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.
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.\textsuperscript{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.\textsuperscript{2} DTC has a good prognosis with a longer life expectancy compared with other malignancies and 98% of patients have a 10-year survival.\textsuperscript{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.\textsuperscript{4,5}

Management of DTC includes near-total or total thyroidectomy, followed by radioiodine ablation and administration of levothyroxine.\textsuperscript{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.\textsuperscript{7,10} Metastases can be detected by using ultrasound, $^{131}$I whole body scan (WBS), chest X-ray, and $^{99m}$Tc-MDP bone scan.\textsuperscript{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.\textsuperscript{10} Postthyroidectomy serum Tg is highly correlated with the surgical technique performed.\textsuperscript{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.\textsuperscript{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/VII/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.:

\[
\frac{n_1 = n_2 = \left( \frac{2a\sqrt{2P(1-P)}}{Z_B} \sqrt{P_1(1-P_1) + P_2(1-P_2)} \right)^2}{(n): \text{number of subjects in each group}; Z_B: \text{standard deviation for the selected confidence rate and power test}; P_1, P_2: \text{case and control proportions}).}
\]

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).
Table 1 Subject characteristics

| Variables                | Cases (n=51) | Control (n=51) | p-Value |
|--------------------------|--------------|----------------|---------|
| Age                      | 51 ± 44.35   | 51 ± 44.53a    | 0.070b  |
| Sex                      |              |                |         |
| Males                    | 17 (33.3%)   | 10 (19.6%)     | 0.89c   |
| Females                  | 34 (66.7%)   | 41 (80.4%)     |         |
| Histopathology type      |              |                |         |
| FTC                      | 5 (9.8%)     | 8 (15.7%)      | 0.47c   |
| 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 | 0.0001c |
| TSHs level (µIU/mL)      | 50 (30–107)  | 50 (30–100)d   | 0.224e  |
| Dose of RAI (mCi)        | 100 (30–150) | 80 (30–150)d   | 0.009e  |
| ATA level (ng/mL)        | 25.45 (0–3,000) | 11.90(0–629.0)d | 0.01e   |

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.

* Mean ± standard deviation.
* Unpaired t-test.
* Chi-Square test.
* Median (minimum–maximum).
* Mann–Whitney test.

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).

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 levels.
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 worse prognosis. Malignancy diseases in males are usually more aggressive than females.\(^1,5\) 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 postsurgery 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.\(^1,3\) 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 | 0.08 | 100% | 92.7%|

Abbreviations: NLR, negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; PPV, positive predictive value.
serum Tg$^{2,27–35}$ 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.$^{46}$ 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.$^{46}$ Brendel et al found 79 out of 224 patients (35%) with positive WBS, but negative serum Tg.$^{46}$ 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.
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