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Preradioactive Iodine Thyroglobulin Levels as Predictors of Metastasis in Well-Differentiated Thyroid Carcinoma Patients

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Abstract

Objective The aim of this study was to determine the cut-off value of thyroglobulin (Tg) levels as a predictor of metastases in post total thyroidectomy patients with well-differentiated thyroid carcinoma (DTC).

Materials and Methods A retrospective case-control study with an observational diagnostic approach was done. Subjects were 102 DTC patients divided into a case group with metastases and a control group without metastases. Tg and antithyroglobulin antibody (ATA) levels on thyroid-stimulating hormone (TSH)-stimulated preradioactive iodine were compared with each other. Diagnosis of metastases was based on postradioactive iodine whole-body scan. The cut-off value for Tg preradioactive iodine and the area under the curve (AUC) were obtained from the receiver operating characteristic curve.

Result The characteristics and histopathological type of DTC among these two groups were not significantly different ($p = 0.47$). The Tg levels in the case and control groups were 106 (2.2–6,000) ng/mL and 2.7 (0.3–10.10) ng/mL, respectively ($p = 0.0001$). TSH level in the case group was 50 (30–107) μIU/mL and in the control was 50 (20–100) μIU/mL ($p = 0.224$). ATA levels in the case and control groups were 0–3,000 and 0–629 ng/mL, respectively ($p = 0.01$). The AUC was 0.976 with a 95% confidence interval of 0.924 to 0.996 and a standard error of 0.016. The cut-off value of preradioactive iodine Tg was 10.1 ng/mL or higher with sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 96.1, 100, 98.0, 100, and 96.2%, respectively.

Conclusion Preradioactive iodine Tg level 10.1 ng/mL or higher can be used as a predictor of metastasis in patients with DTC.

Keywords
- well-differentiated thyroid carcinoma
- metastasis
- thyroglobulin

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Introduction

Thyroid cancer is an endocrine gland malignancy, is the most common type of endocrine cancer in the world, and three out of four cases occur in women.[1] Well-differentiated thyroid cancer (DTC) originates from epithelial cells of the thyroid gland and is the most histopathological type of all thyroid cancers. One-third of DTC patients present with metastatic lesions.[2] DTC has a good prognosis with a longer life expectancy compared with other malignancies and 98% of patients have a 10-year survival.[1,3] Papillary type of DTC was the most common histopathological type with 80 to 85% of all cases and 10 to 15% are follicular type. The prognosis of these types is almost the same, except a small number of variant type with tall and columnar cells being more aggressive.[4,5]

Management of DTC includes near-total or total thyroidectomy, followed by radioiodine ablation and administration of levothyroxine.[6–9] Metastasis in DTC patients is one of the factors affecting the efficacy of radioiodine therapy and the amount of ^{131}I dose required.[7,10] Metastases can be detected by using ultrasound, ^{131}I whole body scan (WBS), chest X-ray, and ^{99m}Tc-MDP bone scan.[11–13] Since each of these modalities has its limitations, it is necessary to look for other modalities that can be used to predict the presence of metastases before the number of doses of ^{131}I is given.

Thyroglobulin (Tg), a large glycoprotein, is a marker of thyroid hormone biosynthesis. Tg is secreted by normal thyroid tissue and neoplastic thyroid tissue. It is assumed that the higher the Tg level the greater the remaining functional thyroid tissue after thyroidectomy. It is estimated that 1 g of neoplastic thyroid tissue can increase serum Tg levels by approximately 0.5 to 1 ng/mL in the absence of thyroid-stimulating hormone (TSH) stimulation and an increase of 10 times if stimulated by TSH.[10] Postthyroidectomy serum Tg is highly correlated with the surgical technique performed.[14] The pre-radioactive iodine (RAI) serum Tg level after thyroidectomy can be used as a predictor to assess the failure of therapy in patients with DTC.[10,15–17]

The aims of this study were to determine the diagnostic value and cut-off of pre-RAI Tg levels as predictors of metastases in DTC patients.

Materials and Methods

A retrospective study using an observational diagnostic approach was performed on the medical records of DTC patients who underwent ablation or therapy using ^{131}I at the Department of Nuclear Medicine and Molecular Imaging, Dr. Hasan Sadikin Hospital/Faculty of Medicine, Padjadjaran University, Bandung, Indonesia from 2013 to 2017. This study was conducted after obtaining approval from the Research Ethics Committee of Dr. Hasan Sadikin General Hospital (no. L8.04.01/A05/EC/251/VIII/2017). The inclusion criteria of the subject were patients with DTC, who had undergone total thyroidectomy. Postsurgery histopathological types were papillary, follicular, or papillary variant follicular type of thyroid carcinoma. Tg and antithyroglobulin antibody (ATA) levels measured under TSH stimulation before ^{131}I ablation and post-RAI WBS and single-photon emission computed tomography (SPECT)/computed tomography (CT) should be available. Metastases are determined based on the results of post-RAI WBS. WBS and SPECT/CT were performed 1 week after administration of ^{131}I using a Symbia T-6 Siemens, high-energy high-resolution collimator. CT was used for localization and attenuation.

The data were obtained by tracing the medical records of the subjects who met the inclusion criteria. Subjects were divided into case group with metastases and control group without metastases.

The sample size was determined using the sample size formula for the control case test, i.e.:

$$n1 = n2 = \left(\frac{Z\alpha\sqrt{2P(1-P)} \quad + Z\beta \quad \sqrt{P1(1-P1) + P2(1-P2)}}{(P1-P2)^2} \right)^2$$

(n: number of subjects in each group; $Z\alpha$, $Z\beta$: standard deviation for the selected confidence rate and power test; P: total proportion; $P1$, $P2$: case and control proportions).

The level of confidence chosen in this study was 95% ($Z = 1.96$) and the power test was 90% ($Z = 1.28$). The proportion of the control group selected based on the previous study was 70.9%. Based on this formula, a minimum sample size should be at least 12.

Statistical Analysis

The statistical software IBM SPSS version 21 was used for statistical analysis. Numerical variables with normal data distribution such as age were analyzed using unpaired t-test. Categorical variables such as gender and histopathological type of DTC were analyzed using the chi-square test. Numerical variables with abnormal data distribution such as pre-ablation Tg levels, TSH levels, ATA levels, and radioiodine dose were analyzed using the Mann–Whitney test.

The receiver operating characteristic (ROC) curve was used to illustrate the relation between sensitivity and specificity. The optimal cut-off value of pre-RAI Tg level for metastatic decision was calculated from the different value of sensitivity and specificity. The area under the curve (AUC) values were obtained from the ROC curve as well. The AUC values were divided into: less than 0.50 = very weak, 0.50–0.75 = weak, 0.75–0.92 = moderate, 0.92–0.97 = good, and 0.97–1.00 = very good.

Results

A total of 102 subjects who met the inclusion criteria were included in this study. Each group consisted of 51 subjects. The characteristics of the subjects can be seen in ►**Table 1**. The mean age in the case group was 44.35 (14–82) years and in the control group 44.53 (20–66) years. The case group consisted of 17 (33.3%) males and 34 (66.7%) females, while the control group consisted of 10 (19.6%) males and 41 (80.4%) females. There were no significant differences in the variables of age ($p = 0.070$) and gender ($p = 0.89$).

Papillary thyroid cancer (PTC) is a type of histopathology which is mostly found in both case and control groups compared with follicular thyroid carcinoma (FTC). The

Table 1 Subject characteristics

Variables	Cases ($n = 51$)	Control ($n = 51$)	p-Value
Age	51 ± 44.35	51 ± 44.53[a]	0.070[b]
Sex			
Males	17 (33.3%)	10 (19.6%)	0.89[c]
Females	34 (66.7%)	41 (80.4%)	
Histopathology type			
FTC	5 (9.8%)	8 (15.7%)	0.47[c]
PTC	43 (84.3%)	38 (74.4%)	
PTCvF	3 (5.9%)	5 (9.8)	
Tg level (ng/mL)	106 (2.2–6,000)	2.7 (0.3–10.10)[d]	0.0001[e]
TSHs level (μIU/mL)	50 (30–107)	50 (30–100)[d]	0.224[e]
Dose of RAI (mCi)	100 (30–150)	80 (30–150)[d]	0.009[e]
ATA level (ng/mL)	25.45 (0–3,000)	11.90(0–629.0)[d]	0.01[e]

Abbreviations: ATA, antithyroglobulin antibody; FTC, follicular thyroid cancer; PTC, papillary thyroid cancer; PTCvF, papillary thyroid cancer variant follicular; RAI, radioactive iodine; TSH, thyroid-stimulating hormone.
[a]Mean ± standard deviation.
[b]Unpaired *t*-test.
[c]Chi-Square test.
[d]Median (minimum–maximum).
[e]Mann–Whitney test.

number of cases with PTC, FTC, and PTC follicular variant in the case group was 43 (84.3%), 5 (9.8%), and 3 (5.9%), respectively, while in the control group was 38 (74.4%), 8 (15.7%), and 5 (9.8), respectively. There was no significant difference based on the type of histopathology in the two groups ($p = 0.47$). The Tg level in the case group was significantly higher than the control group with 106 (2.2–6,000) ng/mL and 2.7 (0.3–10.10) ng/mL respectively ($p = 0.0001$). There was no significant difference in TSH levels in both groups ($p = 0.224$). The TSH level in the case group was of 50 (30–107) μIU/mL, while that in the control group was 50 (20–100) μIU/mL ($p = 0.224$). The RAI dose of ^{131}I for all subjects varied from 30 to 150 mCi ($p = 0.009$). The level of ATA in the case group was 0 to 3,000 ng/mL, while that in the control group was 0 to 629 ng/mL ($p = 0.01$).

All subjects in both groups showed remnant normal thyroid tissue on post-RAI WBS. Metastases involving regional lymph nodes, lungs, and/or bones were found in 51 subjects. Lymph node metastases only found in 31 subjects, 7 subjects with lymph nodes and lungs metastases, 6 subjects with bone metastases only, 4 subjects with lung and bone metastases, 2 subjects with metastases to lymph nodes and bone, and 1 subject with pulmonary metastases only (►**Table 2**).

The area under the ROC curve was 0.976 with a 95% confidence interval of 0.924 to 0.996 and a standard error of 0.016, which means that Tg levels were very good at predicting the presence of metastases before radioiodine therapy (►**Fig. 1**).

The cut-off value of pre-RAI Tg level obtained from the ROC curve was 10.1 ng/mL or higher (►**Table 3**). By using this cut-off, as many as 49 subjects in the case group had Tg levels above the cut-off value. Two subjects with Tg levels less than the cut off value showed metastases at lymph node based on postradioiodine therapy WBS. Among the various cut-off values of pre-RAI Tg levels in predicting metastasis in patients with DTC, the cut-off value with the best diagnostic value was 10.1 ng/mL or higher with sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of 96.1, 100, 98.0, 100, and 96.2%, respectively (►**Table 3**). In the relation to its prevalence, the cut-off value of pre-RAI Tg level 10.1 ng/mL or higher has the highest positive likelihood ratio and negative likelihood ratio of 49% and 0.04% respectively compared with other cut-off values in predicting metastasis in patients with well-differentiated thyroid carcinoma (►**Table 3**).

Table 2 Post-radioiodine ablation whole-body scan

Variable	Case ($n = 51$)	Control ($n = 51$)
Remnant normal thyroid tissue	51 (100%)	51 (100%)
Metastases		
Lymph nodes only	31 (78.4%)	0
Lymph nodes + lung	7 (23.5%)	0
Lymph nodes + bone	2 (23.5%)	0
Lung only	1 (23.5%)	0
Lung + bone	4 (23.5%)	0
Bone only	6 (25.5%)	0

Discussion

In this study, there were significant differences in the characteristic variables of case and control subjects with p-value less than 0.05. These characteristic variables were pre-RAI Tg

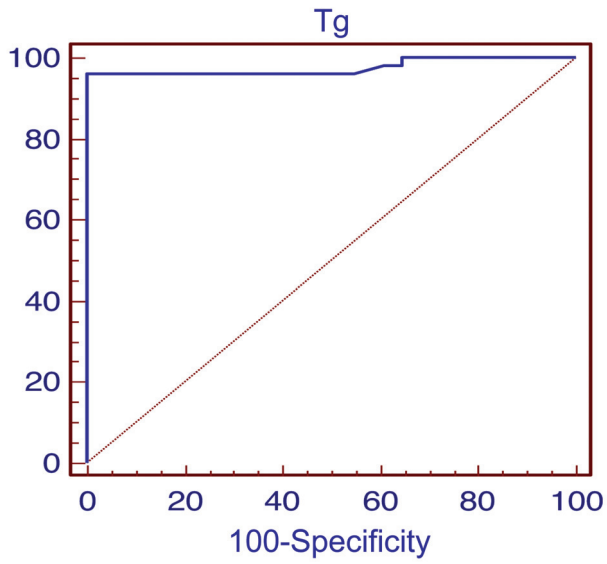

Fig. 1 ROC curve of preradioactive iodine Tg level in the presence of metastases with AUC = 0.976 and 95% confidence interval of 0.924–0.996. AUC, area under the curve; ROC, receiver operating characteristic.

and ATA levels and the dose of RAI with *p*-values of 0.0001, 0.01, and 0.009, respectively. Other characteristic variables that did not have a significant difference with *p*-value greater than 0.05 were age, gender, histopathological type of DTC, and TSH levels with *p*-values of 0.07, 0.89, 0.47, and 0.224, respectively. Female subjects were more than men and the histopathological type of papillary thyroid carcinoma was more than the other types. This is in accordance with several literature reports which showed that DTCs in women have a three times higher risk than men and older patients have a worse prognosis. Malignancy diseases in males are usually more aggressive than females.[4,18] The results of this study were also in accordance with data from several epidemiological studies showing that three out of four cases of well-differentiated thyroid carcinoma occur in women and papillary thyroid carcinoma is a histological type of DTC most commonly found.[1,5]

Tg can be used as a tumor marker to determine the status and an indicator of remnant normal thyroid tissue in post-surgery patient with DTC. Undetectable Tg is an indication of complete tumor removal at the time of surgery.[1,3] However, in this study, post-RAI showed that the remaining functional thyroid tissue was still visible in all subjects. This discrepancy between Tg level and WBS results could be related to the surgical technique used and the skill of the surgeon.[15] These results showed that optimal surgery (total thyroidectomy) is very important for successful RAI in patients with DTC.[19] The causes of radioiodine uptake at the thyroid bed after total thyroidectomy and ablation therapy are unclear, but in general, it is believed to be due to residual functional thyroid tissue.[20]

Based on the area under the ROC curve of 0.976 with 95% confidence interval of 0.924 to 0.996 and a standard error of 0.016, it can be concluded that the preablation Tg value was very good in predicting metastasis of DTC patients prior to radioiodine therapy. A diagnostic test of pre-RAI Tg levels was also performed using the ROC curve and a cut-off value of 10.1 ng/mL or greater. It can be explained that the high Tg level is secreted not only by remnant normal thyroid tissue, but also by neoplastic thyroid tissue, as well its metastases.[2] A higher Tg level indicates a larger mass of remaining functional thyroid tissue.[2]

Several studies showed that high Tg levels correlate with failure of RAI ablation, metastasis, or recurrence.[13,21] A study conducted by Rosário et al showed an association between Tg levels and WBS using ^{123}I. Subjects with preablation Tg levels 10 ng/mL or lower showed no metastases, found on monitoring using ^{131}I WBS, whereas subjects with Tg levels greater than 10 ng/mL showed lymph node metastases or distant metastases.[22] A study conducted by Lee in 2007 using a cut-off serum Tg level 10 ng/mL obtained a mean ablation success rate of 96.7%.[23] Memorial Sloan Kettering Cancer Center suggests the use of large doses of ^{131}I in patients with elevated serum Tg levels postsurgery greater than 10 ng/mL.[24] Other studies showed that tested serum Tg levels in patients with hypothyroidism condition (Tg-off) 10 ng/mL or lower have a high negative predictive value for determining disease-free.[25,26]

In this study, various cut-off points of pre-RAI Tg levels were selected to predict metastasis in patients with DTC, but the cut-off point of Tg levels 10.1 ng/mL or greater showed the best diagnostic value with sensitivity, specificity, and accuracy of 96.1, 100, and 98.0%, respectively. In addition, the positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value were 0.04, 49.00, 100, and 96.2%, respectively. If using cut-off value of 10.1 ng/mL, there were 49 subjects in the case group who showed pre-RAI Tg levels above and 2 subjects below cut-off value. Two subjects with Tg levels less than cut-off value showed lymph node metastases on posttherapy WBS. Several studies showed that the presence of a very small tumor mass can be detected with WBS, although with a negative

Table 3 Diagnostic value of pre-radioactive iodine Tg in predicting metastases in patients with well-differentiated thyroid cancer

Cut-off value	Sensitivity	Specificity	Accuracy	PLR	NLR	PPV	NPV
≥ 1	100%	11.8%	100%	1.13%	0.00%	53.1%	100%
≥ 5.1	96.1%	68.6%	98.0%	3.06%	0.06%	75.4%	94.6%
≥ 10.1	96.1%	100%	98.0%	49.00%	0.04%	100%	96.2%
≥ 13.6	92.2%	100%	96.1%		0.08%	100%	92.7%

Abbreviations: NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.

serum Tg.[2,27–35] ^{131}I uptake as shown on thyroid bed during RAI ablation or therapy can be due to microscopic thyroiditis occurring up to 6 months after total thyroidectomy. This phenomenon can be confirmed by post-RAI WBS 6 months after initial ablation. WBS shows no radioiodine uptake on the thyroid bed.[15] Undetected postsurgery serum Tg levels do not always correlate with the perfection of surgery, but it could be associated with the presence of ATAs.[28,36–39] Increased ATA levels can be found in DTC patients in 6 months to several years after RAI ablation. This condition is due to the presence of secondary Tg antigen as a result of the destruction of normal remnant thyroid tissue.[40,41] ATA levels in postsurgery and ablation patient with DTC can be used as an important reason for serial determination of ATA levels for monitoring in the long term.[42]

The study conducted by Kim and colleagues showed DTC patients with positive ATA level at the time of preablation, and after 6 to 12 months of monitoring. The results showed that 1% of subjects become negative and more than 50% were decreased.[15] In our study, two PTC subjects with preablation and pretherapy Tg levels of 2.2 and 2.5 ng/mL (below cut-off value) showed lymph nodes metastasis on posttherapy WBS. DTC patients with metastases shown on WBS and negative Tg levels are found in a small proportion of cases.[43–45]

False negative results of Tg test in PTC patients with metastases in the cervical or mediastinal lymph nodes were reported by Brendel et al.[45] Subcentimeter lesions are unable to secrete Tg, which leads to undetectable Tg.[44] False negatives were also found in a 54-year-old woman with follicular thyroid cancer. In this subject, the presence of bony metastases was seen on WBS with undetected serum Tg levels.[46] Bredel et al found 79 out of 224 patients (35%) with positive WBS, but negative serum TG.[45] In this study, we found 7 (13.7%) subjects with preablation Tg levels less than 26.83 ng/mL and positive cervical lymph node metastases on posttherapy WBS. Factors that could be the reasons for those false negative finding include low sensitivity of the Tg assay method, such as the "hook effect." This effect happens when the excessive amount of Tg in the preparation exceeds the amount of antibody regent. Another reason is inactive Tg which is produced by the tumor cell which contains a characteristic epitope and changes a biochemical form. This biochemical form is difficult to recognize by the antibodies resulting a false low positive result.[47] De-differentiated thyroid cancer cells can still accumulate iodine but unable to synthesize and secrete Tg. It is also found in metastases of DTC which have weak differentiation ability, so they tend to be associated with low Tg levels.[47]

Conclusion

Pre-RAI thyroglobulin level of 10.1 ng/mL or greater can be used as a predictor of metastasis in patients with well-differentiated thyroid cancer. The thyroglobulin level can be considered as a changing strategy factor for radioactive therapy.

Conflicts of Interest

There are no conflicts of interest.

References

1 Gharib H, Papini E, Paschke R, et al; AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. J Endocrinol Invest 2010;33(5, Suppl):51–56

2 Cooper DS, Doherty GM, Haugen BR, et al; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11): 1167–1214

3 Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga WEuropean Thyroid Cancer Taskforce. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006;154(06): 787–803

4 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(01):1–133

5 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(01):33–37

6 Pacini F, Ladenson PW, Schlumberger M, et al. Radioiodine ablation of thyroid remnants after preparation with recombinant human thyrotropin in differentiated thyroid carcinoma: results of an international, randomized, controlled study. J Clin Endocrinol Metab 2006;91(03):926–932

7 Hagag P, Strauss S, Weiss M. Role of ultrasound-guided fine-needle aspiration biopsy in evaluation of nonpalpable thyroid nodules. Thyroid 1998;8(11):989–995

8 Wexler JA. Approach to the thyroid cancer patient with bone metastases. J Clin Endocrinol Metab 2011;96(08):2296–2307

9 Robenshtok E, Fish S, Bach A, Domínguez JM, Shaha A, Tuttle RM. Suspicious cervical lymph nodes detected after thyroidectomy for papillary thyroid cancer usually remain stable over years in properly selected patients. J Clin Endocrinol Metab 2012;97 (08):2706–2713

10 Schlumberger M, Pacini F, eds. Papillary and follicular thyroid carcinoma. Follow-up: lessons from the past. In: Thyroid Tumors. 2nd ed. Paris: Nucleon; 2006:147–164

11 Rosário PW, Ward LS, Carvalho GA, et al; Sociedade Brasileira de Endocrinologia e Metabologia. Thyroid nodules and differentiated thyroid cancer: update on the Brazilian consensus. Arq Bras Endocrinol Metabol 2013;57(04):240–264

12 Muratet JP, Giraud P, Daver A, Minier JF, Gamelin E, Larra F. Predicting the efficacy of first iodine-131 treatment in differentiated thyroid carcinoma. J Nucl Med 1997;38(09):1362–1368

13 Park HJ, Jeong GC, Kwon SY, 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(04): 255–261

14 Shah J, Patel SG, Singh B, eds. Jatin Shah's Head and Neck Surgery Oncology. 4th ed. Philadelphia, PA: Elsevier; 2012:471–525

15 McDougall IR, ed. Thyroid Cancer in Clinical Practice. 1st ed. London: Spinger; 2007:53–91

16 American Cancer Society. Alabama cancer facts & figures [Internet]. Atlanta, GA: American Cancer Society; 2015. Accessed May 20, 2016 at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html

17 Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for

low-risk patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 2003;88(04):1433–1441
18 American Cancer Society Key statistics about thyroid cancer [Internet]. Atlanta, GA: American Cancer Society; 2015. Accessed January 12, 2015 https://www.cancer.org/cancer/thyroid-cancer/about/key-statistics.html
19 Cooper DS, Doherty GM, Haugen BR, et al; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1167–1214
20 Rosário PW, Reis JS, Barroso AL, Rezende LL, Padrão EL, Fagundes TA. Efficacy of low and high 131I doses for thyroid remnant ablation in patients with differentiated thyroid carcinoma based on post-operative cervical uptake. Nucl Med Commun 2004;25 (11):1077–1081
21 Tuttle RM, Sabra MM. Selective use of RAI for ablation and adjuvant therapy after total thyroidectomy for differentiated thyroid cancer: a practical approach to clinical decision making. Oral Oncol 2013;49(07):676–683
22 Elrasad S, Abdelhafez Y, Abdelkareem M, Amin R, Elrefaei S. The value of postoperative baseline serum thyroglobulin in prediction of the outcome of radioactive I-131 thyroid ablation in differentiated thyroid carcinoma. Egyptian J Nucl Med 2014;10(02):73–84
23 Pacini F, Capezzone M, Elisei R, Ceccarelli C, Taddei D, Pinchera A. Diagnostic 131-iodine whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment. J Clin Endocrinol Metab 2002;87 (04):1499–1501
24 Lee HJ, Rha SY, Jo YS, 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(01):63–68
25 Polachek A, Hirsch D, Tzvetov G, et al. Prognostic value of post-thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer. J Endocrinol Invest 2011;34(11):855–860
26 Cabezón C, Löwenstein A, Orlandi A, Sartorio G, Sobrado PMiembros del Departamento de Tiroides de la Sociedad Argentina de Endocrinología y Metabolismo (SAEM) Usefulness of preablation serum thyroglobulin as a predictor of the evolution of patients with differentiated thyroid carcinoma. Rev Argent Endocrinol Metab 2011;48(04):25–33
27 Park EK, Chung JK, Lim IH, et al. Recurrent/metastatic thyroid carcinomas false negative for serum thyroglobulin but positive by posttherapy I-131 whole body scans. Eur J Nucl Med Mol Imaging 2009;36(02):172–179
28 Van Nostrand D, Aiken M, Atkins F, et al. The utility of radioiodine scans prior to iodine 131 ablation in patients with well-differentiated thyroid cancer. Thyroid 2009;19(08):849–855
29 Schlumberger MJ, Pacini F. The low utility of pretherapy scans in thyroid cancer patients. Thyroid 2009;19(08):815–816
30 McDougall IR. The case for obtaining a diagnostic whole-body scan prior to iodine 131 treatment of differentiated thyroid cancer. Thyroid 2009;19(08):811–813
31 Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab 2000; 85(01):175–178
32 Baudin E, Do Cao C, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M. Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. J Clin Endocrinol Metab 2003;88(03):1107–1111
33 Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab 2008;93(02):504–515
34 Rubino C, de Vathaire F, Dottorini ME, et al. Second primary malignancies in thyroid cancer patients. Br J Cancer 2003;89(09): 1638–1644
35 Ronckers CM, McCarron P, Ron E. Thyroid cancer and multiple primary tumors in the SEER cancer registries. Int J Cancer 2005; 117(02):281–288
36 Hyer S, Kong A, Pratt B, Harmer C. Salivary gland toxicity after radioiodine therapy for thyroid cancer. Clin Oncol (R Coll Radiol) 2007;19(01):83–86
37 Alexander C, Bader JB, Schaefer A, Finke C, Kirsch CM. Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. J Nucl Med 1998;39(09):1551–1554
38 Müller-Gärtner HW, Schneider C. Clinical evaluation of tumor characteristics predisposing serum thyroglobulin to be undetectable in patients with differentiated thyroid cancer. Cancer 1988; 61(05):976–981
39 Spencer C, Petrovic I, Fatemi S. Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer. J Clin Endocrinol Metab 2011;96(05):1283–1291
40 Lim D-J, , O JH, Kim M-H, et al. Clinical significance of observation without repeated radioiodine therapy in differentiated thyroid carcinoma patients with positive surveillance whole-body scans and negative thyroglobulin. Korean J Intern Med 2010;25(04): 408–414
41 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 2005;90(10): 5566–5575
42 Rubio IG, Silva MN, Knobel M, et al. Peripheral blood levels of thyroglobulin mRNA and serum thyroglobulin concentrations after radioiodine ablation of multinodular goiter with or without pre-treatment with recombinant human thyrotropin. J Endocrinol Invest 2007;30(07):535–540
43 Benvenga S, Bartolone L, Squadrito S, Trimarchi F. Thyroid hormone autoantibodies elicited by diagnostic fine needle biopsy. J Clin Endocrinol Metab 1997;82(12):4217–4223
44 Kim WG, Yoon JH, Kim WB, et al. 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): 4683–4689
45 Brendel AJ, Lambert B, Guyot M, 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(01):35–38
46 Mertens IJ, De Klerk JM, Zelissen PM, et al. Undetectable serum thyroglobulin in a patient with metastatic follicular thyroid cancer. Clin Nucl Med 1999;24(05):346–349
47 Torréns JI, Burch HB. Serum thyroglobulin measurement. Utility in clinical practice. Endocrinol Metab Clin North Am 2001;30(02): 429–467

