〈Regular Article〉

Longitudinal change of postoperative serum anti-thyroglobulin antibody levels in patients without total thyroidectomy and remnant ablation

Katsuhiro TANAKA, Yuna FUKUMA, Tsuyoshi MIKAMI, Azusa JYO,
Ryohei OGATA, Yoshikazu KOIKE, Tsunehisa NOMURA, Yutaka YAMAMOTO

Department of Breast and Thyroid Surgery, Kawasaki Medical School

ABSTRACT **Backgroud:** There is little information regarding postoperative anti-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 papillary thyroid carcinoma from 1996 to 2018. The median follow-up period of measurement serum Tg and Tg Ab 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 209 patients were enrolled. In the preoperative analysis, 41 (31%) patients had positive TgAb values, and 91 were negative (69%). Seventeen years after the operation, a TgAb value over 800 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 45.5%. The number of patients with consistently negative and positive TgAb values was 140 (67.0%) and 47 (22.5%), respectively. The number of patients with a mixture of positive and negative TgAb values was 10 (4.8%). The number of patients who changed from positive to negative values was six (2.9%) and, inversely, six (3.9%).

Conclusions: We found positivity of TgAb after surgery gradually increases up to 45.5% over about 10 years in patients with normal remnant thyroid. We might continue to measure both serum Tg and TgAb values concurrently for the patients with remnant thyroid tissue throughout.

doi：10.11482/KMJ-E202248201 *(Accepted on November 28, 2022)*

Key words：Thyroglobulin, Anti-thyroglobulin antibody, Non-total thyroidectomy, Postoperative, Thyroid tumor

Corresponding author
Katsuhiro Tanaka
Department of Breast and Thyroid Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan

Phone : 81 86 462 1111
Fax : 81 86 462 1199
E-mail: tanakaka@med.kawasaki-m.ac.jp

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 papillary thyroid carcinoma 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 according to the recommendation of Japanese clinical treatment[4]. 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. TSH suppression level was controlled nearly or under the lower limination of normal range of TSH. 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 lU/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). Informed consent was obtained from the enrolled patients. This study protocol was reviewed and approved by the Kawasaki Medical School Ethics Committee (No. 3169-3).

RESULTS

Patient characteristics

The characteristics of the patients enrolled in this study are shown in Table 1. A total of 209 patients were enrolled: 169 were women (80.9%) and 40 were men (19.1%). The median age was 52 years, with a range of 23 to 91. 149 patients (71.3%) were classified as stage I and 58 patients (27.8%) were classified as stage II according to 2016 UICC classification. All papillary carcinoma patients except eight patients had lymph node dissection. Cetral lymph node dissection underwent for 67 patients (32.1%) and lateral cervical lymph node dissection for 134 patients (64.1%). Among 201 patients who underwent cervical lymp node dissection, 132 patients (65.7%) had lymph node metastases. The median period of clinical surveillance was 10 years (3-24.5 years). The

Table 1

Gender	male	40(19.1%)
	female	169(80.9%)
Age * (year)		52(23-91)
stage classification **	I	149(71.3%)
	II	58(27.8%)
	III	2(0.9%)
	no dissection	8(3.8%)
nodal dissection	central	67(32.1%)
	lateral	134(64.1%)
pN ***	N0	69(34.3%)
	N1	132(65.7%)
Follow-up Period of Measurement of serum Tg and Tg Ab * (year)		3.5(1-7.5)
Follow-up Period of clinical surveillance * (year)		10(3-24.5)

・The parenthesis indicates the range. Other parentheses indicate percentage.
・** According to UICC classification, 2016 version
・*** except unknow cases due to no dissection

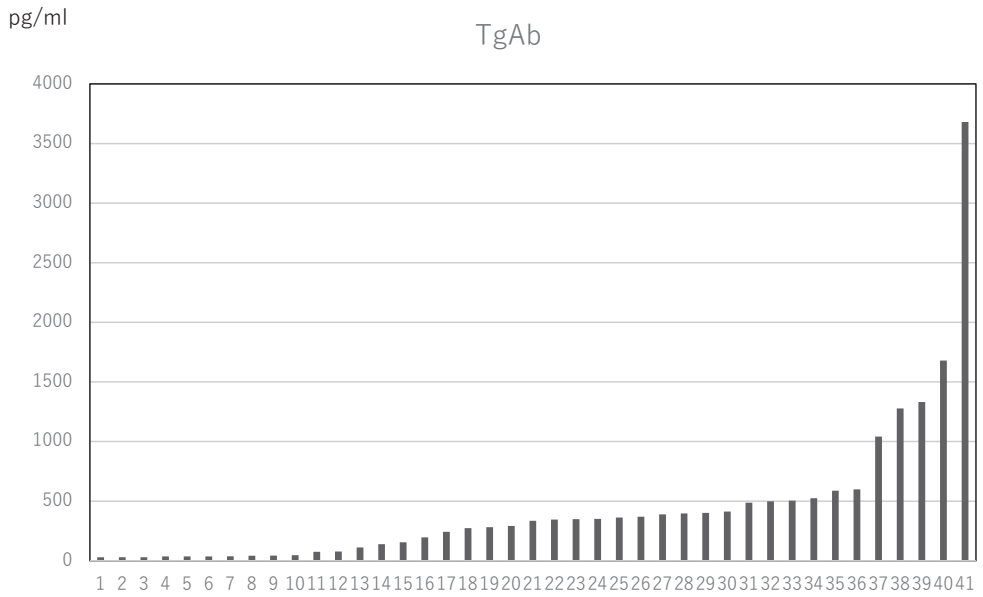

Fig. 1. Plot of preoperative anti-thyroglobulin antibody (TgAb) value of patients with positive value.

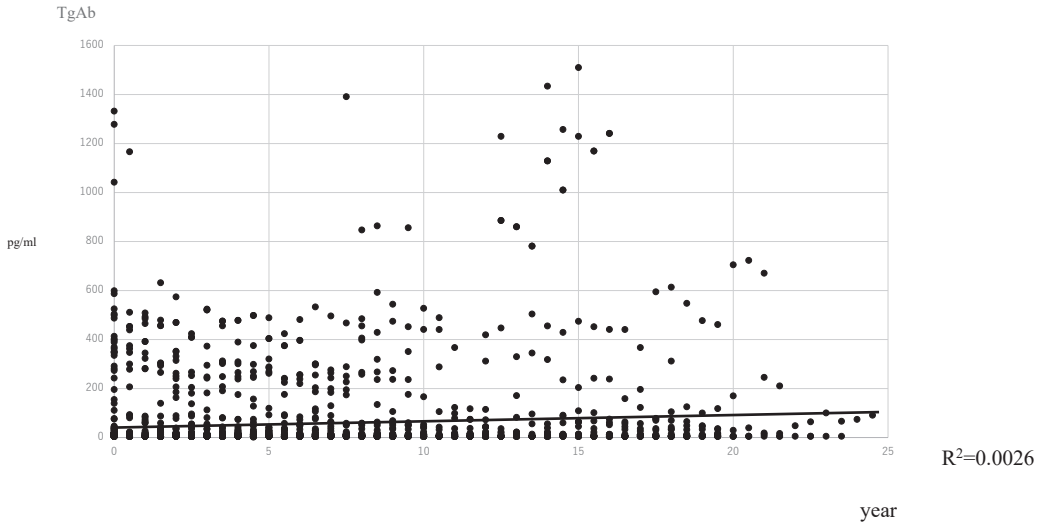

Fig. 2 Plot of anti-thyroglobulin antibody (TgAb) value during follow-up. A value of 3681 IU/ml at preoperative, four values of 4000 IU/ml within 2 years after operation are not shown in Fig. 2. Seventeen years after surgery, the TgAb value over 1000 IU/ml was not seen. However, the approximation straight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

median follow-up period of measurement of serum Tg and Tg Ab was 3.5 years (1-7.5 years).

TgAb analysis during surveillance

1) Positive perioperative TgAb levels (Fig. 1)

The perioperative Tg levels combined with TgAb were obtained from 132 of 209 eligible patients. A total of 77 patients had combined Tg and TgAb measurement values from the middle of the surveillance period. A total of 41 (31%) patients had positive TgAb values, and 91 were negative (69%). The distribution of perioperative positive TgAb values is shown in Fig 1. 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 1600 IU/ml during the entire surveillance period. Seventeen years after the operation, a TgAb value over 800 IU/ml was not seen. However, the approximation straight line showed an extremely moderate increase in the long term after the operation ($R^2 = 0.0026$).

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

The positive ratio of Tg was almost stable during surveillance after the removal of the thyroid tumors. The positive ratio of TgAb was almost stable within 12 years (20-30%); however, that positivity tended to increase from 14 years onward 25.4% in 0~13 years to 38.3% over 14 years after operation. The highest positive rate of TgAb was 45.5% over 20 years after the operation. Regardless of serum TgAb changes, the postoperative serum Tg value 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 140 (67.0%), and this was the majority. The number of patients with consistently positive TgAb was 47 (22.5%), the second majority. Of 187 patients (89.5%), there were no cross-changes between positive and negative TgAb values during course surveillance.

The number of patients with a mixture of positive

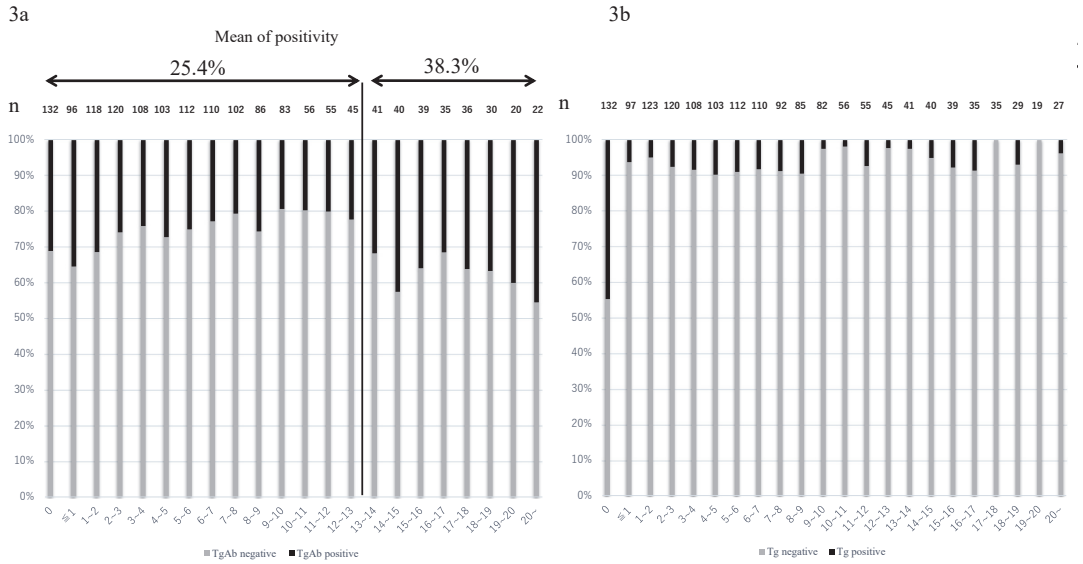

Fig. 3a. Ratio of presence and absence of anti-thyroglobulin antibody (TgAb) during follow-up. The ratio of positivity of TgAb was almost stable for 12 years (20%-30%); however, its positivity gradually increased from 13 years onward.

Fig. 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 anti-thyroglobulin antibody.

Table 2

Pattern of Changes of Anti-thyroglobulin antibody	No. of patients	Age At Operation *	Male：Female	Period from operation (year) *
Consistently positive	47(22.5)	48(18-84)	7：47	8(1-24.5)
Turning to positive	6(2.9)	32(16-32)	1：5	11.25(2.5-14)
Mixture of negative or positive	10(4.8)	47(25-60)	1：4	9(3-20)
Turning to negative	6(2.9)	50(18-55)	1：5	6(2-16.5)
Consistently Negative	140(67.0)	53(23-53)	28：112	9(1-23.5)

* The parenthesis indicates the range. Other parentheses indicate percentage.

and negative TgAb values was 10 (4.8%). The number of patients turning to positive from negative was six (2.9%), and those turning to negative value were six (2.9%). There was no significant difference in age at operation, gender, and the period from operation between groups according to TgAb pattern changes.

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[5]. 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 in 2013 earlier, it was determined that Tg measurement

has a very high negative predictive value but a low positive predictive value for monitoring DTC patients[6].

The production of Tg is limited to recurrent and/or persistent disease in patients of differentiated thyroid cancer who underwent total thyroidectomy and adjuvant radioiodine ablation. 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[7]. After a median follow-up of 5 years (2.5-22 years), serum Tg levels were undetectable (1 ng/ml) in 274 of 290 thyroid cancer 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[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 unlike preoperative measurement[2].

If a patient with thyroid neoplasm has anti-thyroid antibody by chance, he or she should be considered to have chronic thyroiditis according to Japanese guideline[10]. 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)[11]. 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[12]. 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. The most frequent prevalence of Hashimoto disease is reported 35% in thirties and 21% in forties as the second in the Japanese patients, its frequency is reported to decrease gradually[13]. TPOAb were significantly associated with hypo-or hyperthyroidism, but TgAb were not[14]. 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[15]. Our result of consistently positive TgAb values of 21.6% and consistently negative TgAb values of 68% was similar to other reports. Therefore, the presence of remnant normal thyroid tissue might produce autothyroid antibodies to disturbe the measurement of serum Tg during long-term surveillance.

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[16, 17]. 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. TgAb would appear when the remaining thyroid was concerned to Hashimoto thyroiditis. 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%). Those were assumed to attribute to developing Hashimoto disease and/or decreasing antigen in the remnant thyroid lobe because of volume reduction and/or contining TSH suppression therapy. The continuation of L-T4 administration might effect the activities of TgAb and thyroid hormone autoantibody titers for long surveillance[18].

The prevalence of thyroid autoantigen has been reported to be about 10 % in each age except 40-49 years-old in female people unlike male[19]. In 2,350 normal Japanese subjects, it showed that forty one subjects (2.3%) have TgAb and its incidence is pregressively greater with age , especially in sixties[20]. We found that the transition of TgAb after surgery occurred in 10.4% of patients with remnant normal thyroid. 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. Those also might be attributed to overt developing choronic thyroiditis in the remnat normal thyroid.

CONCLUSIONS

We found the transit of TgAb after operation occur in 10.5% of patients with remnant normal thyroid. Furhtermore, its positivity of TgAb after surgery gradually tended to increase up to 45.5% over about 10 years. Continuingly, we might measure both serum Tg and TgAb values concurrently for the patients with remnant thyroid tissue for a long time to measure serum Tg precisely.

DISCLOSURE OF CONFLICT OF INTEREST

We all authors have no conflict of interest.

REFERENCES

1） Cooper DS, Doherty GM, Haugen BR, *et al.*: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009; 19: 1167-1214. doi: 10.1089/thy.2009.0110.

2） Haugen BR, Alexander EK, Bible KC, *et al.*: 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer.Thyroid. 2016; 26: 1-133. doi: 10.1089/thy.2015.0020.

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.

4） Imai T, Kitano H, Sugitani I, Wada N: CQ19. Does Dissection of the Lateral Compartment Improve the Prognosis of Papillary Carcinoma Patients?. Treatment of Thyroid Tumor (In: Takami H, Ito Y, Noguchi H, Yoshida A, Okamoto T). Tokyo, springer. 2013, 115-117. doi: 10.1007/978-4-431-54049-6_26.

5） 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. doi: 10.1002/1096-9098(200010)75:2<108::aid-jso7>3.0.co;2-v.

6） 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. doi: 10.1210/jc.2013-3156.

7） McLeod DS, Cooper DS, Ladenson PW, *et al.*: Prognosis of differentiated thyroid cancer in relation to serum thyrotropin and thyroglobulin antibody status at time of diagnosis. Thyroid. 2014; 24: 35-42. doi: 10.1089/thy.2013.0062.

8） Durante C, Montesano T, Attard M, *et al.*: 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. doi: 10.1210/jc.2012-1123.

9) Park S, Jeon MJ, Oh HS, *et al.*: Changes in serum thyroglobulin levels after lobectomy in patients with low-risk papillary thyroid cancer. Thyroid. 2018; 28: 997-1003. doi: 10.1089/thy.2018.0046.

10) Guideline for the diagnosis of chronic thyroiditis (Hashimoto disease). https://www.japanthyroid.jp/en/guidelines.html#Chr, Japan Thyroid Association edited, (2022.9.14)

11) Spencer CA: Challenges of serum thyroglobulin (Tg) measurement in the presence of Tg autoantibodies. J Clin Endocrinol Metab. 2004; 89: 3702-3704. doi: 10.1210/jc.2004-0986.

12) 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. doi: 10.1177/0004563213480492.

13) https://www.ito-hospital.jp/02_thyroid_disease/02_5_1about_hashimoto.html (2022.10.22)

14) Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE, Serum TSH: $T(_4)$, 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. doi: 10.1210/jcem.87.2.8182.

15) Jia X, Pang P, Wang L, *et al.*: Clinical Analysis of Preoperative Anti-Thyroglobulin Antibody in Papillary Thyroid Cancer Between 2011 and 2015 in Beijing, China: A Retrospective Study. Front Endocrinol (Lausanne). 2020; 11: 452. doi: 10.3389/fendo.2020.00452.

16) Görges 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. doi: 10.1530/eje.1.01940.

17) Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, Grasso L, Pinchera A: Dissappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann Intern Med. 2003; 139: 346-351. doi: 10.7326/0003-4819-139-5_part_1-200309020-00010.

18) Ikekubo K, Hino M, Saiki Y, Kajikawa M, Hattori N, Ishihara T, Moridera K, Kurahachi H: Three thyroid patients showing fluctuation of thyroid hormone autoantibody titers during long-term treatment. Nihon Naibunpi Gakkai Zasshi. 1995; 71: 695-708. doi: 10.1507/endocrine1927.71.5_695.

19) Pandey JP, Fudenberg HH, Ainsworth SK, Loadholt CB: Autoantibodies in healthy subjects of different age groups. Mech Ageing Dev. 1979; 10: 399-404. doi: 10.1016/0047-6374(79)90021-6.

20) Nagaoka K, Sakurami T, Fukase M, Ogawa R: Incidence of thyroglobulin and microsomal antibodies in normal subjects (author's transl). Nihon Naibunpi Gakkai Zasshi. 1975; 51: 98-102. doi: 10.1507/endocrine1927.51.2_98.