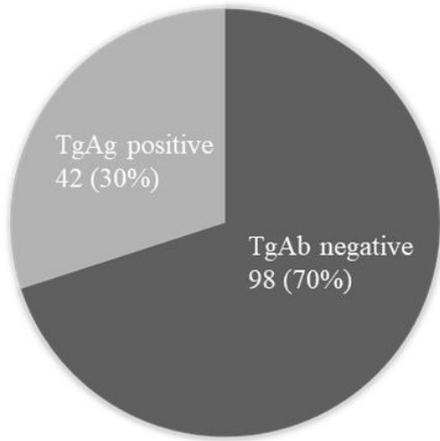
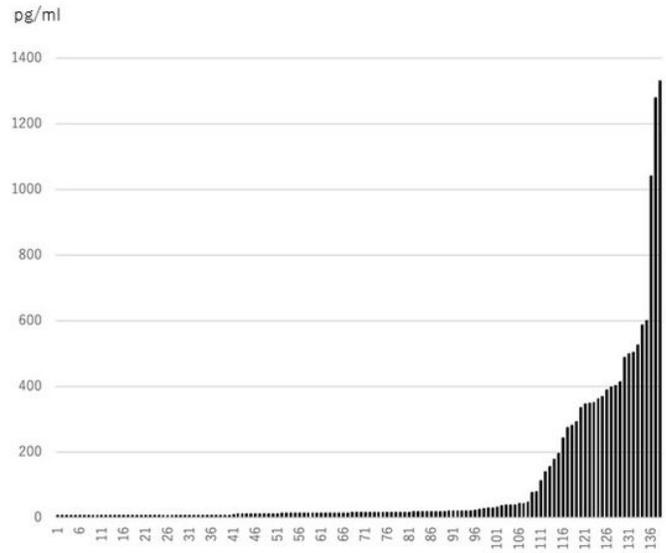


Fig. 1b



TgAb 3681 IU/ml is not shown.

Figure 1

1a. Preoperative presence of serum thyroglobulin antibody (TgAb); 42 patients (30%) had higher TgAb serum values (upper limit; 28 IU/ml), and 98 (70%) had TgAb within normal range. 1b. Plot of preoperative thyroglobulin antibody (TgAb) value of each patient. The highest TgAb value 3681 IU/ml is not shown.

Fig. 2

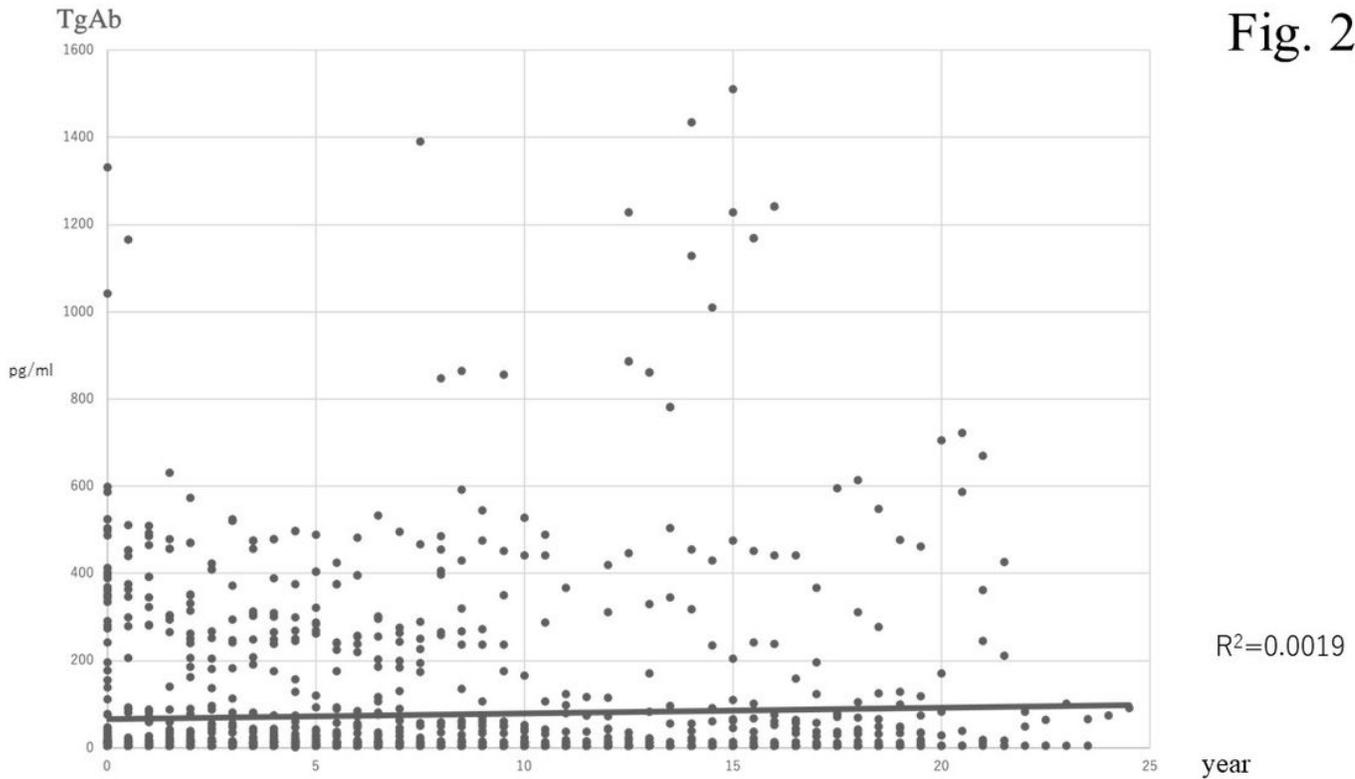


Figure 2

Plot of thyroglobulin antibody (TgAb) value during follow-up. A value of 3681 IU/ml at preoperative, four values of 4000 IU/ml within 2 years after operation are not shown in Fig. 2. Seventeen years after surgery, the TgAb value over 1000 IU/ml was not seen. However, the approximation straight line showed an extremely moderate increase in the long term after surgery ($R^2 = 0.0019$).

Fig. 3

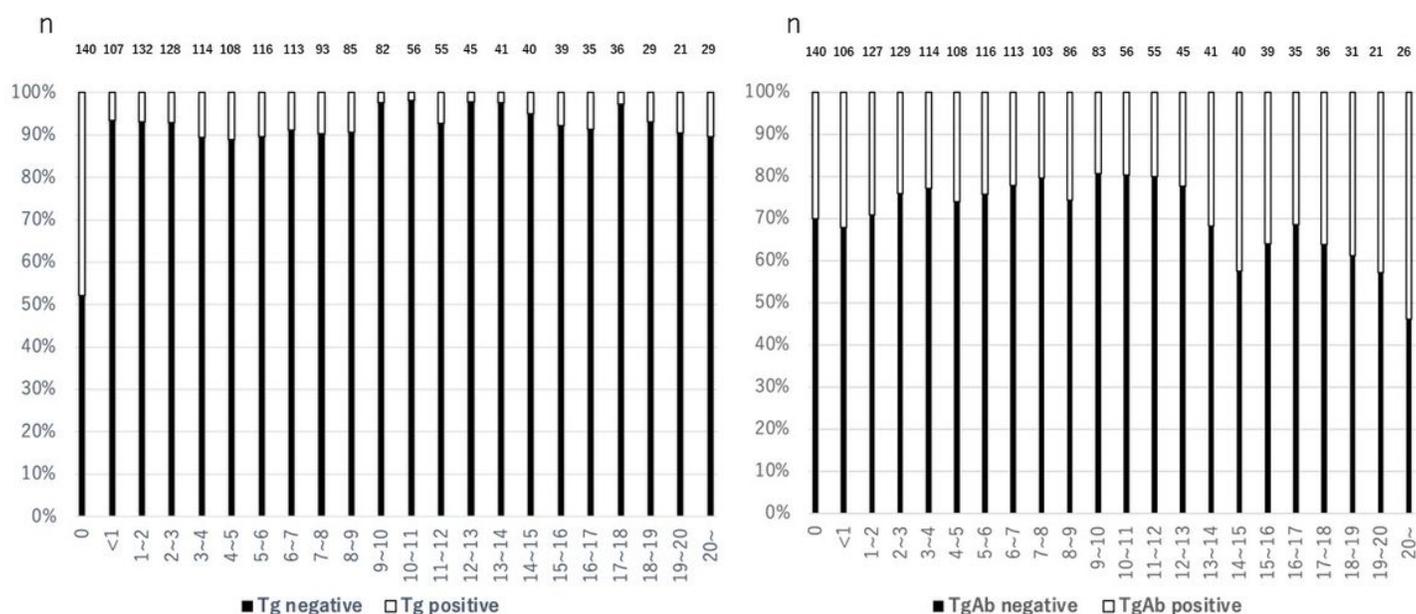


Figure 3

3a. Ratio of presence and absence of thyroglobulin antibody (TgAb) during follow-up. The ratio of positivity of TgAb was almost stable for 12 years (20%–30%); however, its positivity gradually increased from 13 years onward. 3b. Ratio of the presence and absence of thyroglobulin (Tg) during follow-up. The serum Tg value was stable during follow-up except during the preoperative period. The negative rate of Tg value transitioned about 90% during surveillance in spite of minor changes of thyroglobulin antibody.