

Antithyroglobulin Antibody as a Marker of Successful Ablation Therapy in Differentiated Thyroid Cancer

Ayu Rosemeilia Dewi, Budi Darmawan, Achmad Hussein Sundawa Kartamihadja, Basuki Hidayat, Johan S. Masjhur

Department of Nuclear Medicine and Molecular Imaging, School of Medicine, Dr. Hasan Sadikin Hospital, Padjadjaran University, Bandung, West Java, Indonesia

Abstract

The aim of this study was to determine the role of antithyroglobulin antibody (ATA) serum as a marker of successful I-131 ablation therapy in differentiated thyroid cancer (DTC) patients with low serum thyroglobulin (Tg). A retrospective study was conducted on 60 patients (10 males and 50 females). All patients underwent posttotal thyroidectomy and received 2.96 to 3 GBq I-131 ablation. Subjects were divided into two groups with successful and unsuccessful I-131 ablation therapies. The data of age, gender, histopathologic type, tumor size, and metastasis were collected. Preablation serum Tg and ATA level (Tg1 and ATA1) 6–12 months after ablation (Tg2 and ATA2) were measured. The success of ablation therapy was evaluated by diagnostic whole body scan (DxWBS) 6–12 months after ablation. There were no significant differences in age, gender, type of histopathology, tumor size, and nodal metastasis between the two groups. ATA2 ≤ 30 kIU/L were found in 23 (62.2%) subjects with successful ablation therapy, and ATA2 >30 kIU/L in 16 (69.6%) subjects belonged to the unsuccessful group ($P = 0.017$). Changes between ATA1 and ATA2 levels did not differ significantly in both the groups ($P = 0.062$). Tg1 <10 $\mu\text{g/L}$ was found in 26 (57.8%) subjects with successful therapy ($P = 0.037$). Multivariate analysis showed ATA2 and Tg1 as the independent factors for the success of ablation therapy ($P = 0.007$ and 0.015). Adjusted odds ratio of postablation ATA was 5.379 [95% confidence interval (CI) 1.590 to 18.203] and preablation Tg was 5.822 (95% CI 1.418 to 23.902). ATA levels at 6–12 months after ablation, by considering the preablation Tg levels, is a useful marker to determine successful ablation therapy in WDTC patients with low serum Tg. Changes in serum ATA levels, although not statistically significant, can provide additional information about the course of the disease.

Keywords: Antithyroglobulin antibody (ATA), I-131 ablation, thyroglobulin (Tg), thyroid cancer

Introduction

Survival of differentiated thyroid cancer (DTC) is relatively good with adequate therapy and follow-up. However, 35% of DTCs are likely to relapse.^[1] Successful ablation of functional thyroid remnant with I-131 plays an important role in reducing the incidence of recurrence and improves the survival

rate in DTC patients.^[1-5] Serum thyroglobulin (Tg) level during follow-up serves as a biological marker of residual or recurrent DTC,^[6-8] with high negative predictive value (98–99.5%).^[2,9] The presence of antithyroglobulin antibody (ATA) in 25% DTC patients can interfere with Tg measurement, particularly with immunoradiometric assay (IRMA) method, resulting in unreliable low Tg value.^[2,7] ATA has been proposed as a surrogate tumor marker for DTC^[10-12] although many literatures showed no correlation between ATA and DTC outcome.^[13,14] The aim of this study is to determine the role of ATA serum as a marker of

Address for correspondence:

Dr. Ayu Rosemeilia Dewi,
Department of Nuclear Medicine and Molecular Imaging, School of
Medicine, Dr. Hasan Sadikin Hospital, Padjadjaran University,
Jl. Pasir Kaliki No. 192, Bandung - 40161, West Java, Indonesia.
E-mail: ayu11005@mail.unpad.ac.id

Access this article online

Quick Response Code:



Website:
www.wjnm.org

DOI:
10.4103/1450-1147.174714

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Dewi AR, Darmawan B, Kartamihadja AH, Hidayat B, Masjhur JS. Antithyroglobulin antibody as a marker of successful ablation therapy in differentiated thyroid cancer. World J Nucl Med 2017;16:15-20.

successful I-131 ablation therapy in DTC patients with low serum Tg level.

Materials and Methods

Patients

This study was conducted after approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran. This retrospective study involved 332 posttotal thyroidectomy DTC patients receiving I-131 ablation therapy from 2009 to 2014 in the Department of Nuclear Medicine and Molecular Imaging, Dr. Hasan Sadikin General Hospital. Subjects' characteristic such as tumor type, tumor size, and nodal metastasis at the time of surgery were noted. Subjects were followed up clinically, biochemically, and with diagnostic whole body scan (DxWBS). Subjects with uptake outside the thyroid bed on postablation whole body scan (RxWBS) and those with Tg2 > 3 µg/L were excluded.

Serum thyroglobulin and antithyroglobulin antibody measurement

Serum Tg and ATA measurements were performed under stimulated thyrotropin [thyroid-stimulating hormone (TSH)] condition through thyroid hormone withdrawal (TSH \geq 30 mIU/L). The first measurement was done at least 4 weeks after surgery (Tg1, ATA1, and TSH1) and then monitored at 6–12 months after ablation of 2.96–3 GBq I-131 (Tg2, ATA2, and TSH2). Serum ATA level was determined using the radioimmunoassay (RIA) method (Izotop Anti-hTG ¹²⁵I RIA KIT, The Institute of Isotopes Co. Ltd., Budapest, Hungary, reference range 30–3,000 kIU/L. A serum level above functional sensitivity value with interassay variation coefficient 20% (30 kIU/L) was considered positive. Serum Tg level determination was conducted using IRMA method (Izotop hTG ¹²⁵I IRMA KIT, The Institute of Isotopes Co. Ltd.), reference range 0–250 µg/L. The value of analytical sensitivity was 0.022 µg/L. Serum TSH was measured by IRMA method (Izotop TurboTSH ¹²⁵I IRMA KIT, The Institute of Isotopes Co. Ltd.) with reference range 0–100 mIU/L. Changes of ATA level were measured by subtracting ATA1 level by ATA2 level. Changes were further classified as decreased \geq 50%, constant, and increase. Constant ATA level was defined as no change in ATA level or <50% decrease in ATA2 level.

Evaluation of tumor status

Subjects were classified as having successful remnant ablation or failure based on DxWBS performed 6–12 months after ablation therapy. Subjects were defined as successful ablation when there was no uptake on the thyroid bed.

Statistical analysis

Statistical analysis was done using Chi-square and Fisher's tests. *P* value of less than 0.05 was considered significant. Logistic regression analysis was conducted to measure a relationship between variables.

Results

Sixty subjects (10 males and 50 females) aged 45,67 ± 12,108 years were divided into two groups based on ablation outcomes. Papillary type was the most common type found in the study (83.3%), with follicular as the rest of it [Table 1].

Evaluation of treatment outcomes

As described in Table 1, postoperative staging showed that most of the subjects, i.e. 23 (38.3%) belonged to the T1 group^[15] of American Joint Committee of Cancer (AJCC) classification. Nodal metastasis was found in four subjects who had neck dissection. On 6–12 months of postablation follow-up, ATA2 were negative in 37 subjects (61.67%) and positive on the other subjects. WBS at 6–12 months after ablation showed I-131 nodal uptakes in two subjects. Two subject showed metastases, one with bone metastasis and the other with pulmonary metastasis.

Comparison of antithyroglobulin antibody 2 between groups

ATA2 significantly differed in both the groups (*P* = 0.017). Negative ATA2 was present in 23 out of 30 subjects (median 4.5 kIU/L) in the successful group. Those subjects had ATA1 levels ranging 0–105.80 kIU/L (median 13.0 kIU/L). Fifteen of those 23 subjects were aged \geq 45 years. Postoperative assessment showed 11 of 23 subjects (47.8%) classified as T1, and most of the subjects (95.7%) had no nodal metastasis. In the unsuccessful group, 16 subjects showed positive ATA2, one of which reached 3,000 kIU/L. ATA1 levels ranged 0–3,000 kIU/L (median 50.85 kIU/L). Ten out of 16 subjects were aged \geq 45 years. On the postoperative assessment, more than half (nine subjects) were in the advanced stage (T3 and T4). No nodal metastasis was found in these subjects.

Comparison of thyroglobulin 1 between groups

Tg1 levels differed significantly in both the groups (*P* = 0.037) [Table1]. Tg1 <10 µg/L was found in 26 out of 30 subjects (57.8%) in the successful group (median 1.5 µg/L). From these subjects, 15 (57.7%) were \geq 45 years. On postoperative assessment, 50% of the subjects were classified as T1 and none as T4. Nodal metastases were found in two subjects. Eleven out of 30 subjects in the unsuccessful group had Tg1 levels \geq 10 µg/L (median

23.70 µg/L). Follicular histopathologic types were found in four subjects. Postoperative assessment showed that one subject was T3, whereas two subjects were T4. One subject showed nodal metastasis.

Antithyroglobulin antibody 1 and changes between antithyroglobulin antibody 1 and antithyroglobulin antibody 2

ATA1 and changes of ATA levels showed no significant difference in both the groups ($P = 0.299$ and $P = 0.062$). In the successful group, 19 (55.9%) subjects showed negative ATA1. Changes of ATA levels were as follows: 17 (68%) subjects showed $\geq 50\%$ ATA decrease, 4 (36.4%) subjects with ATA remained constant, and 9 (37.5%) subjects were with increased ATA. In the unsuccessful group, half (15 subjects) of the subjects showed levels that were ATA1-positive. Change of ATA levels were noted to be increased in 15 (62.5%) subjects while they remained constant in 7 (63.6%) subjects, and a decrease $\geq 50\%$ was seen in 8 (32%) subjects.

Bivariate analysis showed that two consecutive variables, ATA2 and Tg1, had a significant relationship with the successful of ablation therapy. Changes in ATA levels could be considered as an indication of successful remnant ablation ($P < 0.25$) and was thus, included in the multivariate analysis. Multivariate analysis on these variables showed ATA2 and Tg1 as independent prognostic factors for the success of remnant ablation [Table 2], with P value 0.007 and 0.015, respectively. Adjusted odds ratios (ORs) ATA2 was significant [OR = 5.379; 95% confidence interval (CI) = 1.590 to 18.203] and increased compared to the previous analysis.

Discussion

In this study, age, sex, type of histopathology, tumor size, nodal metastasis as well as pre- and postablation TSH levels were not related to the success of therapy, which supported previous studies by Tobeau *et al.* and Lee *et al.*^[16,17] Those variables are known to be a prognostic factor of recurrence in many previous studies on the long-term DTC monitoring.^[18-20] In general, those clinical factors reflect DTC prognosis in long-term follow-up but do not depict short-term end point such as success or failure of the therapy and the presence of recurrence.^[21,22]

Based on bivariate analysis, ATA2 was the most important marker for successful ablation therapy compared to other parameters. ATA2-positive was most commonly found in subjects with unsuccessful ablation. The results supported some previous studies in that there was a significant correlation between ATA levels with DTC recurrences. In those studies, the levels of ATA < 100 kIU/L were considered negative,^[10,11,23]

Table 1: Subjects' characteristics

Characteristics	Successful (n=30)	Unsuccessful (n=30)	Total (n=60)	P
Age	44.80±12.110	48.00±11.252		0.566
Gender				
Female	24	26	50	0.488
Male	6	4	10	
Type of tumor				
Papillary	26	24	50	0.488
Follicular	4	6	10	
Tumor size ^a				
T1	13	10	23	0.726
T2	7	8	15	
T3 and T4	10	12	12	
Nodal metastasis				
N1	2	2	4	1.000
N0	28	28	56	
TSH level median (minimum-maximum)				
TSH1	69.55 (0.30-100.00)	79.97 (1.10-100.00)	60	0.679
TSH2	100.0 (50.00-100.00)	100.00 (30.70-100.00)	60	0.487
Tg1 level				
<10 µg/L	26	19	45	0.037
≥ 10 µg/L	4	11	15	

^aT1, tumor 2 cm or less in greatest dimension limited to the thyroid. T2, tumor more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid. T3, tumor more than 4 cm in greatest dimension limited to the thyroid or any tumor with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues). T4, advanced disease. TSH: Thyroid-stimulating hormone

Table 2: Multivariate analysis of factors that influence the success of ablation therapy

Variables	Crude OR [†] (95% CI) [‡]	Adjusted OR (95% CI)
ATA2	3.755 (1.239-11.385)	5.379 (1.590-18.203)
Tg1	3.763 (1.038-13.646)	5.822 (1.418-23.902)

[†]OR: Odds ratio; [‡]CI: Confidence interval; ATA: Antithyroglobulin antibody

which was inappropriately high to use for postsurgical and postablation DTC.^[24] Verburg, *et al.* recommended functional sensitivity as cutoff value for determining ATA positivity in DTC, as used in this study.^[23]

Seven of the 23 subjects with positive ATA2 levels showed successful ablation. Those seven subjects had Tg1 levels < 10 µg/L (median 0.40 µg/L) and were ATA1-positive (median 254.0 kIU/L). A decrease of serum ATA levels $\geq 50\%$ was found in four of the seven subjects, whereas one subject showed a 29% rise of ATA serum levels, which on 6 months of follow-up was no longer detected. On those subjects, decreased ATA level might be slower than most subjects, as described by Chiovato, *et al.* Memory cells may contribute to the synthesis of ATA in a long time so that in such cases the levels of ATA remained positive even up to 3 years after Tg no longer being produced.^[14,25,26] Verburg, *et al.* recommended measuring ATA levels at 6 months after ablation, as it was good enough to be evaluated. In

such cases, as long as ATA levels decreased or were constant, tumor remission can be assumed. Clinicians are advised to perform further clinical monitoring and other examinations. However, if there is increasing ATA level during monitoring, recurrences should be suspected.^[20] Another explanation is that on those subjects, there may still be residual malignancy that is too small to be detected in I-131 DxWBS.^[27-28] I-131 DxWBS has been known to have lower sensitivity than the RxWBS. A study by Keizer, *et al.* demonstrated I-131 uptakes on RxWBS in 11 out of 16 patients with previously negative DxWBS despite detectable Tg. In the subsequent monitoring, administration of those empiric therapies effectively reduced Tg.^[29] In addition, examination of the F-18 FDG PET may be useful in those cases. Seo, *et al.* reported recurrence detection in 37 patients with positive ATA yet DxWBS and ultrasound were negative.^[30] Thus, empiric therapy and F-18 FDG PET imaging need to be considered in such cases.

Another two subjects showed constant ATA level. In those subjects, although there was no longer any I-131 uptake in the thyroid-bed; one of whom suffered nodal metastasis (ATA2 = 575.40 kIU/L) and the other one had bone metastasis (ATA2 = 3000.00 kIU/L). The presence of metastasis even without residual tumor on the thyroid bed could be expected to trigger the synthesis of ATA. Previous studies reported ATA seroconversion to positive in five DTC patients who developed metastasis during follow-up. Other studies reported that ATA levels >400 kIU/L were found in 88% of the subjects with metastasis.^[13,27]

Unsuccessful ablation therapy was found in 14 out of 37 subjects with negative ATA2 (median 11.95; kIU/L). ATA2 levels were undetectable in two subjects, whereas in other subjects, it varied 1–21.40 kIU/L. Undetected ATA might be due to lack of normal Tg morphology synthesis. Tg with abnormal morphology may have a different epitope and faster plasma clearance than normal Tg, causing undetected Tg by routine IRMA methods, even in the absence of ATA, or if ATA was present, it seems to have an abnormal morphology as Tg.^[31-33] Another thing that might explain this condition is the use of RIA as ATA evaluation method. As in Tg measurement, RIA is relatively less sensitive to detect low levels of analytes. In such cases, the Tg and ATA measurements using different kit from other manufacturers may be useful to confirm the results.^[20] Another 12 subjects have ATA levels below the cutoff value. Cubero, *et al.* also reported that ATA levels below the cutoff value could still affect the Tg measurement, and may caused falsely undetected Tg.^[34]

Multivariate analysis showed a Tg of pre-ablation effect on the relationship between the ATA and the success of postablation therapy. Value of adjusted OR Tg1 was

5.882 (95% CI 5.822; 1.418 to 23.902), with *P* value = 0.017. Tg1 has been widely known to have predictive value for disease recurrence or DTC metastases with different cutoff values.^[16,35-37] Previous studies suggested that a cut-off value of 10 µg/L in condition of negative ATA, is good in predicting therapeutic efficacy in DTC with 86.7% sensitivity and 83.6% specificity.^[16] Another study showed, Tg1 >10 µg/L has a sensitivity and specificity values of 40.7% and 96.7% respectively, at ATA level >27.8 kIU/L, which increased to 68.3% and 90.0%.^[37] In this study, 12 of 21 subjects with Tg1 <10 µg/L and positive ATA1 showed unsuccessful ablation therapy. It may be caused by ATA interference on Tg measurement resulting falsely low Tg IRMA assay.^[23]

Another study showed that the diagnostic value of postablation Tg was a higher value of preablation Tg.^[17] All subjects selected in this study showed uniformly low Tg2 levels according to the cutoff value used in our institution, which was 3 µg/L. Thus, the relationship between Tg2 and the successful ablation therapy was not further analyzed.

In contrast to some previous studies,^[10,11] this study showed no significant relationship between the changes of ATA levels with the success of therapy. Previous studies only assessed ATA changes in subjects with ATA levels above the cutoff value. To avoid selection bias, ATA changes of all subjects in this study were assessed, regardless of the levels. This may explain the discrepancy between the results. Smooke-Praw, *et al.* also showed no association of ATA changes with the course of the disease on the subject either with a low or high Tg levels.^[38] ATA changes may have a prognostic value only in a limited population such as in patients with positive ATA2 with low Tg levels.

Conclusion

ATA levels on 6–12 months after ablation can be used as a surrogate marker for assessing the outcome of ablation therapy in DTC with low Tg level. The prognostic value was increase after taking into account the preablation Tg levels. In such circumstances, when postablation ATA and Tg are below the cutoff value there may still be a chance for a residual disease, that should be confirmed with other diagnostic modalities. Although the changes of ATA levels did not differ significantly in both the groups, changes ATA gave important information that was useful in patient management. Further research should be conducted with a larger sample size and a longer follow-up to determine the role of ATA in long-term DTC management, and its relation with other prognostic factors.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab* 2001;86:1447-63.
- Cooper D, Doherty G, Haugen B, Kloos R, Lee S, Mandel S, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167-214.
- Nostrand DV. Prescribed activity for radioiodine ablation. In Wartofsky L, Nostrand DV, editors. *Thyroid Cancer*. 2nd ed. Totowa: Humana Press Inc.; 2006. p. 273-82.
- Sawka AM, Thephamongkhon K, Brouwers M, Thabane L, Browman G, Gerstein HC. Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab* 2004;89:3668-76.
- Verburg FA, de Keizer B, Lips CJ, Zelissen PM, de Klerk JM. Prognostic significance of successful ablation with radioiodine of differentiated thyroid cancer patients. *Eur J Endocrinol* 2005;152:33-7.
- Park HJ, Jeong GC, Kwon SY, Min JJ, Bom HS, Park KS, et al. Stimulated serum thyroglobulin level at the time of first dose of radioactive iodine therapy is the most predictive factor for therapeutic failure in patients with papillary thyroid carcinoma. *Nucl Med Mol Imaging* 2014;48:255-61.
- Dufour DR. Thyroglobulin and thyroglobulin antibodies. In: Wartofsky L, Nostrand DV, editors. *Thyroid Cancer*. 2nd ed. Totowa: Humana Press Inc.; 2006. p. 297-304.
- Oyen WJ, Verhagen C, Saris E, van den Broek WJ, Pieters GF, Corsten FH. Follow-up regimen of differentiated thyroid carcinoma in thyroidectomized patients after thyroid hormone withdrawal. *J Nucl Med* 2000;41:643-6.
- Kloos RT, Mazzaferri EL. A single recombinant human thyrotropin-stimulated serum thyroglobulin measurement predicts differentiated thyroid carcinoma metastases three to five years later. *J Clin Endocrinol Metab* 2005;90:5047-57.
- Chung JK, Park YJ, Kim TY, So Y, Kim SK, Park DJ, et al. Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. *Clin Endocrinol (Oxf)* 2002;57:215-21.
- Tsushima Y, Miyauchi A, Ito Y, Kudo T, Masuoka H, Yabuta T, et al. Prognostic significance of changes in serum thyroglobulin antibody levels of pre- and post-total thyroidectomy in thyroglobulin antibody-positive papillary thyroid carcinoma patients. *Endocr J* 2013;60:871-6.
- Rubello D, Casara D, Gireffi ME, Piccolo M, Busnardo B. Clinical meaning of circulating anti-thyroglobulin antibodies in differentiated thyroid cancer: A prospective study. *J Nucl Med* 1992;33:1478-80.
- Pacini F, Mariotti S, Formica N, Elisei R, Anelli S, Capotorti E, et al. Thyroid autoantibodies in thyroid cancer: Incidence and relationship with tumour outcome. *Acta Endocrinol (Copenh)* 1988;119:373-80.
- Görge R, Maniecki M, Jentzen W, Sheu SN, Mann K, Bockisch A, et al. 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.
- American Joint Committee of Cancer. *AJCC Cancer Staging Atlas. A Companion to the Seventh Editions of the AJCC Cancer Staging Manual and Handbook*. 2nd ed. In: Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK, editors. New York: Springer-Verlag New York; 2012. p. 113-20.
- Lee HJ, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, et al. Predictive value of the preablation serum thyroglobulin level after thyroidectomy is combined with postablation ¹³¹I whole body scintigraphy for successful ablation in patients with differentiated thyroid carcinoma. *Am J Clin Oncol* 2007;30:63-8.
- Toubeau M, Touzery C, Arveux P, Chaplain G, Vaillant G, Berriolo A, et al. Predictive value for disease progression of serum thyroglobulin levels measured in the postoperative period and after ¹³¹I ablation therapy in patients with differentiated thyroid cancer. *J Nucl Med* 2004;45:988-94.
- Rouxel A, Hejblum G, Bernier MO, Boëlle PY, Ménégau F, Mansour G, et al. Prognostic factors associated with the survival of patients developing loco-regional recurrences of differentiated thyroid carcinomas. *J Clin Endocrinol Metab* 2004;89:5362-8.
- Durante C, Haddy N, Baudin E, Leboulleux S, Hartl D, Travagli JP, et al. Long-term outcome of 444 patients with distant metastases from papillary and follicular thyroid carcinoma: Benefits and limits of radioiodine therapy. *J Clin Endocrinol Metab* 2006;91:2892-9.
- Verburg FA, Stokkel MP, Düren C, Verkooijen RB, Mäder U, van Isselt JW, et al. No survival difference after successful ¹³¹I ablation between patients with initially low-risk and high-risk differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging* 2010;37:276-83.
- Wartofsky L. Papillary carcinoma clinical aspect. In: Wartofsky L, Nostrand DV, editors. *Thyroid Cancer A Comprehensive Guide to Clinical Management*. 2nd ed. Totowa: Humana Press Inc; 2006. p. 253-60.
- Schlumberger M, Pacini F. *Thyroid Tumor*. 3rd ed. Paris: Nucleons; 2006. p. 111-25.
- Verburg FA, Luster M, Cupini C, Chiovato L, Duntas L, Elisei R, et al. Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: A clinical position statement. *Thyroid* 2012;23:1211-25.
- Spencer C. Commentary on: Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: A clinical position statement. *Thyroid* 2013;23:1190-2.
- Chiovato L, Latrofa F, Braverman LE, Pacini F, Capezzone M, Masserini L, et al. Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. *Ann Intern Med* 2003;139:346-50.
- Hjiyannakis P, Mundy J, Harmer C. Thyroglobulin antibodies in differentiated thyroid cancer. *Clin Oncol (R Coll Radiol)* 1999;11:240-4.
- Rubello D, Girelli ME, Casara D, Piccolo M, Perin A, Busnardo B. Usefulness of the combined antithyroglobulin antibodies and thyroglobulin assay in the follow-up of patients with differentiated thyroid cancer. *J Endocrinol Invest* 1990;13:737-42.
- Kumar A, Shah DH, Shrihari U, Dandekar SR, Vijayan U, Sharma SM. Significance of antithyroglobulin autoantibodies in differentiated thyroid carcinoma. *Thyroid* 1994;4:199-202.
- de Keizer B, Koppeschaar HP, Zelissen PM, Lips CJ, van Rijk PP, van Dijk A, et al. Efficacy of high therapeutic doses of iodine-131 in patients with differentiated thyroid cancer and detectable serum thyroglobulin. *Eur J Nucl Med* 2001;28:198-202.
- Seo JH, Lee SW, Ahn BC, Lee J. Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: Special emphasis on

- using (18)F-FDG PET/CT. *Clin Endocrinol (Oxf)* 2010;72:558-63.
31. Brendel A, Lambert B, Guyot M, Jeandot R, Dubourg H, Roger P, *et al.* Low levels of serum thyroglobulin after withdrawal of thyroid suppression therapy in the follow up of differentiated thyroid carcinoma. *Eur J Nucl Med* 1990;16:35-8.
 32. Ma C, Kuang A, Xie J, Ma T. Possible explanations for patients with discordant findings of serum thyroglobulin and 131I whole-body scanning. *J Nucl Med* 2005;46:1473-80.
 33. Cherk MH, Francis P, Topliss DJ, Bailey M, Kalff V. Incidence and implications of negative serum thyroglobulin but positive I-131 whole-body scans in patients with well-differentiated thyroid cancer prepared with rhTSH or thyroid hormone withdrawal. *Clin Endocrinol (Oxf)* 2012;76:734-40.
 34. Cubero J, Rodríguez-Espinosa J, Gelpi C, Estorch M, Corcoy R. Thyroglobulin autoantibody levels below the cut-off for positivity can interfere with thyroglobulin measurement. *Thyroid* 2003;13:659-61.
 35. Kim TY, Kim WB, Kim ES, Ryu JS, Yeo JS, Kim SC, *et al.* Serum thyroglobulin levels at the time of 131I remnant ablation just after thyroidectomy are useful for early prediction of clinical recurrence in low-risk patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab* 2005;90:1440-5.
 36. Hall FT, Beasley NJ, Eski SJ, Witterick IJ, Walfish PG, Freeman JL. Predictive value of serum thyroglobulin after surgery for thyroid carcinoma. *Laryngoscope* 2003;113:77-81.
 37. Aras G, Gultekin SS, Kucuk NO. The additive clinical value of combined thyroglobulin and antithyroglobulin antibody measurements to define persistent and recurrent disease in patients with differentiated thyroid cancer. *Nucl Med Commun* 2008;29:880-4.
 38. Smooke-Praw S, Ro K, Levin O, Ituarte PH, Harari A, Yeh MW. Thyroglobulin antibody levels do not predict disease status in papillary thyroid cancer. *Clin Endocrinol (Oxf)* 2014;81:271-5.