PROGNOSTIC VALUE OF SERUM THYROGLOBULIN KINETICS FOR PREDICTING RECURRENCE IN DIFFERENTIATED THYROID CANCER

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Abstract

Background: Although absolute serum thyroglobulin (Tg) levels are routinely used to monitor differentiated thyroid cancer (DTC), a single measurement may not accurately predict disease progression in patients who have already achieved remission. While Tg kinetics have shown prognostic value, the optimal thresholds for detecting early recurrence in this specific excellent-response population remain poorly defined.

Objectives: The study aimed to evaluate the usefulness of serum thyroglobulin doubling time (Tg-DT) and thyroglobulin velocity (TgV) during thyroid-stimulating hormone (TSH) suppression for predicting tumor recurrence among patients with DTC who achieved remission.

Methods: This retrospective study analyzed 270 patients with DTC who underwent total/near-total thyroidectomy followed by radioactive iodine (RAI) ablation at Siriraj Hospital between January 2007 and December 2011. Eligible patients had achieved remission (Tg < 1 ng/mL with negative imaging) and had ≥ 4 Tg measurements obtained during TSH suppression. Tg-DT and TgV was calculated using non-linear regression and linear formulas, respectively.

Results: During the follow-up period, three patients (1.1%) experienced disease recurrence. Receiver operating characteristic analysis tentatively identified optimal exploratory cutoffs as Tg-DT ≤ 1 year and TgV ≥ 0.1 ng/mL/year. At these specific thresholds, both markers predicted recurrence with a sensitivity of 66.7% (95% CI: 9.4% -99.2%), a specificity of 100% (95% CI: 98.6% - 100%), and an overall accuracy of 99.6% (95% CI: 97.9% -99.9%). These high estimates should be interpreted with caution, given the wide confidence intervals resulting from the low event rate. Nominally shorter mean recurrence-free survival was observed among patients exceeding these thresholds compared to those below (2.8 years [95% CI: 2.6 -2.9] vs. 9.9 years [95% CI: 9.9 -10.0]; $p < 0.0005$).

Conclusion: Within this cohort, a Tg-DT ≤ 1 year and a TgV ≥ 0.1 ng/mL/year were associated with disease recurrence and may serve as highly specific preliminary indicators during remission. However, given the low number of recurrence events inherently observed in excellent-response patients, these kinetic markers should be interpreted as preliminary tools that complement, rather than replace, comprehensive clinical surveillance. Larger-scale studies are required to validate their routine clinical applicability.

Keywords: thyroid cancer, thyroglobulin, recurrence, thyroglobulin doubling-time, thyroglobulin velocity

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Introduction

Differentiated thyroid cancer (DTC) accounts for approximately 93% of all thyroid cancer cases. Standard treatment consists of total or near-total thyroidectomy, followed by radioactive iodine (RAI) ablation and lifelong thyroid-stimulating hormone (TSH) suppression therapy. Despite the generally favorable prognosis, recurrence occurs in 10%-20% of patients within 5–15 years after initial treatment.[1]

Serum thyroglobulin (Tg) is a highly specific marker for monitoring patients with DTC.[2] Although absolute Tg levels are routinely used in clinical practice, a single positive stimulated Tg does not always indicate disease recurrence. Recent evidence suggests that Tg kinetics — specifically thyroglobulin doubling-time (Tg-DT) and thyroglobulin velocity (TgV) — may provide superior predictive value for disease progression.[3, 4, 5] However, the optimal thresholds for these kinetic markers in patients who have already achieved remission remain poorly defined, particularly given the varying sensitivities of laboratory assays. This study aimed to compare the sensitivity, specificity, and accuracy of Tg-DT and TgV in predicting recurrence among DTC patients at Siriraj Hospital who had previously achieved remission.

Methods

Study design and population

This retrospective descriptive study was conducted at the Division of Nuclear Medicine, Siriraj Hospital. Ethical approval was obtained from the Siriraj Institutional Review Board (Si082/2017). Patients were included if they met the following criteria: pathologically confirmed DTC; underwent total or near-total thyroidectomy, followed by high-dose RAI ablation (≥ 80 mCi); achieved remission, defined as stimulated Tg < 1 ng/mL with a negative diagnostic I-131 total body scan (DxTBS) or neck ultrasound; and had ≥ 4 serum Tg measurements obtained during TSH suppression (suppressed Tg measured while TSH < 0.5 mIU/L).

Patients were excluded if they had a follow-up period of less than 5 years; positive anti-thyroglobulin antibodies (TgAb > 40 IU/mL); received additional thyroid cancer treatments, e.g., radiotherapy, chemotherapy, radiofrequency ablation, or targeted therapy prior to the assessment of disease recurrence; or were non-adherent to TSH suppression therapy.

Biochemical assays

Serum Tg and TgAb were measured using platforms and assay generations that varied with the longitudinal follow-up period. In 2007, measurements were performed manually using radioimmunoassay (RIA). From 2008 to 2011, samples were analyzed using the Elecsys 2010 system. The laboratory subsequently transitioned to the cobas e411 analyzer from 2012 to 2017, and has utilized the cobas e601 analyzer from 2017 to the present. All tests were performed at the Nuclear Chemistry Laboratory, Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University. This facility has maintained continuous international accreditation under the ISO 15189 standard since 2008. An internal laboratory validation was specifically performed in accordance with the National Academy of Clinical Biochemistry (NACB) guidelines. The functional sensitivity, defined as the target concentration resulting in a 20% coefficient of variation (CV), was established at 0.11 ng/mL for Tg, 28.3 IU/mL for TgAb, and 0.014 μIU/mL for TSH.

Prior to 2014, Tg levels were measured using the first-generation Elecsys® Tg assay (Roche Diagnostics, Mannheim, Germany), which had a measuring range of 0.1-500 ng/mL. Since 2014, the second-generation Elecsys® Tg II assay (Roche Diagnostics) has been utilized. This assay applies the sandwich principle via electrochemiluminescence immunoassay (ECLIA) and provides a measuring range of 0.04 to 500 ng/mL, with automated instrument dilution capabilities up to 1:400. To minimize between-method discordances and ensure accurate longitudinal tracking, the serum Tg assays were standardized against the Certified Reference Material 457 (CRM-457).

TgAb was measured using the Elecsys® Anti-Tg assay (Roche Diagnostics), which utilizes a competitive immunoassay principle via ECLIA and has a measuring range of 10 to 4,000 IU/mL.

Measurement of Tg kinetics

Tg-DT and TgV calculations strictly utilized all available serial serum suppTg measurements obtained prior to the structural or clinical confirmation of disease recurrence.

Tg-DT was calculated by non-linear regression using a logarithmic curve:

$$\log y = \log a + bx$$

$$Tg\text{-}DT = (\log 2)/b$$

(Where x = years after remission and y = Tg level)

TgV was calculated as:

$$TgV = \frac{(Tg2 - Tg1)}{\text{time elapsed in years}}$$

using the Kaplan-Meier method, and differences between survival curves were assessed using log-rank tests. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The initial study population comprised 730 patients with DTC treated between January 2007 and December 2011. After applying the predefined inclusion and exclusion criteria, 460 patients were excluded. Consequently, 270 patients were included in the final analysis (**Figure 1**).

Of the 270 patients, 231 (85.6%) were female. The mean age was 44.3 years. During a mean follow-up period of 5.87 years, three patients (1.1%) developed disease recurrence. The sites of recurrence included the thyroid bed, the supraclavicular lymph node, and the lung. Baseline variables, including gender, age, cancer stage, histological type, surgical approach, and

For TgV calculation, Tg1 and Tg2 were defined according to clinical status. In patients who developed disease recurrence, Tg1 was defined as the suppressed Tg level at the time of recurrence, and Tg2 as the subsequent measurement. In patients who remained in remission, Tg1 and Tg2 were determined based on the interval of any observed Tg fluctuations, if applicable. Furthermore, when Tg levels were suppressed and below the analytical sensitivity limit (< 0.04 ng/mL), a value of 0.04 ng/mL was assigned for calculation.

Demographic and clinical characteristics were summarized using descriptive statistics. Categorical variables were expressed as frequencies and percentages. Continuous variables, including Tg-DT and TgV, were reported as mean ± standard deviation (SD). Data distribution was assessed to ensure that assumptions for statistical analyses were met prior to testing. One-way analysis of variance (ANOVA) was utilized to compare continuous data between the study groups, including the recurrence and non-recurrence groups. Optimal cutoff values for Tg-DT and TgV were determined using Receiver Operating Characteristic (ROC) curve analysis. Recurrence-free survival was estimated

cumulative RAI dose administered prior to remission, were not significantly associated with recurrence (**Table 1**).

Clinical course and characteristics of patients with disease recurrence

Case 1: An 82-year-old female was diagnosed with papillary thyroid cancer (PTC) with thyroid capsular invasion, staged as T3N0M0 and categorized as intermediate risk. She underwent total thyroidectomy followed by radioactive iodine (RAI) therapy with a dose of 150 mCi. The pre-ablation stimulated Tg (stimTg) level was 1.18 ng/mL, and TgAb were undetectable. Remission was achieved 7 months later, as evidenced by a negative DxTBS and stimTg level < 1 ng/mL. In January 2015, structural recurrence was detected in a right supraclavicular lymph node via ultrasonography and confirmed pathologically. At the time of recurrence, the patient's Tg-DT was 0.46 years, and the TgV was 0.94 ng/mL/year.

Case 2: A 55-year-old female was diagnosed with follicular thyroid cancer (FTC) with cervical lymph node and focal lung metastasis. She underwent complete thyroidectomy and received a cumulative RAI dose of 300 mCi administered over two treatment sessions. Remission was confirmed in May 2011 based on a negative DxTBS and suppressed Tg levels. However, in April 2014, structural disease recurrence was detected via computed tomography (CT), which revealed enlarging pulmonary lesions. These findings were associated with a Tg-DT of 0.7 years and a TgV of 0.58 ng/mL/year.

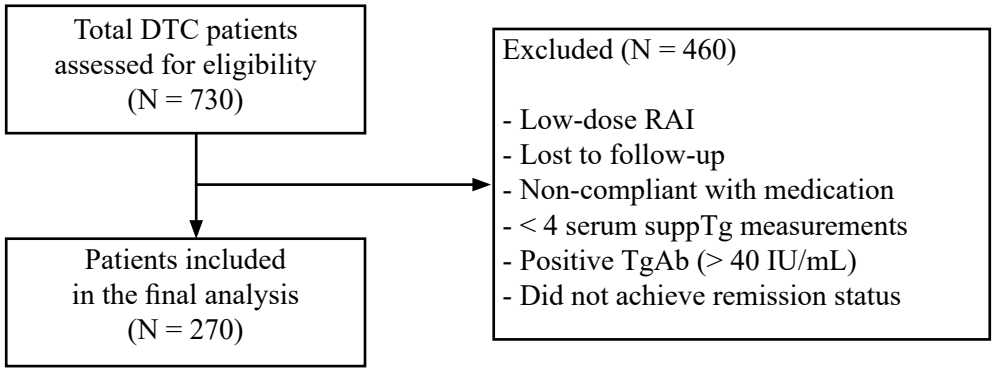

Figure 1. Study flow diagram

Table 1. Patient characteristics and recurrence

Characteristics		Recurrence (%) N = 3	Non-recurrence (%) N = 267	*p*-value
Gender	male	1 (33.3)	38 (14.2)	0.375
	female	2 (66.7)	229 (85.8)	
Age	< 45 years	1 (33.3)	135 (50.6)	0.621
	≥ 45 years	2 (66.7)	132 (49.4)	
TNM Staging	T1-2	2 (66.7)	183 (68.5)	1
	T3-4	1 (33.3)	84 (31.5)	
	N0-N1a	2 (66.7)	185 (69.3)	1
	N1b	1 (33.3)	82 (30.7)	
	M0	2 (66.7)	253 (94.8)	0.158
	M1	1 (33.3)	14 (97.8)	
Cell types	Papillary	2 (66.7)	223 (83.5)	0.423
	Follicular	1 (33.3)	44 (16.5)	

Table 1. Patient characteristics and recurrence (Cont.)

Characteristics		Recurrence (%) N = 3	Non-recurrence (%) N = 267	*p*-value
Thyroidectomy	Total	2 (66.7)	148 (55.4)	1
	Complete[1]	1 (33.3)	115 (43.1)	
	Subtotal	0	4 (1.5)	
Cumulative I-131 dose	< 600 mCi	3 (100)	262 (96.1)	1
	≥ 600 mCi	0	5 (1.9)	

[1]Complete thyroidectomy after the previous thyroid lobectomy.

Case 3: A 35-year-old female was diagnosed with PTC and cervical lymph node metastasis (T1N1aM0), classified as intermediate risk. Initial treatment included total thyroidectomy with right modified radical neck dissection, followed by a single session of 150 mCi RAI therapy. Remission was achieved in January 2012. In June 2016, structural recurrence was detected after ultrasonography identified a 1.92 cm mass in the left thyroid bed. At that time, the calculated Tg kinetics showed a Tg-DT of 1.82 years and a TgV of 0.04 ng/mL/year.

Predictive performance of Tg kinetics

Performance comparison and cutoff selection for Tg-DT

The mean Tg-DT in the recurrence group was 0.993±0.726 years, compared with 0.573±1.578 years in the non-recurrence group. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal Tg-DT cutoff for predicting recurrence. Two potential thresholds (≤ 6 months and ≤ 1 year) were evaluated. Both cutoffs yielded an area under the curve (AUC) of 1.0. A Tg-DT ≤ 1 year demonstrated superior overall diagnostic performance, with a sensitivity of 66.7% (95% CI: 9.4% – 99.2%), specificity of 100% (95% CI: 98.6% – 100%), and accuracy of 99.6% (95% CI: 97.9% – 99.9%) (**Table 2**), though these high estimates should be interpreted with caution due to the wide confidence intervals caused by the low event rate. Representative non-linear regression curves for Tg-DT calculation are shown in **Figure 2.**

Due to its higher sensitivity, overall diagnostic accuracy, and practical applicability in clinical settings, a Tg-DT threshold of ≤ 1 year was selected for further analysis. Consequently, the study population was categorized into two groups: patients with Tg-DT ≤ 1 year (n=2) and those with a Tg-DT > 1 year (n=268). The latter group included patients with stable or declining Tg levels. Patients with Tg-DT of ≤ 1 year had a significantly higher risk of disease recurrence compared with those in other groups ($p \leq 0.0005$) (**Table 3**).

Table 2. Comparison of diagnostic performance between Tg-DT cutoffs (≤ 6 months and ≤ 1 year) and TgV thresholds (≥ 0.05 ng/mL/year and ≥ 0.1 ng/mL/year)

Tg Threshold	Sensitivity	Specificity	Accuracy
Tg-DT ≤ 6 months	33.3%	100%	99.3%
Tg-DT ≤ 1 year	66.7%	100%	99.6%
TgV ≥ 0.05 ng/mL/year	66.7 %	98.9 %	98.5 %
TgV ≥ 0.1 ng/mL/year	66.7 %	100 %	99.6 %

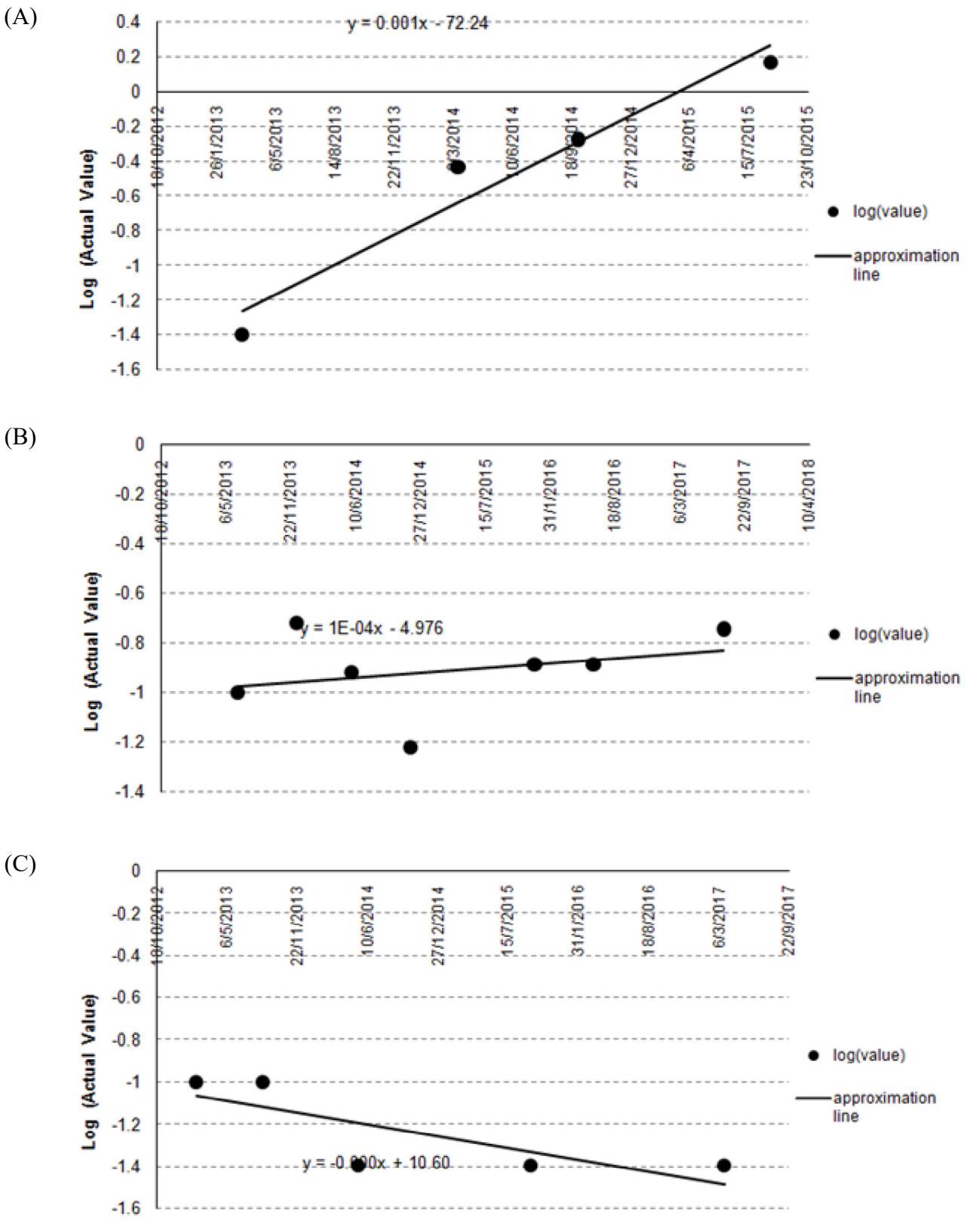

Figure 2. Representative non-linear regression curves for Tg-DT: (A) a patient with Tg-DT ≤ 1-year group; (B) a patient with Tg-DT > 1-year and a positive slope; and (C) a patient with Tg-DT > 1-year and a negative value.

Recurrence-free survival (RFS) was analyzed using Kaplan-Meier curves. Comparison between the Tg-DT ≤ 1 year and Tg-DT > 1 year groups showed a statistically significant difference in RFS ($p < 0.0005$). The mean RFS was 2.8 years (95% CI: 2.6 – 2.9) in the Tg-DT ≤ 1 year group and 9.9 years (95% CI: 9.9– 10.0) in the Tg-DT > 1 year group (**Figure 3**).

Performance comparison and cutoff selection of Tg-V

The mean TgV in the recurrence group was 0.536±0.427 ng/mL/year, compared with -0.123±0.419 ng/mL/year in the non-recurrence group. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal TgV cutoff for predicting tumor recurrence. The analysis indicated that TgV thresholds of ≥0.05 ng/mL and ≥0.1 ng/mL per year were both effective in identifying recurrence risk (**Table 2**).

The TgV threshold of ≥ 0.1 ng/mL/year was selected as the primary predictor of disease recurrence, as it demonstrated superior specificity (100%) and diagnostic accuracy (99.6%). Patients with TgV ≥ 0.1 ng/mL/year had a significantly higher probability of recurrence compared with those with TgV < 0.1 ng/mL/year ($p < 0.0005$) (**Table 3**).

Kaplan-Meier survival analysis showed a statistically significant difference in RFS between the two groups ($p < 0.0005$). The mean RFS was 2.8 years (95% CI: 2.6 -2.9) in patients with TgV ≥ 0.1 ng/mL/year, compared with 9.97 years (95% CI: 9.9-10.0) in those with TgV < 0.1 ng/mL/year (**Figure 4**).

Discussion

Monitoring protocols for patients following radioactive iodine (RAI) ablation have traditionally included diagnostic I-131 whole-body scans (DxTBS), stimulated Tg (stimTg) measurements, and neck ultrasonography.[1] However, improvements in the functional sensitivity of contemporary Tg assays have largely eliminated the routine need for DxTBS and stimulated Tg testing. Updated clinical standards, such as the 2015 American Thyroid Association (ATA) management guidelines, no longer recommend DxTBS or stimulated Tg testing for routine follow-up.[1] Instead, these guidelines prioritize serum Tg monitoring and adopt a suppTg cutoff of 0.2 ng/mL. Given that Tg values measured at a single time point have inherent limitations, the ATA 2015 guidelines also emphasize the clinical importance of Tg trends (kinetics) for effective long-term surveillance.

The findings of this study demonstrate that Tg-DT and TgV are highly specific markers for identifying disease recurrence in DTC patients who have achieved remission. Patients who exceed the identified diagnostic thresholds — specifically a Tg-DT of ≤ 1 year or a TgV of ≥ 0.1 ng/mL/year — should undergo intensified clinical surveillance to enable early detection of recurrent disease.

Our findings regarding the prognostic impact of Tg-DT are consistent with the landmark study by Miyauchi et al.[3] Although Miyauchi's cohort included a broader patient population — including those who did not receive postoperative RAI or had not yet achieved an "excellent response" — the current study focused specifically on

Table 3: Comparison of tumor recurrence according to Tg-DT and TgV status during TSH suppression

Tg threshold	Recurrence (N)	Non-recurrence (N)	*p*-value
Tg-DT ≤ 1 year	2	0	< 0.0005
Tg-DT > 1 year	1	267	
TgV ≥ 0.1 ng/mL/year	2	0	< 0.0005
TgV < 0.1 ng/mL/year	1	267	

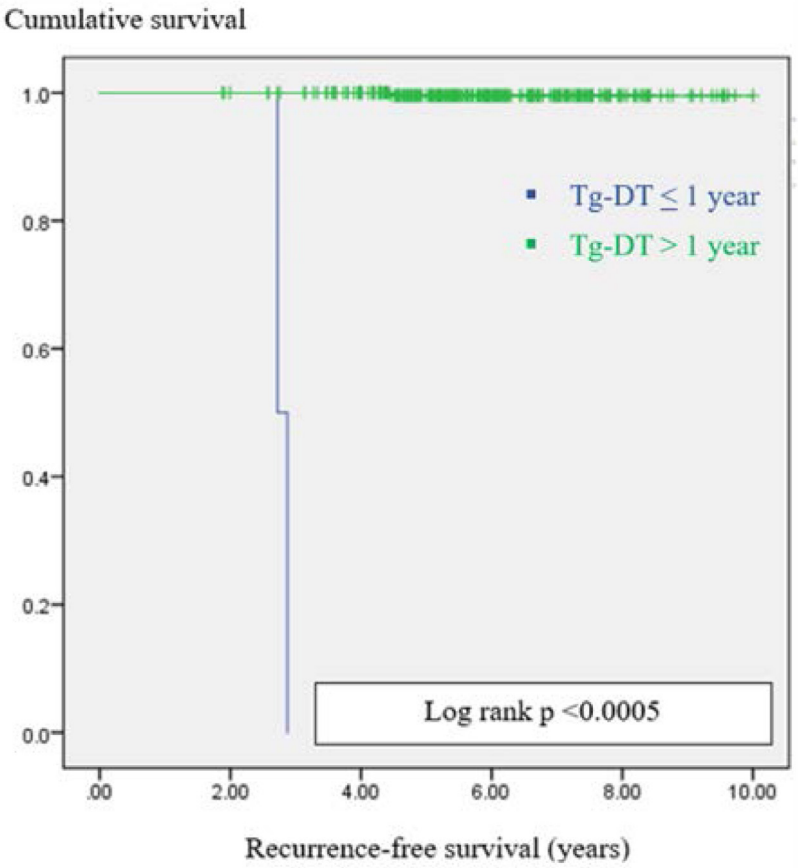

Figure 3. Kaplan-Meier survival analysis for recurrence-free survival (RFS) stratified by Tg-DT status. The mean RFS was significantly shorter in the Tg-DT ≤ 1 year group (2.8 years, 95% CI: 2.6-2.9) than in the Tg-DT > 1 year group (9.9 years, 95% CI: 9.9-10.0). The differences between the groups were statistically significant ($p < 0.0005$).

patients in remission. Despite the inherently low recurrence rate of 1% to 4% typically observed in "excellent response" patients, our study confirms that Tg-DT remains a reliable marker for recurrence in this subgroup.

A systematic review and meta-analysis by Giovanella et al.[5] evaluated five studies examining the relationship between Tg-DT and recurrence or disease progression across heterogeneous DTC patients. Four of these five studies demonstrated a significant positive association between Tg-DT < 1 year and tumor recurrence or progression. The only outlier was the study by Iwasaki et al., which focused on metastatic DTC patients undergoing tyrosine kinase inhibitor (TKI) therapy and found no significant correlation between Tg-DT and disease progression.[6]

However, the clinical utility of Tg-DT is limited by the need for at least 4 serial Tg measurements, which necessitates a prolonged follow-up period before a reliable prognosis can be established. While digital tools, such as the doubling-time calculator provided by the American Thyroid Association (ATA), are available, the time-intensive nature of gathering sufficient data points remains a limitation.

In contrast, TgV represents a more efficient clinical alternative, as it can be calculated from only two serial measurements obtained approximately six months apart, enabling earlier prediction of recurrence over a significantly shorter interval. Our findings are largely consistent with those reported by Wong et al,[4] who identified TgV as an independent predictor of recurrence in papillary thyroid cancer (PTC). While Wong et al. utilized a TgV cutoff of ≥ 0.3 ng/mL/year in a cohort with detectable Tg levels (> 0.2 ng/mL), our study identified a lower threshold of 0.1 ng/mL/year. This difference is likely attributable to our inclusion of patients with consistently

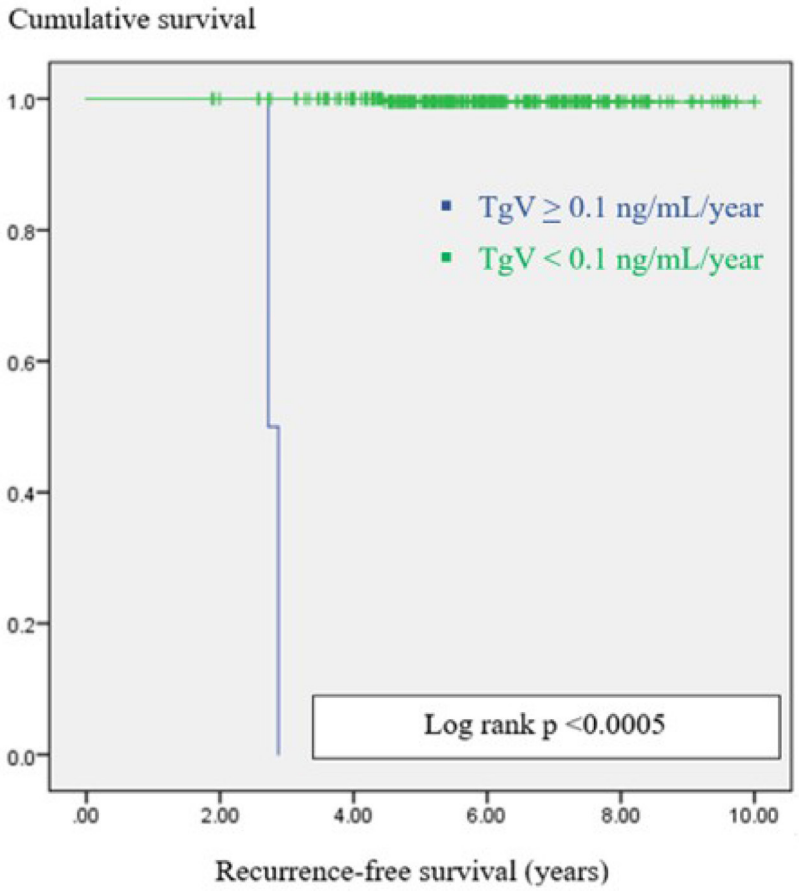

Figure 4. Kaplan-Meier survival curves for recurrence-free survival (RFS) stratified by TgV status. A statistically significant difference in survival was observed between the two cohorts ($p < 0.0005$). The mean RFS was 2.8 years (95% CI: 2.6-2.9) for patients with TgV ≥ 0.1 ng/mL/year and 9.97 years (95% CI: 9.9-10.0) for those with TgV < 0.1 ng/mL/year.

undetectable suppTg levels during follow-up, suggesting that a more conservative threshold may be appropriate for monitoring patients who have achieved complete remission.

This concept is directly supported by a recent 2025 study by Chiewvit et al.[7], which evaluated Tg kinetics in a cohort of patients with biochemical incomplete response (BIR) at our institution. In that BIR population, the optimal thresholds for predicting structural recurrence were significantly higher, specifically identifying a Tg-DT of less than 3.5 years and a TgV of 0.6 ng/mL/year or greater. The contrast between their BIR findings and our remission cohort cutoffs (Tg-DT ≤1 year and TgV ≥ 0.1 ng/mL/year) strongly reinforces the premise that a patient's baseline clinical status dictates their kinetic risk thresholds. Patients who have achieved an excellent response require more conservative kinetic cutoffs to detect early, subtle recurrence than those with an established biochemical incomplete response.

Although this study provides valuable insights into the prognostic utility of Tg kinetics, several limitations must be acknowledged. A major limitation of this study is the statistical fragility of analyzing a cohort with only 3 recurrence events. While an 'excellent response' to initial therapy naturally yields a low recurrence rate, this limited the statistical power of our analysis. Consequently, the ROC-derived diagnostic performance—including the AUC of 1.0 and the 100% specificity estimates—suggests that this perfect discrimination is likely due to overfitting to this specific dataset, given the extremely small number of outcome events (n=3), and must be interpreted with high caution. Therefore, the diagnostic thresholds identified here (Tg-DT ≤ 1 year and TgV ≥ 0.1 ng/mL/year) represent preliminary,

hypothesis-generating observations rather than definitive clinical guidelines. As highlighted by the low event rate, the findings underscore the need for future large-scale, multicenter longitudinal studies to properly validate the clinical utility of these kinetic markers.

As a retrospective, single-center study, the findings may be influenced by inherent selection biases. They may not be fully generalizable to other clinical settings or populations with different follow-up protocols. The retrospective design also limits the ability to control for all potential confounding variables.

The median follow-up period was relatively short, given the natural history of DTC, which often requires decades of surveillance to detect late recurrences. Consequently, only a small number of recurrent events were observed (n = 3), precluding multivariate analysis to adjust for potential confounders. Furthermore, the low event rate prevented an evaluation of disease-specific survival (DSS).

Patients with positive TgAb > 40 IU/mL were excluded due to the known interference of these antibodies with Tg assays.[8] However, current TgAb positivity thresholds are primarily established for the diagnosis of autoimmune thyroiditis rather than for defining meaningful interference in Tg monitoring. It remains unclear whether the exclusion of all patients with positive TgAb is strictly necessary for kinetic analyses.[9] Future studies should aim to establish TgAb cutoff values that optimize the balance between data inclusion and assay reliability.

In addition, recent clinical guidelines support de-escalation of RAI therapy, including omission of RAI or administration of a low-dose (30 mCi) in selected low- to intermediate-risk patients[10]. In the present study, patients who received low-dose RAI were specifically excluded from the analysis. Consequently, the diagnostic thresholds and prognostic implications of Tg-DT and TgV identified in our cohort may not be directly generalizable to patients managed with these more conservative RAI protocols.

Our results require prospective validation in larger cohorts. Future studies should focus on a direct head-to-head comparison of Tg kinetics (Tg-DT and TgV) and absolute Tg values at specific time points to determine which method offers the greatest clinical net benefit across various risk groups.

Conclusion

Our preliminary findings suggest that serum Tg-DT ≤ 1 year and TgV ≥ 0.1 ng/mL/year may serve as specific indicators of early tumor recurrence in patients with differentiated thyroid cancer who have previously achieved remission. Due to the small number of recurrence events (n = 3) within this cohort, the absolute clinical generalizability of these thresholds remains limited. These kinetic markers are best used as hypothesis-generating screening thresholds to prompt closer clinical monitoring, underscoring the need for robust, multicenter, longitudinal validation before routine implementation.

Data availability statement

The data supporting this study's findings are not publicly available due to privacy and ethical restrictions under the Personal Data Protection Act (PDPA) of Thailand. Data may be available from the first author (K.R.) upon reasonable request and with permission from the Siriraj Institutional Review Board.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Conceptualization and methodology, K.R. and A.C.; Investigation and formal analysis, K.R.; Writing – original draft, K.R.; Writing – review and editing, K.R. and A.C.; Supervision, A.C. All authors have read and agreed to the final version of the manuscript.

Use of artificial intelligence

The authors used AI (Gemini Pro) to improve the grammar, clarity, and style of the manuscript text. AI was not used for data collection, statistical analysis, result interpretation, or the generation of figures and tables. All final content, including all scientific claims and conclusions, was reviewed and edited by the authors, who are fully responsible for the integrity of the work.

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