



Predictivity of stimulated serum thyroglobulin and antithyroglobulin antibodies for the efficacy of thyroid remnant ablation on patients with differentiated thyroid carcinoma

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Abstract

Differentiated thyroid cancers (DTC) are the most frequently occurring endocrine malignancies and accounts for $\geq 90\%$ of all thyroid cancers. It was suggested that after total or near total thyroidectomy, the stimulated thyroglobulin (sTg) and quantified uptake in whole body scintigraphy (WBS) are significant predictors for the successful ablation and disease-free status. We aimed to evaluate preablative thyroid stimulating hormone (TSH), sTg and anti-thyroglobulin antibodies (TgAbs) levels, after following thyroid hormone withdrawal, and compare them with diagnostic WBS (DxWBS) uptake for predict the efficacy of radioiodine (RAI) ablation therapy in DTC patients. We retrospectively investigated 100 consecutively patients which followed up for DTC in Ankara Numune Education and Research Hospital at Department of Endocrinology and Metabolism between January 2006 and June 2013. Patients had histologically confirmed DTC and underwent RAI remnant ablation therapy without clinical or radiological evidence of distant metastases. ¹³¹I was used generally from 30-200 mCi dosage in all 100 patients. (median dose, 100 mCi). Preablation TSH, preablation sTg, postablation TSH, postablation sTg, postablation TgAbs levels, tumor size and tumor multifocality did not differ between DxWBS uptake negative and positive groups, while the preablation TgAbs level was found significantly lower in DxWBS uptake negative group ($p < 0.001$). The cut-off value of preablation Tg for predicting postablation WBS uptake was found 0.31 ng/mL with 67.4% sensitivity and 54.5% specificity. After RAI remnant ablation therapy, postablation WBS and DxWBS, are useful for follow up patients with high or intermediate risk of persistent disease. We found that preablation TgAbs positivity can effect the postablation WBS and DxWBS uptake in DTC patients.

Keywords: Differentiated thyroid cancers, Anti-thyroglobulin antibodies, ¹³¹I whole body scintigraphy

Introduction

Differentiated thyroid cancers (DTC) are the most frequently occurring endocrine malignancies and accounts for $\geq 90\%$ of all thyroid cancers [1]. They are seen in approximately 2% of all malignancies [2]. The most common types of DTC are papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), whose frequency levels are approximately 80% and 15% of all thyroid cancers, respectively [3]. After consideration of initial clinical and pathological stage, the postoperative status of the disease is significant to determine the treatment. Evaluation of disease status should be performed by serum thyroglobulin (Tg), antithyroglobulin antibodies (TgAbs), neck ultrasonography (USG) in early postoperative period. Stimulated Tg (sTg) level after

complete thyroid ablation is a sensitive marker for detecting tumor persistence and recurrence [4]. It was suggested that after total or near total thyroidectomy, the Tg and quantified uptake in whole body scintigraphy (WBS) are significant predictors for the successful ablation and disease-free status [5]. The predictive value of the postoperative Tg levels are influenced by some variable factors including the amount of residual thyroid cancer tissue, normal thyroid tissue, the TgAbs titers, the thyroid stimulating hormone (TSH) level at the time of thyroglobulin measurement and the sensitivity of the Tg assay methods.

The TgAbs occurs in 10% of the general population [6]. The prevalence of TgAbs in DTC patients is approximately 25%, nearly twice that of the general population [7], and can falsely lower the serum Tg concentrations in immunometric assays [8]. Following total thyroidectomy and Radioactive Iodine (RAI) remnant ablation, TgAbs usually disappear over a median of about 3 years in patients without evidence of persistent disease [9]. After following thyroid hormone withdrawal or recombinant

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human thyroid stimulating hormone (rhTSH), 6–12 months after adjuvant RAI remnant ablation therapy, diagnostic

WBS (DxWBS) should be done with ¹³¹I or low activity

¹³¹I in the follow-up of patients with high or intermediate risk of persistent disease. Negative DxWBS uptake with low serum sTg levels often shows complete remission as well as positive DxWBS and/or increased serum sTg levels may be the sign of recurrence or persistence of disease. However, patients with unknown metastases but with elevated serum Tg and/or TgAbs and negative WBS uptake seems to be a diagnostic dilemma.

The aim of this study is following after withdrawal of thyroid hormone to evaluate preablation TSH, sTg and TgAbs levels and compare them with diagnostic WBS (DxWBS) uptake for predict the efficacy of radioiodine (RAI) ablation therapy in DTC patients.

Materials and Methods

Patients and Methods

We retrospectively investigated 100 consecutively patients which followed up for DTC in Ankara Numune Education and Research Hospital at Department of Endocrinology and Metabolism between January 2006 and June 2013. All patients underwent total or near total thyroidectomy (n=100) by experienced surgeons (>100 cases/year). Of 100 patients, 18 underwent unilateral, 7 bilateral modified radical neck dissection therapeutically. Patients had histologically confirmed DTC without clinical or radiological evidence of distant metastases. The exclusion criteria of patients were who had distant metastases at the time of remnant ablation and postoperative follow up period was less than one year. In all cases no grossly visible thyroid remnants remained. Patients with undetectable sTg (<1.0 ng/mL), no clinical evidence of thyroid carcinoma by imaging techniques; no evidence of tumor on a DxWBS and neck USG 6-12 months after ¹³¹I ablation therapy were defined as disease free. Before ¹³¹I therapy the neck USG was performed by an experienced endocrinologist. Serum sTg levels were obtained from all patients by withdrawal levothyroxine therapy at least 4 weeks except 12 patients were used rhTSH. Serum TSH and sTg levels were measured approximately 3 days before RAI remnant ablation therapy. The cut-off value between TgAbs positivity and negativity was 115 U/mL. All patients underwent RAI remnant ablation under hypothyroid conditions. (TSH >30 µIU/mL). ¹³¹I was used generally from 30-200 mCi dosage in all 100 patients. (median dose, 100 mCi). A postablation WBS was performed 3-7 days after the administration of ¹³¹I. Thyroid hormone replacement started 2-3 days after ¹³¹I administration to reduce the serum TSH to low levels according to disease risk status. (intermediate or high risk <0.1 or low risk 0.1-0.5). The DxWBS with 5 mCi of ¹³¹I and neck USG was performed 6-12 months after ¹³¹I ablation therapy. Also TSH, sTg, and TgAbs were

measured in these states. Eleven patients were not included the study because the postablation WBS uptake was found negative, so the comparison of DxWBS cannot be made among these. Remained 89 cases were compared as postablation WBS and DxWBS uptake 6-12 months after ¹³¹I ablation therapy. If the post-therapy scans did not reveal uptake outside the thyroid bed, it was defined as negative (-) WBS, therewithal in the presence of detectable

¹³¹I uptake was defined as positive (+) WBS. If the scintigraphy scans revealed only one focus in thyroid beds it was described as unifocal uptake as well as multifocal focuses described as multifocal uptake. The definition of postablation WBS scans was also the same for DxWBS. The study was approved by the local Ethics Committee of the Ankara Numune Education and Research Hospital.

Laboratory Analyses

Serum Tg, TSH values and TgAbs were measured in all the samples by using Electrochemiluminescence (ECLIA) method with Modular Analytics E170 analyzer (Roche Diagnostics, Poland). Normal reference range for TSH was 0,27 - 4,2 µIU/mL, for TgAbs was < 115 IU/mL and for Tg was 1,4-78 ng/mL. A sTg level of <1.0 ng/mL was considered undetectable.

Statistical Analysis

Data of statistical analyses were performed by SPSS software, version 18.0 (SPSS Inc., Chicago, IL, United States). A p value less than 0.05 was considered statistically significant. Whether the distributions of continuous variables were normally or not was determined by Kolmogorov-Smirnov test. Data were shown as mean ± SD or median (min-max), where applicable. While the mean differences between groups were compared by Student's t test, otherwise, Mann-Whitney U test was applied for comparisons of the median values. Nominal data were analyzed by Pearson's Chi-square or Fisher's exact test, where applicable. The receiver-operating characteristic (ROC) curve was analyzed to identify the optimal cutoff value of the preablation Tg for predicting postablation WBS uptake.

Results

All patients had undergone total or near total thyroidectomy (n=100). The patients were 87 female (87%) and 13 male (13%). At the time of diagnosis the mean age was 49±11.2 years and the mean body mass index (BMI) was 29.7±4.8 kg/m². Histologic examination had revealed papillary carcinomas in 94 patients and follicular carcinomas in 6 patients. Tumor diameters ranged between 5 and 50 mm (mean: 10.3 ± 10.6 mm) (Table 1).

Table 1. Demographical and clinicopathological features of patients with DTC

Variables	Patients (n=100)
Age (years)	49 ± 11.2
Gender	
Female	87 (87.0%)
Male	13 (13.0%)
BMI	29.7±4.8
Tumor characteristic	
Papillary	94 (94%)
Follicular	6 (6%)
Unifocal tumor	
Absent	27 (27%)
Present	73 (73%)
Multifocal tumor	
Absent	73 (73%)
Present	27 (27%)
TgAbs positivity	
Absent	89%
Present	11%

BMI: Body mass index **TgAbs:** Anti-thyroglobulin antibodies

Table 2. Comparison of preablation and postablation TSH, thyroglobulin, TgAbs levels and tumor size and tumor focus between DxWBS uptake positive and negative groups.

Variables	DxWBS positive group (n= 13)	DxWBS negative group (n= 76)	P value
Preablation TSH (µIU/mL)	61.9±31.0	68.0±36.4	0.572
Preablation sTg (ng/mL)	8.8±20.2	10.2±24.2	0.843
Preablation TgAbs (IU/mL)	113±83.2	61.5±31.4	<0.001
Postablation TSH (µIU/mL)	66.5±33.9	71.2±36.8	0.667
Postablation sTg (ng/mL)	6.0±18.7	1.3±6.7	0.102
Postablation Tg (ng/mL)	55.7±51.06	56.1±27.6	0.965

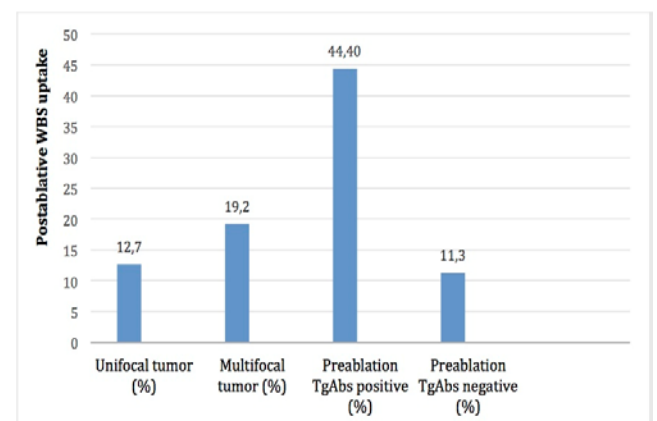
TSH: Thyroid stimulan hormone **sTg:** Stimulated thyroglobulin **TgAbs:** Anti-thyroglobulin antibodies **DxWBS:** Diagnostic ¹³¹I whole-body scintigraphy

Among 63 patients who had unifocal tumor and 26 patients who had multifocal tumor, the postablation WBS uptake was found in 8 (12.7%), and 5 (19.2%) of them respectively (p= 0.427). Fifty-eight patients which postablation WBS revealed multifocal neck uptake, 11 of them DxWBS uptake was more likely to be positive (21.6%), on the other hand 38 patients whom postablation WBS revealed unifocal neck uptake, only 2 had positive DxWBS uptake (5.3%) (p=0.037). Also 9 patients who had preablative TgAbs positivity, 4 of them had preablative WBS uptake (44.4%), whereas among 80 patients who had negative TgAbs, in 9 of them the preablative WBS uptake was found positive (11.3%) (p = 0.024). In 13 patients which had positive DxWBS uptake, high preablation sTg levels were found in 4 (%30.8); while 76 who had negative DxWBS uptake, in 5 patients preablation sTg levels were found high (%6.6) (p=0.986) (Figure 1 and 2).

The cut-off value of sTg for predicting postablation WBS uptake was found 0.31 ng/mL with 67.4% sensitivity and 54.5% specificity (Area under the curve = 0.618, 95% CI = 0.466-0.770) (Figure 3). However, for patients who had preablative sTg values above and below this cut-off value, the postablation WBS uptake was not statistically significantly different (90.9% vs. 85.3% respectively,

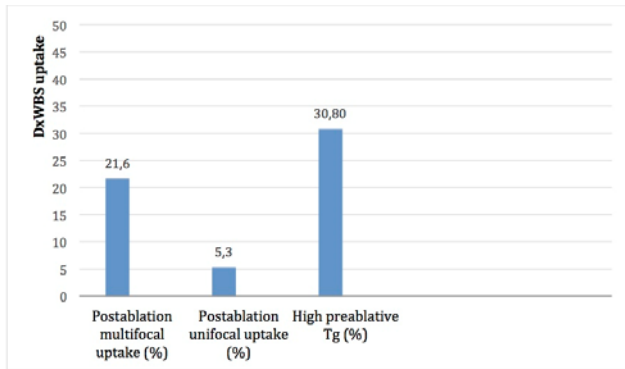
After exclusion of 11 postablation WBS uptake negative patients, for the remaining 89 cases with DTC, no statistically significant difference was found between tumor histological type and DxWBS uptake (p=0.341). Among all 89 patients 13 of them the DxWBS uptake has continued at 6-12 months after RAI remnant ablation therapy. Preablation TSH, preablation sTg, postablation TSH, postablation sTg and postablation TgAbs levels did not differ between DxWBS uptake negative and positive groups. (p=0.572, 0.843, 0.667, 0.102, 0.965, 0.896, 0.427; respectively), while the preablation TgAbs level was found significantly lower in DxWBS uptake negative group (p<0.001) (Table 2).

p=0.395). Even if no statistically significance was found in the difference, for the patients who had preablative Tg values above this cut-off value, the postablation WBS showed higher rates of multifocal neck uptake but not statistically significant (61.7% vs 44.8%, p = 0.133).



TgAbs: Anti-thyroglobulin antibodies **WBS:** Whole body scintigraphy

Figure 1. The percentages of tumor focus, preablation TgAbs levels and postablative WBS uptake in DTC patients



Tg: Thyroglobulin DxBWS: Diagnostic ¹³¹I whole-body scintigraphy

Figure 2. The percentages of postablation multifocal and unifocal uptake and preablative Tg levels at DxBWS uptake in DTC patients

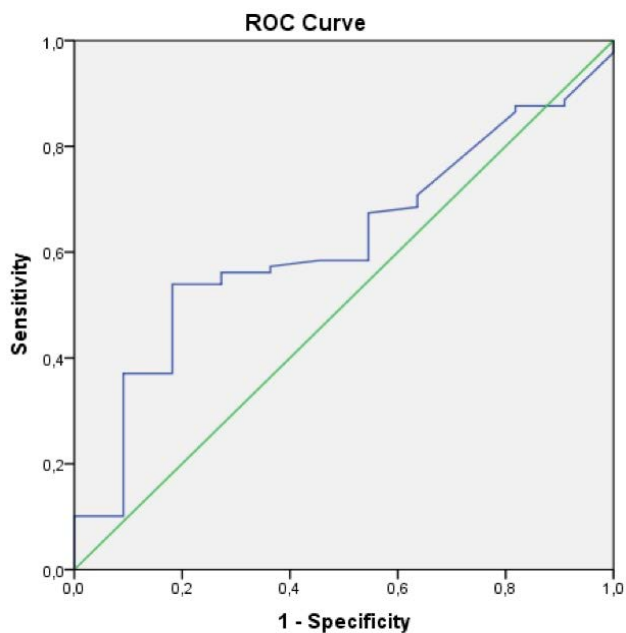


Figure 3. Receiver operating characteristic (ROC) curve analysis of sTg in postablative WBS uptake. Area under the curve = 0,618 (95% CI = 0466-0770). The best cut-off value of sTg for predicting postablative WBS uptake was 0.31 ng/mL with 67.4 % sensitivity and 54.5 % specificity

Discussion

In patients with DTC after total or near total thyroidectomy following remnant RAI ablation therapy, 10.3% have neck recurrences by evidence of laboratory and screening findings with TSH stimulated levels of elevated serum Tg [10]. Some recent studies evaluated the serum Tg level at the time of the first ablative radioiodine treatment to predict the presence of persistent and recurrent disease in patients with DTC. [11,12].

According to the 2009 American Thyroid Association (ATA) guidelines, preablation measurement of serum Tg levels is an important modality to monitor patients for residual or recurrent disease [13]. In the absence of Tg

antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest degrees of sensitivity noted following thyroid hormone withdrawal or stimulation using rhTSH [14]. A recent study demonstrates that preablation Tg measurement has the potential to serve as a useful negative predictor of persistent and recurrent DTC. A low preablation Tg should be considered a favorable risk factor in patients with DTC [15]. Lee et al. indicate that the combined use of serum Tg levels measured just before ablation and the ¹³¹I WBS patterns after ablation may be an early predictor of ablation success in patients with differentiated thyroid carcinoma who received total thyroidectomy and high-dose ¹³¹I ablation therapy [16]. Many studies have confirmed an increased risk of recurrence sTg > 1-2 ng/mL at the time of ablation [17, 18].

After preparation with thyroid hormone withdrawal sTg values greater than 6 ng/mL was associated with a 5 fold greater risk of failing ablation after an activity of 30 mCi. [19]. In this study we found preablation and postablation sTg levels were not differ between the DxBWS uptake positive and negative groups. None of our patients had distant metastases we think that the significance differences may occur in metastatic disease conditions.

Some studies showed that sTg measurement may fail to identify patients with clinically significant tumor, due to TgAbs less commonly to defective or absent production and secretion of immunoreactive Tg by tumor cells [20,21]. In this study we found preablation TgAbs levels tend to be higher in patients with postablation WBS uptake positive and DxBWS uptake positive patients. Tsushima et al. demonstrated that the lack of a decrease or increase of postoperative TgAbs may be a prognostic factor for disease free status than prognostic factors such as tumor size, extrathyroidal invasion, and age [22]. Because of TgAbs usually disappear over 3 years, in postablation period this should be taken into consideration. Chung et al. reported that the recurrence rate of TgAbs positive patients was higher than TgAbs negative patients. During follow-up, patients with recurrent cancer, who showed responses to surgical operation or radioiodine treatment, also showed a decreased TgAbs level. Persistently elevated TgAbs levels appear to serve as a useful marker for recurrent or persistent DTC in patients with undetectable serumTg results [23, 24]. In our study also in patients who had postablation WBS multifocal neck uptake, the DxBWS neck uptake was found positive. There was no appearance of distant metastases in these patients. We consider that it may be due to persistent disease status.

The limitations of this study, first because it was a retrospective study, we could not reach simultaneous neck USG records of all patients at the time of postablation WBS and DxBWS. Second the follow-up period of these

patients was not long enough and we cannot predict the disease status in long time period. We consider longer-term studies are needed to evaluate these patients.

Conclusion

After RAI remnant ablation therapy, postablation WBS and DxWBS, are useful for follow up patients with high or intermediate risk of persistent disease. Patients with DTC which had positive TgAbs and no evidence of distant metastasis, the positive DxWBS uptake revealed that involvement continues. We found that higher TgAbs levels can effect the postablation WBS and DxWBS uptake in DTC patients and may be helpful to understand disease conditions after underwent RAI remnant ablation therapy. Further studies are needed to evaluate the high dose RAI requirement for ¹³¹I remnant radio iodine ablation in these patients.

References

- Busaidy NL, Cabanillas ME. Differentiated thyroid cancer: management of patients with radioiodine nonresponsive disease. *J Thyroid Res.* 2012;2012:618985.
- Institute, National Cancer; Surveillance, Epidemiology, and End Results (SEER) Program. SEER Cancer Statistics Factsheets. Thyroid Cancer. Bethesda, MD: National Cancer Institute; 2014
- Lebastchi AH, Callender GG. Thyroid cancer. *Curr Probl Cancer.* 2014;38(2):48-74.
- Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab.* 2001;86(4):1447-63.
- Lim I, Kim SK, Hwang SS, Kim SW, Chung KW, Kang HS, Lee ES. Prognostic implication of thyroglobulin and quantified whole body scan after initial radioiodine therapy on early prediction of ablation and clinical response for the patients with differentiated thyroid cancer. *Ann Nucl Med.* 2012;26(10):777-86.
- Hollowell JG, Staehling NW, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum thyrotropin, thyroxine, and thyroid antibodies in the United States population (1988 to 1994): NHANES III. *J Clin Endocrinol Metab.* 2002;87(2):489-99.
- Spencer CA, LoPresti JS, Fatemi S, Nicoloff JT. Detection of residual and recurrent differentiated thyroid carcinoma by serum thyroglobulin measurement. *Thyroid.* 1999;9(5):435-4.
- Spencer CA, Bergoglio LM, Kazarosyan M, Fatemi S, LoPresti JS. Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management of patients with differentiated thyroid carcinomas. *J Clin Endocrinol Metab.* 2013;90(10):5566-75.
- Gorges 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(1):49-55.
- Frasoldati A, Pesenti M, Gallo M, Caroggio A, Salvo D, Valcavi R. Diagnosis of neck recurrences in patients with differentiated thyroid carcinoma. *Cancer.* 2003;97(1):90-6.
- Bernier MO, Morel O, Rodien P, Muratet JP, Giraud P, Rohmer V, Jeanguillaume C, Bigorgne JC, Jallet P. Prognostic value of an increase in the serum thyroglobulin level at the time of the first ablative radioiodine treatment in patients with differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2005;32(12):1418-21.
- Tenenbaum F, Corone C, Schlumberger M, Parmentier C. Thyroglobulin measurement and postablative iodine-131 total body scan after total thyroidectomy for differentiated thyroid carcinoma in patients with no evidence of disease. *Eur J Cancer.* 1996;32A(7):1262.
- American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Hauger 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(11):1167-214.
- Eustatia-Rutten CF, Smit JW, Romijn JA, van der Kleij- Corssmit EP, Pereira AM, Stokkel MP, Kievit J. Diagnostic value of serum thyroglobulin measurements in the follow-up of differentiated thyroid carcinoma. a structured meta-analysis. *Clin Endocrinol (Oxf).* 2004;61(6):61-74.
- Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, Burch HB. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. *J Clin Endocrinol Metab.* 2012;97(8):2754-63.
- Lee HJ¹, Rha SY, Jo YS, Kim SM, Ku BJ, Shong M, Kim YK, Ro HK. 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(1):63-8.
- Peltari H, Valimaki MJ, Loytyniemi E, Schalin-Jantti C. Post-ablative serum thyroglobulin is an independent predictor of recurrence in low-risk differentiated thyroid carcinoma: a 16-year follow-up study. *Eur J Endocrinol.* 2010;163:757-63.
- Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J, Burch HB. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. *J Clin Endocrinol Metab.* 2012;97:2754-63.
- Tamila M, Al-Kahtani N, Rochon L, Hier MP, Payne RJ, Holcroft CA, Black MJ. 2011 Serum thyroglobulin predicts thyroid remnant ablation failure with 30 mCi iodine-131 treatment in patients with papillary thyroid carcinoma. *Nucl Med Commun.* 32:212-220.
- Giovannella L, Suriano S, Ceriani L, Verburg FA. Undetectable thyroglobulin in patients with differentiated thyroid carcinoma and residual radioiodine uptake on a postablation whole-body scan. *Clin Nucl Med.* 2011;36:109-12.
- Bachelot A, Leboulleux S, Baudin E, Hartl DM, Caillou B, Travaglini JP, Schlumberger M. Neck recurrence from thyroid carcinoma: serum thyroglobulin and high-dose total body scan are not reliable criteria for cure after radioiodine treatment. *Clin Endocrinol (Oxf).* 2005;62:376-9.
- Tsushima Y, Miyauchi A, Ito Y, Kudo T, Masuoka H, Yabuta T, Fukushima M, Kihara M, Higashiyama T, Takamura Y, Kobayashi K, Miya A, Kikumori T, Imai T, Kiuchi T. 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(7):871-6.
- Chung JK, Park YJ, Kim TY, So Y, Kim SK, Park DJ, Lee DS, Lee MC, Cho BY. Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. *Clin Endocrinol.* 2002;57(2):215-21.

24. Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. *J Clin Endocrinol Metab.* 2008;93(12):4683-9.