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Integrating TERT promoter mutations into risk stratification of papillary thyroid cancer

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Abstract

Objective: The impact of telomerase reverse transcriptase (TERT) promoter mutations on short-term prognosis in papillary thyroid carcinoma (PTC) remains unclear. Clarifying this association may improve early risk stratification and guide timely management. This study aimed to evaluate the influence of TERT promoter mutations on short-term clinical outcomes in PTC and propose an enhanced risk stratification model incorporating TERT status.

Methods: This study analyzed 3,078 patients who underwent thyroidectomy for PTC at a tertiary referral center in South Korea from 2019 to 2021. Among these, 57 had TERT promoter mutations. Using propensity score matching (4:1) by age and sex, 227 patients with wild-type TERT promoter were selected. Short-term outcomes were categorized as no evidence of disease (NED), biochemical incomplete, or structural incomplete response. A novel classification system (risk stratification system-TERT (RSS-T)) integrating TERT status into the 2015 American Thyroid Association (ATA) risk stratification system was developed to improve risk prediction.

Results: Patients with TERT promoter mutations showed more aggressive disease and received more intensive treatments. Mutation carriers had poorer short-term outcomes, with lower NED rates and higher structural incomplete response rates. Among intermediate- and high-risk groups, TERT promoter mutations were associated with significantly worse outcomes. The RSS-T system demonstrated superior predictive performance over the ATA system.

Conclusion: TERT promoter mutations are associated with poor short-term outcomes in PTC, especially among intermediate- and high-risk patients. Incorporating TERT status into risk stratification can refine initial risk stratification and facilitate the efficient allocation of medical resources for follow-up care after primary treatment.

Keywords: TERT promoter mutations; papillary thyroid carcinoma; recurrence; prognosis

Introduction

Thyroid carcinoma is the most common endocrine malignancy, and papillary thyroid carcinoma (PTC) is the predominant subtype (1, 2, 3). PTC has a favorable prognosis, with most patients achieving excellent long-term outcomes. However, only a small subset of patients experience persistence, recurrence, or mortality after treatment. Therefore, accurately identifying patients at higher risk of poor outcomes is a critical aspect of PTC management. Numerous studies have investigated prognostic factors for thyroid cancer, which have been incorporated into the tumor-node-metastasis (TNM) staging system for predicting disease-specific mortality and the American Thyroid Association (ATA) initial risk stratification system for assessing the risk of disease recurrence and/or persistence (3, 4).

Telomerase reverse transcriptase (TERT), a molecular marker identified in 2013, is a key component of telomerase that maintains and protects telomeres at the ends of chromosomes. Mutations in the promoter region of TERT increase telomerase activity, enabling cancer cells to acquire immortality through continuous division (5, 6, 7). Consequently, thyroid cancers with TERT promoter mutations exhibit more aggressive characteristics and are associated with an increased risk of recurrence and mortality (8, 9, 10, 11, 12).

However, despite its known utility in predicting long-term prognosis, there are no clear guidelines regarding which patients should undergo TERT testing. Although the 2015 ATA guidelines acknowledge the potential prognostic value of TERT promoter mutations, they do not provide specific recommendations on their use or indicate when testing should be performed (3). Most existing evidence on long-term prognosis has been obtained from selected cohort populations who underwent surgery 10–20 years previously and had access to pathological samples for genetic testing. However, there is no evidence on whether adding TERT test information to actual short-term prognosis prediction in contemporary cohorts is better than the existing classification. In this study, we aimed to investigate the impact of TERT on short-term clinical outcomes and to identify patient groups for whom TERT testing may be beneficial. The subsequent phase of the study investigated whether incorporating TERT into the existing ATA initial risk stratification system improves the prediction of disease recurrence and/or persistence.

Materials and methods

Study population

This retrospective study analyzed data from 3,083 patients who underwent thyroid surgery for PTC and were evaluated for TERT promoter mutations at a tertiary referral center in South Korea between

January 2019 and December 2021. Since 2019, the center has routinely conducted TERT promoter gene testing on pathological specimens from all patients who have undergone thyroid cancer surgery.

Of the 3,083 patients, 62 were identified as having TERT promoter mutations. Five of these patients were excluded owing to loss to follow-up, leaving 57 patients with TERT promoter mutations in the final cohort. The remaining 3,021 patients harbored a wild-type TERT promoter.

To address this imbalance in the sample size and minimize potential confounding, we performed propensity score matching (PSM) to select a matched control group with a wild-type TERT promoter. We conducted 4:1 nearest-neighbor matching without replacement, using a caliper width of 0.2 SD of the logit of the propensity score. Age and sex were included in the propensity score model. A total of 284 patients were identified, comprising 57 patients with TERT promoter mutations and 227 matched patients with a wild-type TERT promoter. The absolute standardized mean difference was calculated to assess the balance of the variables used for matching and confirmed that all values were <0.1. The detailed results of the distribution of the matching variables and balance diagnostics are presented in Supplementary Table S1 (see the section on [Supplementary materials](#) given at the end of the article). Clinicopathological information was collected from electronic medical records (EMRs). This study was approved by the Institutional Review Board of our Institution (IRB No. (blinded)). The requirement for informed consent was waived owing to the retrospective nature of this study.

Detection of TERT promoter mutation

Genomic DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) tissue blocks using the Qiagen DNA FFPE Tissue Kit (Qiagen, Germany), following the manufacturer's instructions. TERT promoter mutations were analyzed using semi-nested polymerase chain reaction followed by sequencing, as previously described (13, 14).

Follow-up and outcomes

After surgery, all patients received thyrotropin suppression therapy, and adjuvant radioactive iodine (RAI) therapy was recommended according to the standard guidelines and the clinician's judgment. Follow-up data were collected from the EMRs. The causes and dates of death were obtained from the EMR or the Korean National Statistical Office database.

Short-term clinical outcomes were assessed based on the treatment response at the latest outpatient follow-up within the study period, which ended in June 2024. The median follow-up duration was 46.5 (interquartile range (IQR), 37.0–52.0) months. Treatment response was

determined according to the previously suggested response to therapy classification system (3, 15). Excellent and indeterminate responses were combined and classified as no evidence of disease (NED). Consequently, short-term outcomes were grouped into three categories: NED, biochemical incomplete response, and structural incomplete response.

Structural persistence/recurrence-free survival was defined as the time from initial surgery to the first detection of persistent structural disease or structural recurrence, as confirmed by imaging studies or pathology.

Statistical analyses

Categorical variables are presented as numbers and percentages, and continuous variables are presented as medians with IQRs. Chi-squared test, Fisher's exact test, or linear-by-linear association was used to compare categorical variables, as appropriate. The Mann–Whitney *U* test was used for continuous variables.

The cumulative probability of recurrence was estimated using the Kaplan–Meier method. Log-rank tests were used to compare the curves between the groups. Hazard ratios (HRs) for recurrence in individuals in different risk groups were assessed using the Cox proportional hazards regression model. To evaluate and compare the ATA risk stratification system and the new system incorporating the TERT promoter gene mutation status in prediction performance, the proportions of variance explained (PVE) in the Cox regression models were calculated. In addition, the discrimination performance of the systems was evaluated using C-indices. In addition, to evaluate whether the association between TERT promoter mutations and structural persistence/recurrence was independent of major tumor-related factors, we performed supplementary multivariable Cox regression analyses. One model adjusted for tumor size, extrathyroidal extension, and lymph node status, and another model incorporated TNM stage. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS version 27.0 for Windows (IBM Corp., USA) and R Statistical Software version 3.6.3 (Foundation for Statistical Computing, Austria).

Results

Baseline characteristics and short-term outcomes according to TERT promoter mutation status

Table 1 summarizes the clinical and pathological characteristics and short-term outcomes according to TERT promoter mutation status. The median follow-up duration was 46.5 (IQR, 37.0–52.0) months. Patients with TERT promoter mutations exhibited more aggressive

clinicopathological features than those with wild-type TERT. Tumor size was significantly larger in patients with TERT promoter mutations (2.7 (IQR, 1.1–4.0) vs 1.0 (IQR, 0.7–1.5) cm, *P* < 0.001) than in the wild-type group. Lymph node metastasis (especially N1b involvement) and gross extrathyroidal extension were significantly more frequent in the TERT-mutated group (both *P* < 0.001). Consistent with these aggressive features, patients with TERT promoter mutations were more likely to undergo total thyroidectomy (86.0 vs 45.4%, *P* < 0.001) and receive RAI treatment (91.8 vs 69.9%, *P* = 0.003), reflecting a trend toward more intensive initial treatment. In addition, among 153 patients with available BRAF V600E data, BRAF mutations were identified in 89.5% (51/57) of patients with TERT promoter mutations and 77.1% (74/96) of those with wild-type TERT (*P* = 0.055).

Short-term outcomes based on dynamic risk stratification were also significantly poorer in the TERT-mutated group than in the wild-type group (*P* < 0.001). Although 95.6% of patients with wild-type TERT achieved NED, only 64.9% of those with TERT mutations did. A structural incomplete response was observed in 29.8% of the TERT-mutated group, compared with only 2.2% of the wild-type group.

Short-term outcomes within ATA risk groups according to TERT status

Table 2 further examines short-term outcomes stratified by both ATA risk categories and TERT promoter mutation status. Among patients classified as low risk by the ATA system, all achieved NED regardless of TERT status. However, in the intermediate-risk group, structural incomplete response occurred in 28.6% of patients with TERT mutations, compared with only 3.1% among those with wild-type TERT (*P* < 0.001). Similarly, among high-risk patients, those with TERT mutations had a significantly higher rate of structural incomplete response (39.4 vs 7.7%, *P* = 0.004), while the proportion achieving NED was substantially lower (54.5 vs 88.5%).

Development of the RSS-T system based on ATA risk and TERT mutation status

Given that TERT promoter mutation status had no impact on short-term outcomes in ATA low-risk patients but showed marked prognostic differences within the intermediate- and high-risk groups (Table 2), we developed an alternative stratification system incorporating both ATA risk level and TERT status. This classification, termed the risk stratification system-TERT (RSS-T), categorizes patients into three groups: RSS-T1, ATA low-risk patients regardless of TERT status; RSS-T2, ATA intermediate- or high-risk patients with wild-type TERT; and RSS-T3, ATA intermediate- or high-risk patients with TERT promoter mutations.

Table 1 Baseline characteristics and short-term outcomes according to TERT promoter mutation status.

Characteristic	Total (n = 284)	TERT _{wild type} (n = 227)	TERT _{mutated} (n = 57)	P-value
Sex				0.928
Male	146 (51.4)	117 (51.5)	29 (50.9)	
Female	138 (48.6)	110 (48.5)	28 (49.1)	
Age at diagnosis (years)	60.0 (56.0–68.0)	60.0 (56.0–68.0)	60.0 (55.5–68.5)	0.94
Tumor size (cm)	1.1 (0.8–1.8)	1.0 (0.7–1.5)	2.7 (1.1–4.0)	<0.001
Surgical extent				<0.001
Total thyroidectomy	152 (53.5)	103 (45.4)	49 (86.0)	
Less than total	132 (46.5)	124 (54.6)	8 (14.0)	
Multifocality				0.413
Absent	168 (59.2)	137 (60.4)	31 (54.4)	
Present	116 (40.8)	90 (39.6)	26 (45.6)	
Lymph node metastasis				<0.001
N0/Nx	154 (54.2)	132 (58.1)	22 (38.6)	
N1a	77 (27.1)	62 (27.3)	15 (26.3)	
N1b	53 (18.7)	33 (14.5)	20 (35.1)	
Extrathyroidal invasion				<0.001
Absent	160 (56.3)	141 (62.1)	19 (33.3)	
mETE	66 (23.2)	61 (26.9)	5 (8.8)	
gETE	58 (20.4)	25 (11.0)	33 (57.9)	
AJCC TNM stage				<0.001
I	174 (61.3)	153 (67.4)	21 (36.8)	
II	79 (27.8)	61 (26.9)	18 (31.6)	
III	19 (6.7)	7 (3.1)	12 (21.1)	
IVa	7 (2.5)	6 (2.6)	1 (1.8)	
IVb	5 (1.8)	0	5 (8.8)	
Radioactive iodine treatment				0.003
Yes	117 (77.0)	72 (69.9)	45 (91.8)	
No	35 (23.0)	31 (30.1)	4 (8.2)	
BRAF V600E mutation				0.055
Wild type	28	22 (22.9)	6 (10.5)	
Mutated	125	74 (77.1)	51 (89.5)	
Missing data	131	131	0	
ATA risk stratification				<0.001
Low	114 (40.1)	104 (45.8)	10 (17.5)	
Intermediate	111 (39.1)	97 (42.7)	14 (24.6)	
High	59 (20.8)	26 (11.5)	33 (57.9)	
Dynamic risk stratification				<0.001
No evidence of disease	254 (89.4)	217 (95.6)	37 (64.9)	
Biochemical incomplete	8 (2.8)	5 (2.2)	3 (5.3)	
Structural incomplete	22 (7.8)	5 (2.2)	17 (29.8)	

Data are presented as number (percentage) or median (range).

TERT, telomerase reverse transcriptase; mETE, minimal extrathyroidal extension; gETE, gross extrathyroidal extension; AJCC TNM, American Joint Committee on Cancer TNM classification of malignant tumors; ATA, American Thyroid Association; BRAF, v-Raf murine sarcoma viral oncogene homolog B.

Short-term outcomes according to the ATA risk stratification system and the proposed RSS-T system

Table 3 presents the short-term outcomes according to both the original ATA risk stratification system and the proposed RSS-T system, which incorporates TERT promoter mutation status. In the ATA system, NED was observed in 100, 89.2, and 69.5% of patients in the low-, intermediate-, and high-risk groups, respectively. A structural incomplete response was noted in 0, 6.3, and 25.4% of patients in the same groups.

The RSS-T system exhibited a more refined stratification. All RSS-T1 patients achieved NED. Among RSS-T2 patients,

91.9% achieved NED and 4.1% had a structural incomplete response. In contrast, only 57.4% of RSS-T3 patients achieved NED, while 36.2% had a structural incomplete response, clearly identifying a high-risk subgroup requiring closer follow-up.

Comparative prognostic performance of the ATA risk stratification system and RSS-T system

To compare the prognostic performance, we evaluated the structural persistence/recurrence across the conventional ATA risk stratification system and the proposed RSS-T system (Table 4). In the ATA system, event rates increased with risk level: 0, 6.3, and 25.4%

Table 2 Short-term outcomes within ATA risk groups according to TERT status.

ATA risk	Dynamic risk stratification	TERT _{wild type} (n = 227)	TERT _{mutated} (n = 57)	P-value
Low (n = 114)	NED	104 (100)	10 (100)	NA
	Biochemical incomplete	0	0	
	Structural incomplete	0	0	
Intermediate (n = 111)	NED	90 (92.8)	9 (64.3)	<0.001
	Biochemical incomplete	4 (4.1)	1 (7.1)	
	Structural incomplete	3 (3.1)	4 (28.6)	
High (n = 59)	NED	23 (88.5)	18 (54.5)	0.004
	Biochemical incomplete	1 (3.8)	2 (6.1)	
	Structural incomplete	2 (7.7)	13 (39.4)	

Data are presented as number (percentage).

ATA, American Thyroid Association; TERT, telomerase reverse transcriptase; NED, no evidence of disease.

in the low-, intermediate-, and high-risk groups, respectively. Using the low-risk group as the reference, HRs with confidence intervals (CIs) for structural persistence/recurrence were 14.52 (95% CI, 0.73–290.04, $P = 0.0800$) for the intermediate-risk group and 45.26 (95% CI, 2.31–886.98, $P = 0.0120$) for the high-risk group. The C-index and PVE for the ATA model were 0.794 (95% CI, 0.720–0.868) and 70%, respectively.

In the RSS-T system, RSS-T1 had no events, whereas structural persistence/recurrence occurred in 4.1% of RSS-T2 patients and 36.2% of RSS-T3 patients. Compared with RSS-T1, HRs were 7.47 (95% CI, 0.35–159.06, $P = 0.1976$) for RSS-T2 and 88.56 (95% CI, 4.59–1,707.70, $P = 0.0030$) for RSS-T3. The RSS-T system demonstrated improved predictive performance, with a higher C-index of 0.890 (95% CI, 0.844–0.936) and a PVE of 86%.

Kaplan–Meier analysis further illustrated the differences in structural persistence/recurrence-free survival between the two stratification methods (Fig. 1A and B). Although the ATA risk stratification system demonstrated good predictive performance, with a C-index of 0.794 and a PVE of 70%, the RSS-T system showed significantly

improved discrimination, with a C-index of 0.890 and a PVE of 86%. Notably, the difference in C-indices between the two models was statistically significant ($P = 0.03$).

Discussion

In this study, we found that TERT promoter mutations were associated with significantly worse short-term clinical outcomes in patients with PTC. Although previous studies have established the role of TERT promoter mutations in predicting long-term prognosis (8, 9, 10, 11, 12), our findings highlight their impact on the early disease course. Consistent with previous reports, the known aggressive clinicopathological features associated with TERT promoter mutations, such as larger tumor size, more frequent extrathyroidal extension, and advanced TNM staging, were also observed, further reinforcing the growing recognition of TERT as a key prognostic marker in thyroid cancer.

Beyond identifying its association with short-term prognosis, our study demonstrates that integrating TERT promoter mutation status into the existing ATA risk stratification system improves its ability to predict structural persistence and recurrence. The proposed RSS-T classification refines risk assessment by further stratifying ATA intermediate- and high-risk patients, allowing for better identification of those at a heightened risk of persistence and recurrence. As shown in Fig. 1B, RSS-T2 patients (ATA intermediate-/high-risk without TERT mutations) demonstrated persistence/recurrence-free survival outcomes that remained comparable to those of ATA low-risk patients during the first 3 years after surgery, indicating a relatively favorable early prognosis. In contrast, RSS-T3 patients (ATA intermediate-/high-risk with TERT mutations) exhibited a markedly higher incidence of structural persistence or early recurrence within the first 2 years, emphasizing the need for closer surveillance in this subgroup.

Table 3 Short-term outcomes according to the ATA risk stratification system and proposed RSS-T system.

	Short-term outcome		
	NED	Biochemical incomplete	Structural incomplete
ATA risk stratification			
Low	114 (100)	0	0
Intermediate	99 (89.2)	5 (4.5)	7 (6.3)
High	41 (69.5)	3 (5.1)	15 (25.4)
Alternative grouping			
RSS-T1	114 (100)	0	0
RSS-T2	113 (91.9)	5 (4.1)	5 (4.1)
RSS-T3	27 (57.4)	3 (6.4)	17 (36.2)

Data are presented as number (percentage).

ATA, American Thyroid Association; RSS-T, risk stratification system-TERT; NED, no evidence of disease.

Table 4 Comparative prognostic performance of the ATA risk stratification and RSS-T systems.

	Events/total (%)	Structural persistence/recurrence		
		HR (95% CI)	P-value	C-index (95% CI)
ATA risk stratification				0.794 (0.720–0.868)
Low	0/114 (0)	1.00 (reference)	0.0074	
Intermediate	7/111 (6.3)	14.52 (0.73–290.04)	0.0800	
High	15/59 (25.4)	45.26 (2.31–886.98)	0.0120	
Alternative grouping				0.890 (0.844–0.936)
RSS-T1	0/114 (0)	1.00 (reference)	<0.0001	
RSS-T2	5/123 (4.1)	7.47 (0.35–159.06)	0.1976	
RSS-T3	17/47 (36.2)	88.56 (4.59–1,707.70)	0.0030	

P* = 0.030P*-value represents the comparison of C-indices between the ATA risk stratification and RSS-T models.

ATA, American Thyroid Association; RSS-T, risk stratification system-TERT; HR, hazard ratio; CI, confidence interval.

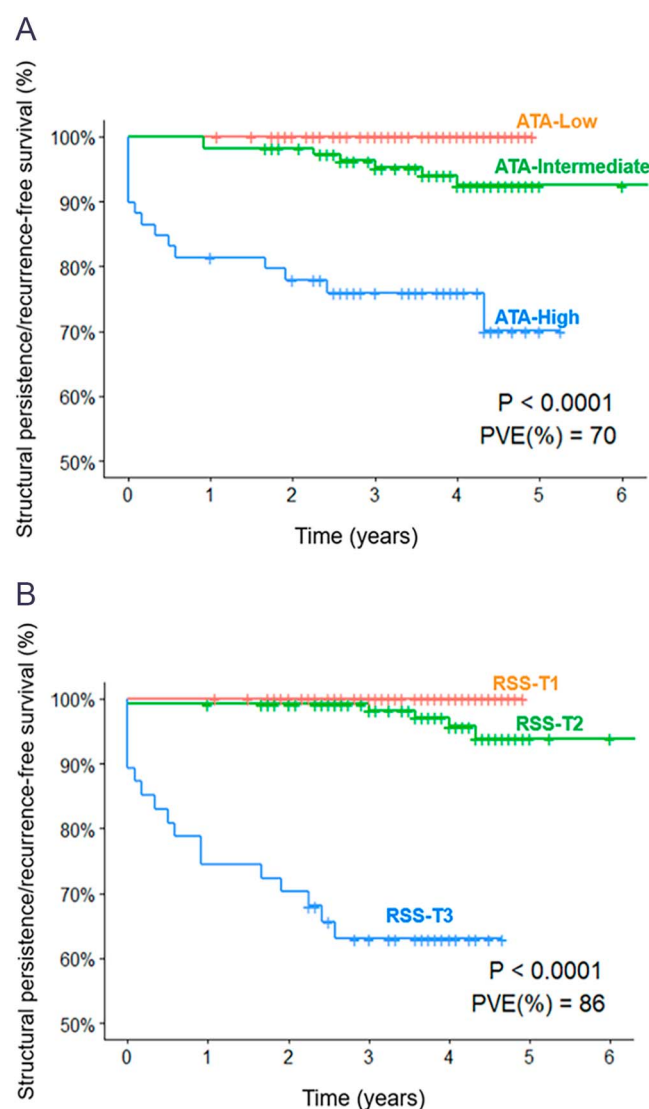
Notably, TERT promoter mutation status was already available to clinicians during the initial treatment period, as routine testing was implemented for all surgical cases in our center. Given the increasing awareness of its association with poor prognosis, patients with TERT mutations more often received intensified initial treatment, including completion thyroidectomy following initial lobectomy and postoperative RAI ablation. In our cohort, total thyroidectomy and RAI ablation were more frequently performed in patients with TERT promoter mutations than in those with wild-type TERT. To further illustrate this tendency within a comparable disease context, treatment patterns were examined among patients with stage I (localized) disease. Even within this early-stage group, total thyroidectomy was performed more frequently in patients with TERT promoter mutations (71.4 vs 29.4%), and RAI ablation was also more often administered (80.0 vs 53.3%). These observations indicate that clinicians tend to adopt more intensive initial treatment strategies when TERT mutations were identified. Despite this intensified management, short-term outcomes remained poorer in patients with TERT mutations. This suggests that TERT promoter mutation status confers prognostic information beyond conventional clinicopathologic factors and supports its potential utility in guiding early risk-adapted surveillance and more tailored follow-up strategies. To further assess whether this prognostic association was attributable to differences in underlying tumor characteristics, we performed supplementary multivariable Cox regression analyses. After adjustment for tumor size, extrathyroidal extension, and lymph node metastasis, TERT promoter mutations remained significantly associated with structural persistence/recurrence. A separate model incorporating TNM stage yielded similar results. These findings indicate that the prognostic association of TERT promoter mutations is not fully explained by baseline tumor characteristics or anatomical stage (Supplementary Table S2).

Furthermore, in our cohort, the prevalence of BRAF V600E mutations appeared numerically higher in the

TERT-mutated group (89.5 vs 77.1%); however, this difference did not reach statistical significance (*P* = 0.055). Because BRAF mutation data were available for only a subset of patients, these descriptive findings should be interpreted with caution. Taken together, although these results should be considered within the context of limited BRAF data availability, the absence of a statistically significant imbalance in BRAF V600E prevalence suggests that differences in BRAF co-mutation frequency are unlikely to fully account for the adverse prognostic impact associated with TERT promoter mutations.

Accurate risk stratification is crucial in PTC management, as most cases follow an indolent course, and identifying patients at higher risk of recurrence allows for optimized follow-up strategies. Attia *et al.* recently proposed that low- and intermediate-risk patients with an excellent response at 6 months and sustained remission for 10 years could safely transition to primary care follow-up (16). However, our findings underscore the importance of early identification of high-risk patients who may require more intensive monitoring and prolonged oncological follow-up. The RSS-T system provides a more precise framework for this differentiation and supports more timely and appropriate clinical decision-making.

Although the 2015 ATA risk stratification system demonstrated excellent predictive performance for structural persistence and recurrence in our cohort (C-index, 0.794; PVE, 70%), recent studies have sought to further refine risk assessment by incorporating additional prognostic factors, such as age, sex, pre-RAI serum thyroglobulin, and molecular markers (17, 18, 19, 20, 21, 22, 23). Our findings align with these efforts and support the potential of molecular integration to enhance the predictive accuracy of existing risk models. Integrating TERT promoter mutations into conventional risk models not only improves prediction but also provides valuable clinical insights into the timing and intensity of follow-up strategies. By identifying high-risk

**Figure 1**

Kaplan-Meier estimates of structural persistence/recurrence-free survival of patients stratified by for review only two systems: (A) the 2015 American Thyroid Association (ATA) risk stratification system and (B) the proposed risk stratification system-TERT (RSS-T) incorporating telomerase reverse transcriptase promoter mutation status. The ATA low-risk and RSS-T1 groups are identical, and no structural persistence or recurrent event was observed. In the ATA system, the discrimination of risk between ATA intermediate- and ATA high-risk groups is moderate. In contrast, the RSS-T system demonstrated an enhanced separation between the RSS-T2 and RSS-T3 groups. Over time, these two groups showed contrasting recurrence patterns. The RSS-T3 group exhibited a precipitous decline in the survival curve during the initial 3 years and was designated as the group with the most unfavorable prognosis. Conversely, the RSS-T2 group exhibited an overall favorable prognosis; however, in certain cases, a pattern of delayed recurrence was observed after the first 3 years. This observation underscores the necessity for continuous monitoring, a feature that distinguishes it from the RSS-T1 group, which exhibits the most favorable prognosis.

patients earlier, clinicians can tailor surveillance and treatment approaches to improve patient outcomes.

This study has several strengths, including the comprehensive analysis of TERT promoter mutations in a large cohort of patients who underwent surgery for PTC over a 3-year period. One notable strength is the routine implementation of TERT promoter mutation testing for all surgical PTC cases during this period, which enabled a complete and unbiased assessment of mutation prevalence and its clinical relevance. In addition, the availability of detailed clinicopathological data and an adequate follow-up duration (median, 46.5 months) allowed for a robust evaluation of short-term prognosis. Furthermore, the proposed RSS-T classification offers a practical and easily applicable extension to the existing ATA risk stratification, potentially improving real-world clinical decision-making.

Despite its strengths, this study has some limitations that should be considered. First, as this was a retrospective study conducted at a single tertiary referral center, there was a potential selection bias, with a higher proportion of patients presenting with advanced disease. Second, PSM was limited to age and sex and tumor-related factors, such as tumor size, extrathyroidal extension, lymph node status, and TNM stage, were not included in the matching process. Although supplementary multivariable analyses were conducted to account for these variables, residual confounding cannot be fully excluded. Third, although integrating TERT promoter mutation status into the ATA system improved risk discrimination, the modest degree of reclassification between the intermediate- and high-risk groups may limit its influence on individualized clinical decision-making within this heterogeneous population. The recently proposed 2025 ATA risk stratification system, which subdivides the intermediate-risk category into low-intermediate and intermediate-high groups, may provide a more suitable framework for future validation (24). In addition, BRAF V600E mutation data were available only for a subset of patients, limiting our ability to perform more comprehensive co-mutation analyses beyond descriptive comparisons. Finally, as all patients were treated at a single tertiary referral center in South Korea, caution is warranted when generalizing these findings to other populations or healthcare settings with different demographic or clinical characteristics. Further prospective multi-center studies with external validation are required to confirm the generalizability and clinical utility of the RSS-T system.

In conclusion, to the best of our knowledge, this is the first study to demonstrate an association between TERT promoter mutations and short-term prognosis in patients with PTC. Our findings show that TERT

mutations are associated with early structural persistence and recurrence and that integrating TERT mutation status into the ATA risk stratification system significantly improves risk discrimination, particularly among intermediate- and high-risk patients. The proposed RSS-T classification enhances the clinical utility of the existing model by enabling the earlier identification of patients who require closer surveillance. It is expected that the alternative initial recurrence risk assessment presented in this paper will help efficiently allocate medical resources for follow-up after primary treatment during both short- and mid-term periods.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-25-0703>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Ethics statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2024-03-114).

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