Prognostic Effects of *TERT* Promoter Mutations Are Enhanced by Coexistence with *BRAF* or *RAS* Mutations and Strengthen the Risk Prediction by the ATA or TNM Staging System in Differentiated Thyroid Cancer Patients

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Condensed abstract: Prognostic effects of *TERT* promoter mutations were enhanced by coexistence with *BRAF* or *RAS* mutations in differentiated thyroid cancer. Genetic screening of *TERT* promoter mutations could strengthen the predictions of mortality and recurrence by the preexisting staging systems including the ATA or TNM system, particularly in high-risk patients.

Abstract

BACKGROUND: Recent reports suggest that mutations in the promoter of the gene encoding telomerase reverse transcriptase (*TERT*) affect thyroid cancer outcomes.

METHODS: Total 551 patients with differentiated thyroid cancer (DTC) enrolled in this study. The median follow-up duration was 4.8 years (interquartile range, 3.4–10.6 years).

RESULTS: *TERT* promoter mutations were detected in 25 DTCs (4.5%): 2.8% in neither *BRAF*- nor *RAS*-mutated, 4.8% in *BRAF*-mutated, and 11.3% in *RAS*-mutated tumors. Moreover, they were frequently observed in 9.1% and 12.9% of the American Thyroid Association (ATA) high-risk and tumor-node-metastasis (TNM) stage III–IV groups, respectively. Coexistence of *BRAF* or *RAS* with *TERT* promoter mutations increased the aggressive clinicopathologic features, recurrence (hazard ratio [HR]=4.64 and 5.36; 95% confidence interval [CI], 1.42−15.18 and 1.20–24.02, for *BRAF* and *RAS*, respectively) and mortality (HR=15.13 and 14.75; 95% CI, 1.55−148.23 and 1.30–167.00, for *BRAF* and *RAS*, respectively) even after adjustment for age at diagnosis and sex, although the significance was lost after additional adjustment for pathologic characteristics. Further, *TERT* promoter mutations significantly increased the risk of both recurrence and mortality in the ATA high-risk (HR=5.79 and 16.16; 95% CI, 2.07−16.18 and 2.10–124.15, for recurrence and mortality, respectively) and TNM stage III–IV (HR=3.60 and 9.06; 95% CI, 1.19–10.85 and 2.09–39.26, for recurrence and mortality, respectively) groups.

CONCLUSIONS: Coexistence of *BRAF* or *RAS* mutations enhanced the prognostic effects of *TERT* promoter mutations. Furthermore, *TERT* promoter mutations strengthened the predictions of mortality and recurrence by the ATA and TNM staging systems, particularly in high-risk patients with DTC.

INTRODUCTION

In the past two decades, the incidence of thyroid cancer has increased dramatically worldwide: 15 fold in South Korea and more than double in the United States.[1,2] Although the majority of thyroid cancer patients have excellent overall survival, 15%–20% experience either recurrence or distant metastasis with an associated overall 10-year survival rate of 40%–85%.[3,4] Therefore, it is important to minimize overtreatment of patients who are likely to have a good prognosis, as well as to identify more accurately high-risk patients who would benefit from aggressive treatment and monitoring.

Telomerase reverse transcriptase (*TERT*) promoter mutation, recently described to be associated with aggressive clinicopathologic features and poor long-term prognosis in thyroid cancer, has received considerable attention as a novel prognostic molecular marker.[5] Further, the coexistence of *BRAF* with *TERT* promoter mutations has been reported as an indicator of the worst prognosis.[6,7] However, the prevalence of *TERT* promoter mutations is variable across countries with results of 7.5%–25.5% (median 11.9%) for papillary thyroid cancer (PTC),[5-13] and 13.8%–36.4% (median 17.1%) for follicular thyroid cancer (FTC).[5,8-11,14,15] In terms of cost-effectiveness, especially in areas with low prevalence, *TERT* promoter mutation assays are difficult to use as routine prognostic tests for all differentiated thyroid cancers (DTC).

In the present study, we aimed to define patient subsets that might benefit from *TERT* promoter mutation tests for prognostication. We investigated whether these mutations can improve the predictability for recurrence and disease-specific mortality among patients with a different *BRAF* or *RAS* mutational status, and among subgroups of high-risk patients classified by the preexisting risk scoring systems including the American Thyroid Association (ATA) and tumor-node-metastasis (TNM) staging systems.

MATERIALS AND METHODS

Patients and Tissue Samples

We studied 551 patients (472 females and 79 males) with DTC, including 432 PTCs and 119 FTCs, who underwent thyroidectomy between 1993 and 2012 at the Seoul National University Hospital, Seoul, Korea. We included 308 patients with PTC from our previous study of *BRAF* mutations,[16] whose tumor DNA samples were available to analyze *TERT* promoter and *RAS* mutations. The prevalence of *BRAF* mutations in Korea (including our hospital) is the highest in the world, whereas that of *RAS* mutations is lower than in other countries.[17] Therefore, we additionally examined 124 patients with *BRAF*-wild-type PTC in order to investigate the effects of *TERT* promoter mutations in *BRAF*-wild-type as well as *RAS*-mutated tumors. Their median follow-up duration was 4.8 years (interquartile range, 3.4–10.6 years). The treatment protocol was same as in previous studies.[18,19] The high-risk group of ATA staging system was defined as the presence of any of the following: macroscopic tumor invasion, incomplete tumor resection, and distant metastasis. This study was conducted according to the guidelines of the Declaration of Helsinki. The research protocol was approved by the Institutional Review Board Committee of the Seoul National University Hospital (No. H-1207-124-420). Informed consent was also obtained from all the subjects.

Mutational Analyses

Standard polymerase chain reaction (PCR) was carried out for genetic sequencing to identify *BRAF*, *RAS*, and *TERT* promoter mutations. Briefly, a fragment of the *BRAF*, *RAS*, or *TERT* promoter was amplified by PCR from genomic DNA by using previously described primers for *BRAF* codon 600, *N-RAS* codon 61, *H-RAS* codon 61, *K-RAS* codon 61, *N-RAS* codon 12/13, *H-RAS* codon 12/13, or *K-RAS* codon 12/13[16,20]; and primers 5′-CACCCGTCCTGCCCCTTCACCTT-3′ (sense) and 5′-CTTCCCACGTGCGCAGCAGGA-3′ (antisense) for *TERT*. The PCR product for *TERT* promoter was 191 bp, including the mutation sites C228T and C250T. Sequencing PCR was performed using the BigDye Terminator v3.1 Cycle Sequencing Ready Reaction Kit (Applied Biosystems, Foster City, CA, USA) and ABI PRISM 3130xl Genetic Analyzer (Applied Biosystems). We confirmed the

mutation-positive samples by sequencing using both forward and reverse primers.

Statistical Analyses

All statistical analyses were performed using SPSS version 20.0 (IBM Co, Armonk, NY, USA). Data are presented either as frequencies (%) or as mean ± standard deviation. Comparisons of categorical variables were performed using either the Pearson's χ^2 or Fisher's exact test (if the number was <5). Either the independent *t* or Wilcoxon-Mann-Whitney test was used for continuous variables. Survival curves were plotted using the Kaplan-Meier method with log-rank statistics. Cox proportional hazard regression was used to assess the risk of recurrence and disease-specific mortality. Statistical significance was defined as two-sided *P* values < .05.

RESULTS

Prevalence of TERT Promoter Mutations

TERT promoter mutations were detected in 25 DTCs (4.5%). Mutations were detected in 18 of 432 PTCs (4.2%) and in 7 of 119 FTCs (5.8%). *BRAF* mutations were found in 58.1% of PTCs, while *RAS* mutations in 9.6% of DTCs, 3.2% of PTCs, and 32.8% of FTCs. Upon estimation of the actual frequency of *TERT* promoter mutations in PTC using the reported frequency of *BRAF* mutations in our country[16] (72.7%, instead of 58.1% in this study), it showed a slight increase to 4.4%.

TERT promoter mutation frequencies were directly proportional to tumor size in PTCs (1.6%, 3.1%, 8.6%, and 28.6% of ≤1.0, 1.1–2.0, 2.1–4.0, and ≥4.1 cm, respectively [*P* for trend <.001]), and FTCs (0.0%, 3.4%, and 16.1% of ≤2.0, 2.1–4.0, and ≥4.1 cm, respectively [*P* for trend = .005]). *TERT* promoter mutations were more frequent in tumors harboring either *BRAF* (4.8%, 12 of 251; *P* = .257 vs. neither *BRAF* nor *RAS* mutations) or *RAS* (11.3%, 6 of 53; *P* = .006 vs. neither *BRAF* nor *RAS* mutations) mutations than in those harboring neither (2.8%, 7 of 247). However, this difference was

not statistically significant for *BRAF* mutations because of the small number of *TERT*-mutated cases.

Of 551 DTC patients, 176 (31.9%) belonged to the ATA high-risk, while 139 (25.2%) belonged to the TNM stage III–IV groups (Table 1). Additionally, prevalence of the *TERT* promoter mutations was increased in the ATA high-risk (9.1% vs. 2.3% in low-risk or 2.5% in intermediate-risk; $P = .005$) and TNM stage III–IV (12.9% vs. 1.7% in TNM stage I–II, $P < .001$) groups.

Association of TERT Promoter Mutations with BRAF and RAS Mutations and Clinicopathologic Characteristics

In the DTC patients harboring *TERT* promoter mutations, most clinicopathologic characteristics, such as older age, larger tumor size, more lymph node metastasis/distant metastasis, and higher rates of recurrent/persistent disease and disease-specific mortality, were more aggressive than in those with no mutations. Similar observations were made in the PTC patients (Table 1).

Since frequencies of *TERT* promoter mutations were higher in subjects carrying either *BRAF* or *RAS* mutations, we next investigated the effect of *TERT* promoter mutations on clinicopathologic outcomes according to the mutational status of *BRAF* and *RAS* (Table 2). In patients with PTC, *BRAF* mutation alone was associated with larger tumor size, extrathyroidal extension, and high ATA risk. Coexistence of *BRAF* and *TERT* promoter mutations conferred additive effects with most aggressive characteristics and worse clinical outcomes. However, *TERT* promoter mutation alone failed to show a significant risk effect because of the number of subjects. Similar results were obtained for *RAS* and *TERT* promoter mutations in DTC patients.

Impact of TERT Promoter Mutations on Recurrence and Disease-Specific Mortality

For DTCs, the tumor recurrence rate was 8.6% (13.43/1,000 person-years [PY]) in patients with wild-type *TERT*, vs. 28.0% (59.55/1,000 PY) in those harboring its mutant counterpart. The presence of *TERT* promoter mutations was associated with significantly increased recurrence risk (log rank *P*

< .001; Fig. 1A). Cox regression analysis revealed that the hazard ratio (HR) of *TERT* promoter mutations for recurrence was 2.98 (95% confidence interval [CI], 1.20–7.39; P = .019) after adjustment for tumor size, extrathyroidal extension, lymph node metastasis, and mutational status of *BRAF* and *RAS* (Table 3).

Further, the disease-specific mortality rate was 0.8% (1.01/1,000 PY) in patients with wild-type *TERT*, vs. 20.0% (29.82/1,000 PY) in those with mutant *TERT*. *TERT* promoter mutations were related to increased disease-specific mortality (log rank P < .001; Fig. 1B). The HR was 21.14 (95% CI, 3.60–124.23; P = .001) after adjustment for age at diagnosis, sex, aggressive tumor behaviors, and mutational status of *BRAF* and *RAS* (Table 4).

Similar effects of *TERT* promoter mutations were observed when we analyzed them in all subjects with PTCs and with PTCs over 1 cm. However, for FTCs, the small number of events precluded the analysis (Tables 3 and 4).

Additional Effects of Coexisting Mutations of BRAF or RAS with TERT Promoter Mutations on Recurrence and Disease-Specific Mortality

Next, we evaluated whether the risks of recurrence or mortality were influenced by the coexistence of *BRAF* or *RAS* mutations with *TERT* promoter mutations. The effects of *BRAF* mutations were analyzed separately in PTC patients. The presence of *BRAF*, *RAS*, or *TERT* promoter mutations alone did not significantly alter the recurrence risk, and the mortality risk of each mutation could not be calculated because of the small number of deaths. Interestingly, their coexistence increased the risk of both recurrence and mortality (Fig. 2, Supporting Tables 1 and 2), and the HRs were significant even after adjustments for age at diagnosis and sex. However, the statistical significance disappeared after additional adjustments for tumor size, extrathyroidal extension, and lymph node metastasis, except for mortality in coexisting *RAS* and *TERT* promoter mutations.

Additional Prognostic Effects of TERT Promoter Mutations on Conventional Risk Assessment Systems

We stratified all patients by using the risk assessment models, ATA and TNM staging systems, and then subdivided patients of the ATA high-risk group and the TNM stage III–IV into two groups based on the mutational status of the *TERT* promoter.

Among the ATA high-risk patients, those with *TERT*-mutated tumors showed 5.79 times higher recurrence risk than those carrying wild-type tumors, even after adjustment for age at diagnosis, sex, tumor size, and mutational status of *BRAF* and *RAS* (95% CI, 2.07−16.18; P = .001; Fig. 3A). Moreover, in the TNM stage III–IV group, the HR for recurrence was 3.60 after adjustment for age at diagnosis, sex, and mutational status of *BRAF* and *RAS* (95% CI 1.19–10.85; P = .023; Fig. 3B and Supporting Table 3). Stratified analysis for the HR among patients with either PTCs or with PTCs over 1 cm revealed that the presence of *TERT* promoter mutations additively increased the recurrence risk in high-risk patients by both models (Supporting Table 3).

Despite the study being limited by low number of deaths (9 of 551 [1.6%]; 2.19/1,000 PY), presence of *TERT* promoter mutations significantly increased disease-specific mortality in the ATA high-risk (adjusted HR, 16.16; 95% CI, 2.10–124.15; P = .007) and advanced-TNM stage (adjusted HR, 9.06; 95% CI 2.09–39.26; P = .003) patients (Figs. 3C and D; Supporting Table 4). Similar results were obtained when this analysis was performed in either patients with PTCs or those with PTCs over 1 cm (Supporting Table 4).

Additionally, we performed the same analysis in high-risk patients by the age-metastasis-extent-size (AMES) and metastasis-age-completeness of resection-invasion-size (MACIS) scoring systems. AMES grouped 16.3% of DTC patients as high-risk, and among them, 18.9% were positive for *TERT* promoter mutations. Meanwhile, 20.1% of the subjects exhibited a MACIS score ≥6.0, and 15.3% were *TERT*-positive. Similarly, the AMES high-risk patients harboring *TERT* promoter mutations presented significantly higher recurrence (HR, 5.38; 95% CI, 1.97–14.71; P = .001) and disease-

specific mortality (HR, 10.33; 95% CI, 2.44–43.85; $P = .002$) than those without the mutations. This observation was similar to that in the group with MACIS score ≥6.0 for recurrence (HR, 6.53; 95% CI, 2.34–18.27; $P < .001$) and mortality (HR, 8.68; 95% CI, 1.93–39.11; $P = .005$) (Supporting Figure 1).

DISCUSSION

TERT promoter mutations were detected in 4.5% of all DTCs and associated with poor prognosis. These mutations were more frequent in tumors also harboring either *BRAF* (4.8%) or *RAS* mutations (11.3%). Further, their coexistence indicated poor long-term prognosis and more aggressive clinicopathologic characteristics than either each mutation alone or no mutation at all. The prevalence of *TERT* promoter mutations was higher in high-risk patients: 9.1% and 12.9% in the ATA high-risk and advanced TNM stage groups, respectively. Among high-risk patients, the presence of *TERT* promoter mutations additively increased the risk of both recurrence and disease-specific mortality.

The strong association between *TERT* promoter mutations and thyroid cancer-specific mortality indicates that these mutations are promising prognostic markers for DTC. However, because the incidence rates of thyroid cancer are gradually increasing, especially for small-sized tumors, it would be important to identify an optimal subset for *TERT* promoter mutation tests. Since the presence of either *BRAF* or *RAS* mutations could increase the risks associated with *TERT* promoter mutations, routine tests of the latter in subjects harboring either *BRAF* or *RAS* mutations might provide additional prognostic information. However, the clinical usefulness of the *BRAF* mutational status has limitations in *BRAF*-prevalent areas. Therefore, we tried to adapt the *TERT* mutational status to staging systems for DTC to predict long-term outcomes. Although several staging systems have been proposed for better prediction of long-term prognosis of DTC,[21-24] currently there is no single, best staging system for both recurrence and mortality. The ATA staging system[23] was designed to assess the risk of recurrence in DTC while the TNM staging system[24] was developed to predict risk for death. However, we found that the limitation with respect to predictability of each staging system could be

overcome by additional information on the *TERT* mutational status. Moreover, the frequencies of *TERT* promoter mutations were enriched in high-risk patients; the proportion of these patients among those with DTC is usually less than one third.[25] Proportions of patients with DTC in the ATA high-risk and TNM stage III–IV groups in this study were 31.9% and 25.2%, respectively. Therefore, these high-risk subsets could benefit from the prediction of recurrence and mortality by routine *TERT* promoter mutation tests. Furthermore, we confirmed additional increase in risks of recurrence and mortality using other risk scoring systems, AMES[21] and MACIS.[22] Further studies on the cost-effectiveness of the tests are required, considering the different prevalence of *TERT* promoter mutations and proportions of high-risk patients in each country.

The adverse effects of *TERT* promoter mutations on clinicopathologic characteristics, recurrence, and mortality in this study were similar to those reported by previous studies.[5-13] Specifically, the coexistence of *TERT* promoter and *BRAF* mutations presented outcomes worse than each mutation alone as reported previously.[6,7,9] With respect to prognostic effect of the coexistence of *TERT* promoter and *RAS* mutations, only one study has reported an association of this coexistence with the prevalence of persistent disease.[11] Our study demonstrates, for the first time, that this coexistence might increase risk of mortality and recurrence, as well as aggressive pathologic features.

In this study, when we categorized *TERT*-positive patients into subgroups of *TERT* alone and coexistence of either *BRAF* or *RAS* and *TERT*, the prognostic role of *TERT* alone was not demonstrated. However, it would be hard to say to be conclusive because of the low frequency of *TERT* promoter mutations in our population (only 5 and 7 patients with *TERT* alone in PTC and DTC, respectively).

The overall prevalence of *TERT* promoter mutations in the current study was lower than that reported in other countries.[6-9,14] Since the frequency of *TERT* promoter mutations is strongly influenced by tumor size, the relatively large portion of small-size tumors in this study might be one of the reasons behind low frequency of the mutations. In this study, 56.9% of patients had PTCs 1 cm

or less compared to 13.7% in a previous study with a 7.5% frequency of *TERT* promoter mutations in PTC.[14] The second possible reason for the low rate of *TERT* promoter mutations is the geographic/ethnic difference. A recent study in European population reported *TERT* promoter mutations in 4.7% of microcarcinomas.[26] This is higher than the prevalence in our study, which was 1.6% of microcarcinomas and 3.1% of tumors 1.1–2.0 cm in size. There may be a selection bias due to the addition of 124 *BRAF*-wild-type PTC cases, which can affect the results especially the mutational frequency. Therefore, we analyzed without the additional patients and the frequency of *BRAF* mutations was raised from 58.1% to 81.5% in PTC patients, as in previous reports,[16] but *TERT* promoter mutation rate was left unchanged as 4.2% (13/308) in PTC. However, there still remains the possibility of some confounding effects due to selection bias in this study.

In conclusion, the coexistence of *BRAF* or *RAS* mutations enhanced the prognostic effects of *TERT* promoter mutations and the presence of *TERT* promoter mutations strengthened the prognostic predictions of conventional staging systems in DTC patients. Genetic screening of *TERT* promoter mutations in high-risk patients with DTC might bolster the prediction of mortality and recurrence.

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FIGURE LEGENDS

Figure 1. Effects of *TERT* promoter mutations on disease-free (A) and disease-specific (B) survival in patients with differentiated thyroid cancer (DTC).

Figure 2. Effects of *TERT* promoter, *BRAF*, and *RAS* mutations, and their coexistence on disease-free (A, B) and disease-specific (C, D) survival in patients with differentiated thyroid cancer (DTC) (A, C). Effects of *TERT* promoter and *BRAF* mutations, and their coexistence in patients with papillary thyroid cancer (PTC) (B, D).

Figure 3. Additional prognostic effects of *TERT* promoter mutations on high-risk patients defined by American Thyroid Association (ATA) (A, C), and tumor-node-metastasis (TNM) (B, D) stages. Effects of *TERT* promoter mutations on disease-free (A, B) and disease-specific (C, D) survival.

TABLE 1. Association of *TERT* Promoter Mutations with Clinicopathologic Outcomes

	PTC			DTC		
Variable	*TERT* (−)	*TERT* (+)	*P*[a]	*TERT* (−)	*TERT* (+)	*P*[a]
N	414 (95.8)	18 (4.2)		526 (95.5)	25 (4.5)	
C228T/C250T	-	15/3		-	21/4	
Sex, male	52 (12.6)	3 (16.7)	.490	73 (13.9)	6 (24.0)	.158
Age at diagnosis, years[b]	45.0 ± 13.2	56.8 ± 13.4	<.001	44.9 ± 13.4	56.3 ± 13.1	<.001
Tumor size, cm[c]	1.2 (0.8–1.9)	2.5 (1.3–4.1)	<.001	1.5 (0.8–2.5)	3.3 (2.0–4.5)	<.001
Extrathyroidal extension	247 (59.7)	14 (77.8)	.124	314 (59.7)	19 (76.0)	.103
Microscopic	134 (32.4)	3 (16.7)		174 (33.1)	7 (28.0)	
Gross	113 (27.3)	11 (61.1)		140 (26.6)	12 (48.0)	
Lymph node metastasis[d]	146 (37.5)	10 (55.6)	.124	147 (31.0)	11 (52.4)	.040
Distant metastasis	3 (0.7)	5 (27.8)	<.001	7 (1.3)	6 (24.0)	<.001
Disease status			.002			<.001
No evidence of disease	372 (89.9)	11 (61.1)		479 (91.1)	16 (64.0)	
Persistence	1 (0.2)	1 (5.6)		2 (0.4)	2 (8.0)	
Recurrence	41 (9.9)	6 (35.3)		45 (8.6)	7 (28.0)	
Disease-free survival, years[c]	4.4 (3.2–10.3)	3.2 (1.6–5.9)		4.6 (3.2–10.5)	4.2 (1.9–6.0)	
Death of disease	3 (0.7)	4 (22.2)	<.001	4 (0.8)	5 (20.0)	<.001
Disease-specific survival, years[c]	4.7 (3.7–10.6)	6.3 (3.2–10.2)		5.3 (3.8–10.9)	5.3 (3.2–10.3)	
ATA stage			<.001			.002
Low risk	127 (30.7)	2 (11.1)		170 (32.3)	4 (16.0)	
Intermediate risk	156 (37.7)	2 (11.1)		196 (37.3)	5 (20.0)	
High risk	131 (31.6)	14 (77.8)		160 (30.4)	16 (64.0)	
TNM stage						
I–II	318 (76.8)	5 (27.8)	<.001	405 (77.0)	7 (28.0)	<.001
III–IV	96 (23.2)	13 (72.2)		121 (23.0)	18 (72.0)	

Abbreviations: DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer.
[a]*P* value for comparison between wild-type and mutant *TERT*.
[b]Data presented as means ± standard deviations.
[c]Data presented as medians (interquartile ranges).
[d]Missing cases: 56 of total DTC, 52 of *TERT* wild-type and 4 of *TERT* mutated DTC; 25 of total PTC, 25 of *TERT* wild-type and none of *TERT* mutated PTC.

TABLE 2. Impact of *BRAF*, *RAS*, *TERT* Promoter Mutations, and Their Coexistence on Clinicopathologic Outcomes

	PTC				DTC			
Variable	No mutation	*BRAF* only	*TERT* only	*BRAF* + *TERT*	No mutation	*RAS* only	*TERT* only	*RAS* + *TERT*
N	162	239	5	12	240	47	7	6
Sex, male	13 (8.0)	36 (15.1)[a]	0 (0.0)	3 (25.0)	29 (12.1)	8 (17.0)	1 (14.3)	2 (33.3)
Age at diagnosis, years[d]	44.5 ± 13.9	45.1 ± 12.6	50.4 ± 18.8	59.5 ± 11.1[a,b]	44.9 ± 14.2	43.9 ± 13.4	50.1 ± 16.3	57.2 ± 12.3[a,b]
Tumor size, cm[e]	1.0 (0.7–1.5)	1.2 (0.8–2.0)[a]	1.0 (0.5–1.7)	3.0 (2.5–4.2)[a,b,c]	1.5 (0.8–2.7)	2.7 (1.5–4.0)[a]	1.4 (0.7–3.3)	5.0 (4.2–5.0)[a,b]
Extrathyroidal extension	82 (50.6)	162 (67.8)[a]	2 (40.0)	12 (100.0)[a,b,c]	129 (53.8)	23 (48.9)	3 (42.9)	4 (66.7)
Microscopic	53 (32.7)	78 (32.6)	0 (0.0)	3 (25.0)	81 (33.8)	15 (31.9)	1 (14.3)	3 (50.0)
Gross	29 (17.9)	84 (35.1)	2 (40.0)	9 (75.0)	48 (20.0)	8 (17.0)	2 (28.6)	1 (16.7)
Lymph node metastasis[f]	62 (40.8)	83 (37.1)	3 (60.0)	7 (58.3)	62 (29.7)	2 (4.9)[a]	3 (60.0)	1 (25.0)
Distant metastasis	1 (0.6)	2 (0.8)	1 (20.0)	3 (25.0)[a,b]	3 (1.3)	2 (4.3)	1 (14.3)	2 (33.3)[a]
Disease status								
No evidence of disease	144 (88.9)	215 (90.0)	4 (80.0)	7 (58.3)[a,b]	219 (91.3)	45 (95.7)	1 (14.3)	3 (50.0)[a,b]
Persistence	0 (0.0)	1 (0.4)	0 (0.0)	1 (8.3)	0 (0.0)	1 (2.1)	0 (0.0)	1 (16.7)[a]
Recurrence	18 (11.1)	23 (9.7)	1 (20.0)	4 (36.4)[a,b]	21 (8.8)	1 (2.2)	1 (14.3)	2 (40.0)[b]
Disease-free survival, years[e]	3.8 (2.7–4.7)	6.1 (4.1–10.7)[a]	3.0 (2.4–6.8)	4.5 (1.2–6.0)	4.0 (2.9–6.2)	4.3 (2.3–11.0)	3.1 (2.9–5.3)	4.4 (0.6–9.2)
Death of disease	1 (0.6)	2 (0.8)	0 (0.0)	4 (33.3)[a,b]	2 (0.8)	0 (0.0)	0 (0.0)	1 (16.7)
Disease-specific survival, years[e]	4.0 (3.3–7.5)	9.6 (4.4–10.8)[a]	3.0 (2.4–10.3)	6.3 (4.4–13.1)[a]	4.3 (3.4–10.6)	5.5 (3.4–11.6)	4.2 (2.9–10.1)	4.0 (2.2–11.3)
ATA stage								
Low risk	57 (35.2)	60 (25.1)[a]	2 (40.0)	0 (0.0)[a,b]	87 (36.3)	23 (48.9)	3 (42.9)	1 (16.7)
Intermediate risk	66 (40.7)	87 (36.4)	1 (20.0)	1 (8.3)[a,b]	94 (39.2)	15 (31.9)	2 (28.6)	2 (33.3)
High risk	39 (24.1)	92 (38.5)	2 (40.0)	11 (91.7)[a,b]	59 (24.6)	9 (19.1)	2 (28.6)	3 (50.0)
TNM stage								
I–II	127 (78.4)	179 (74.9)	3 (60.0)	2 (16.7)[a,b]	185 (77.1)	41 (87.2)	4 (57.1)	1 (16.7)[a,b]
III–IV	35 (21.6)	60 (25.1)	2 (40.0)	10 (83.3)[a,b]	55 (22.9)	6 (12.8)	3 (42.9)	5 (83.3)[a,b]

Abbreviations: DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer.
[a]Significantly different from No mutation group.
[b]Significantly different from *BRAF* only group.
[c]Significantly different from *TERT* only group.
[d]Data presented as means ± standard deviations.
[e]Data presented as medians (interquartile ranges).
[f]Missing cases: 25 of total PTCs (10 of no mutation and 15 of *BRAF* only); 41 of total DTCs (31 of no mutation, 6 of *RAS* only, 2 of *TERT* only, and 2 of *RAS* + *TERT*).

TABLE 3. Hazard Ratios of *TERT* Promoter Mutations for Recurrence

Type of Cancer	Recurrence/N (%)				Recurrences per 1,000 PY		Hazard Ratio (95% CI)			
	Overall	*TERT* wt	*TERT* mut	*P*[a]	*TERT* wt	*TERT* mut	Unadjusted	*P*	Adjusted[b]	*P*
DTC	52/551 (9.4)	45/526 (8.6)	7/25 (28.0)	<.001	13.43	59.55	4.22 (1.90–9.38)	<.001	2.98 (1.20–7.39)	.019
PTC	47/432 (10.9)	41/414 (9.9)	6/18 (33.3)	<.001	16.04	76.66	4.60 (1.95–10.87)	.001	3.72 (1.43–9.65)	.007
PTC >1 cm	38/246 (15.4)	32/232 (13.8)	6/14 (42.9)	<.001	20.54	95.58	4.57 (1.89–11.04)	.001	7.03 (2.34–21.11)	.001
FTC	5/119 (4.2)	4/112 (3.6)	1/7 (14.3)	.135	5.03	25.46	4.57 (0.51–40.94)	.175	–	–

Abbreviations: PY, person-years; CI, confidence interval; wt, wild-type; mut, mutant; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer.

[a]Log-rank *P* values.

[b]Adjusted for age at diagnosis, sex, tumor size, extrathyroidal extension, lymph node metastasis, and mutational status of *BRAF* and *RAS*.

TABLE 4. Hazard Ratios of *TERT* Promoter Mutations for Death from Thyroid Cancer

Type of Cancer	Mortality/N (%)				Deaths per 1,000 PY		Hazard Ratio (95% CI)			
	Overall	*TERT* wt	*TERT* mut	*P*[a]	*TERT* wt	*TERT* mut	Unadjusted	*P*	Adjusted[b]	*P*
DTC	9/551 (1.6)	4/526 (0.8)	5/25 (20.0)	<.001	1.01	29.82	30.43 (8.13–113.83)	<.001	21.14 (3.60–124.23)	.001
PTC	7/432 (1.6)	3/414 (0.7)	4/18 (22.2)	<.001	1.00	31.26	33.57 (7.46–151.09)	<.001	20.48 (2.95–142.08)	.002
PTC >1 cm	6/246 (2.4)	3/232 (1.3)	3/14 (21.4)	<.001	1.59	27.25	19.65 (3.91–98.88)	<.001	19.20 (2.56–144.15)	.004
FTC	2/119 (1.7)	1/112 (0.9)	1/7 (14.3)	.003	1.06	25.18	20.66 (1.26–337.80)	.034	–	–

Abbreviations: PY, person-years; CI, confidence interval; wt, wild-type; mut, mutant; DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer.

[a]Log-rank *P* values.

[b]Adjusted for age at diagnosis, sex, tumor size, extrathyroidal extension, lymph node metastasis, and mutational status of *BRAF* and *RAS*.

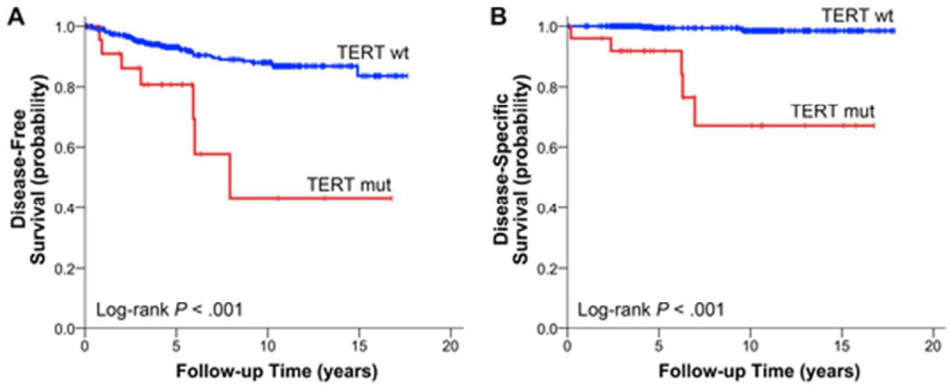

Figure 1. Effects of TERT promoter mutations on disease-free (A) and disease-specific (B) survival in patients with differentiated thyroid cancer (DTC).
24x14mm (600 x 600 DPI)

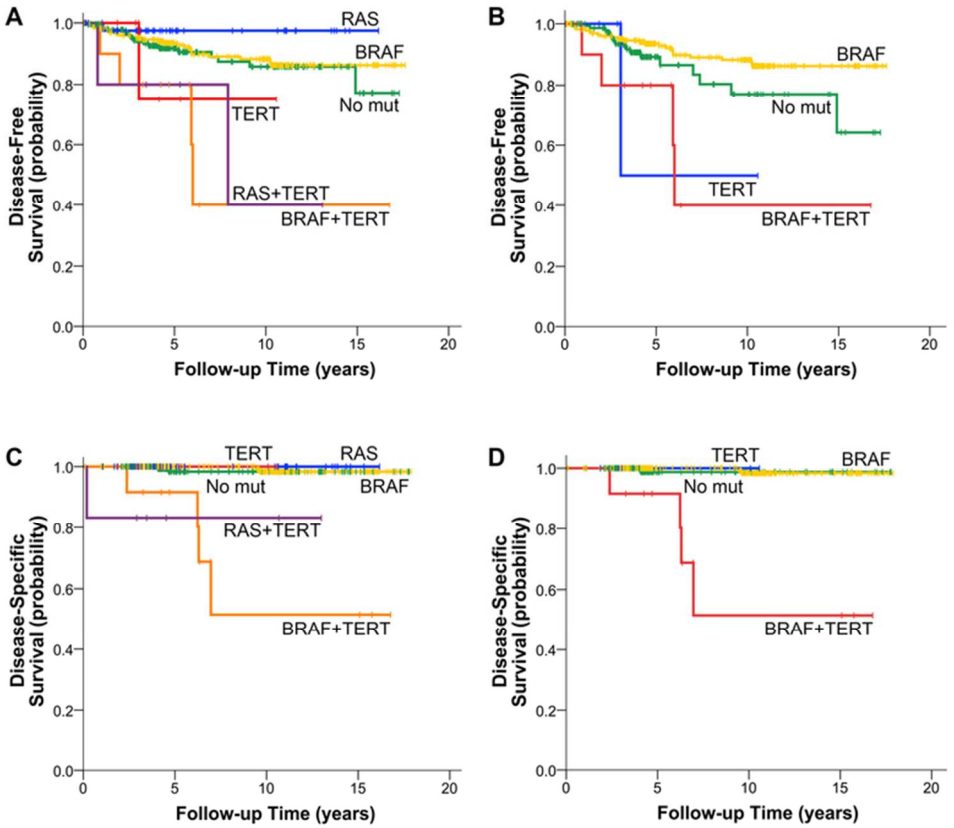

Figure 2. Effects of TERT promoter, BRAF, and RAS mutations, and their coexistence on disease-free (A, B) and disease-specific (C, D) survival in patients with differentiated thyroid cancer (DTC) (A, C). Effects of TERT promoter and BRAF mutations, and their coexistence in patients with papillary thyroid cancer (PTC) (B, D).
34x29mm (600 x 600 DPI)

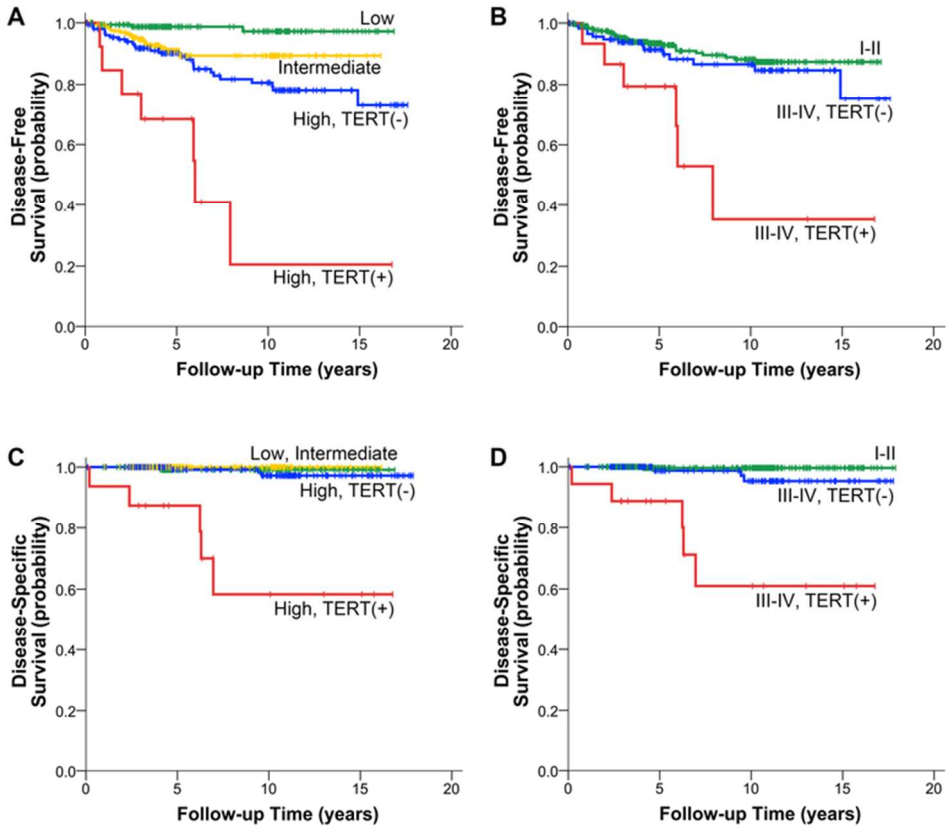

Figure 3. Additional prognostic effects of TERT promoter mutations on high-risk patients defined by American Thyroid Association (ATA) (A, C), and tumor-node-metastasis (TNM) (B, D) stages. Effects of TERT promoter mutations on disease-free (A, B) and disease-specific (C, D) survival.
34x29mm (600 x 600 DPI)

SUPPORTING TABLES

TABLE S1. Hazard Ratios of *TERT*, Other Driver Mutations, or Their Coexistence for Recurrence

	N (%)	Recurrences per 1,000 PY	Unadjusted HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*	Adjusted HR[b] (95% CI)	*P*
PTC								
No mutation	18/162 (11.1)	23.53	1.00	–	1.00	–	1.00	–
BRAF only	23/239 (9.6)	13.08	0.56 (0.30–1.05)	.073	0.58 (0.31–1.09)	.091	0.71 (0.36–1.39)	.314
TERT only	1/5 (20.0)	46.66	1.92 (0.26–14.43)	.525	2.21 (0.29–16.70)	.441	2.53 (0.33–19.74)	.375
BRAF + *TERT*	4/12 (33.3)	71.38	2.98(1.00–8.84)	.049	4.64 (1.42–15.18)	.011	2.30 (0.66–8.02)	.192
DTC								
No mutation	21/240 (8.8)	15.94	1.00	–	1.00	–	1.00	–
RAS only	1/47 (2.1)	3.64	0.24 (0.03–1.79)	.165	0.24 (0.03–1.77)	.160	0.48 (0.06–3.77)	.486
TERT only	1/7 (14.3)	32.34	1.86 (0.25–13.81)	.546	2.03 (0.27–15.18)	.489	2.59 (0.33–20.13)	.364
RAS + *TERT*	2/6 (33.3)	65.39	4.16 (0.97–17.79)	.054	5.36 (1.20–24.02)	.028	3.09 (0.64–14.81)	.159

Abbreviations: PY, person-years; CI, confidence interval; PTC, papillary thyroid cancer; DTC, differentiated thyroid cancer.
[a]Adjusted for age at diagnosis and sex.
[b]Adjusted for age at diagnosis, sex, tumor size, extrathyroidal extension, and lymph node metastasis.

TABLE S2. Hazard Ratios of *TERT*, Other Driver Mutations, or Their Coexistence for Mortality

	N (%)	Deaths per 1,000 PY	Unadjusted HR (95% CI)	*P*	Adjusted HR[a] (95% CI)	*P*	Adjusted HR[b] (95% CI)	*P*
PTC								
No mutation	1/162 (0.6)	1.07	1.00	–	1.00	–	1.00	–
BRAF only	2/239 (0.8)	0.99	0.68 (0.06–7.55)	.751	0.57 (0.51–6.44)	.651	0.83 (0.03–2.64)	.158
TERT only	0/5 (0.0)	0	–	–	–	–	–	–
BRAF + TERT	4/12 (33.3)	42.11	36.31 (4.01–328.92)	.001	15.13 (1.55–148.23)	.020	9.58 (0.42–219.74)	.157
DTC								
No mutation	2/240 (0.8)	1.27	1.00	–	1.00	–	1.00	–
RAS only	0/47 (0.0)	0	–	–	–	–	–	–
TERT only	0/7 (0.0)	0	–	–	–	–	–	–
RAS + TERT	1/6 (16.7)	28.78	20.70 (1.87–228.53)	.013	14.75 (1.30–167.00)	.030	24.34 (1.51–392.20)	.024

Abbreviations: PY, person-years; CI, confidence interval; PTC, papillary thyroid cancer; DTC, differentiated thyroid cancer.
[a]Adjusted for age at diagnosis and sex.
[b]Adjusted for age at diagnosis, sex, tumor size, extrathyroidal extension, and lymph node metastasis.

TABLE S3. Addition of *TERT* Promoter Mutations to High-Risk Patients Defined by ATA or TNM Stage for Recurrence

Type of Cancer		Unadjusted				Adjusted[a]			
		Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
DTC	ATA stage								
	Low	1.00	–	–	–	1.00	–	–	–
	Intermediate	5.46 (1.59–18.77)	.007	–	–	5.45 (1.57–18.98)	.008	–	–
	High, *TERT*(-)	8.69 (2.63–28.72)	<.001	1.00	–	8.71 (2.63–28.88)	<.001	1.00	–
	High, *TERT*(+)	37.91 (9.77–147.03)	<.001	4.53 (1.94–10.56)	<.001	48.91 (11.51–207.87)	<.001	5.79 (2.07–16.18)	.001
	TNM stage								
	I-II	1.00	–	–	–	1.00	–	–	–
	III-IV, *TERT*(-)	1.34 (0.71–2.50)	.368	1.00	–	2.15 (0.98–4.70)	.055	1.00	–
	III-IV, *TERT*(+)	5.20 (2.17–12.45)	<.001	3.82 (1.46–10.02)	.006	11.06 (3.74–32.70)	<.001	3.60 (1.19–10.85)	.023
PTC	ATA stage								
	Low	1.00	–	–	–	1.00	–	–	–
	Intermediate	5.14 (1.50–17.69)	.009	–	–	6.82 (1.78–26.11)	.005	–	–
	High, *TERT*(-)	6.40 (1.91–21.39)	.003	1.00	–	7.87 (2.21–28.06)	.001	1.00	–
	High, *TERT*(+)	26.92 (6.71–108.05)	<.001	4.50 (1.79–11.29)	.001	46.39 (10.14–212.24)	<.001	7.57 (2.51–22.87)	<.001
	TNM stage								
	I-II	1.00	–	–	–	1.00	–	–	–
	III-IV, *TERT*(-)	1.18 (0.60–2.30)	.633	1.00	–	2.14 (0.93–4.89)	.072	1.00	–
	III-IV, *TERT*(+)	5.39 (2.08–13.95)	.001	4.34 (1.51–12.49)	.007	15.05 (4.58–49.45)	<.001	4.00 (1.21–13.22)	.023
PTC >1 cm	ATA stage								
	Low	1.00	–	–	–	1.00	–	–	–
	Intermediate	4.07 (0.89–18.65)	.071	–	–	7.48 (1.26–44.23)	.027	–	–
	High, *TERT*(-)	4.41 (1.03–18.87)	.045	1.00	–	7.29 (1.37–38.66)	.020	1.00	–
	High, *TERT*(+)	17.67 (3.54–88.19)	<.001	4.17 (1.64–10.61)	.003	58.18 (8.97–377.26)	<.001	7.90 (2.56–24.45)	<.001
	TNM stage								
	I-II	1.00	–	–	–	1.00	–	–	–
	III-IV, *TERT*(-)	0.82 (0.38–1.78)	.618	1.00	–	1.91 (0.70–5.25)	.208	1.00	–
	III-IV, *TERT*(+)	3.82 (1.45–10.09)	.007	4.50 (1.48–13.71)	.008	14.04 (3.75–52.59)	<.001	4.69 (1.34–16.38)	.015

Abbreviations: DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; CI, confidence interval.
[a]Adjusted for age at diagnosis, sex, tumor size, and mutational status of *BRAF* and *RAS* in ATA stage; age at diagnosis, sex, and mutational status of *BRAF* and *RAS* in TNM stage.

TABLE S4. Addition of *TERT* Promoter Mutations to High-Risk Patients Defined by ATA or TNM Stage for Thyroid Cancer-Specific Death

			Unadjusted		Adjusted[a]	
Type of Cancer		Death, N (%)	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
DTC	ATA stage					
	Low	1/174 (0.6)	–	–	–	–
	Intermediate	0/201 (0.0)	–	–	–	–
	High, *TERT*(-)	3/160 (1.9)	1.00	–	1.00	–
	High, *TERT*(+)	5/16 (31.3)	23.33 (5.50–98.94)	<.001	16.16 (2.10–124.15)	.007
	TNM stage					
	I-II	1/412 (0.2)	–	–	–	–
	III-IV, *TERT*(-)	3/121 (2.5)	1.00	–	1.00	–
	III-IV, *TERT*(+)	5/18 (27.8)	13.20 (3.14–55.48)	<.001	9.06 (2.09–39.26)	.003
PTC	ATA stage					
	Low	1/129 (0.8)	–	–	–	–
	Intermediate	0/158 (0.0)	–	–	–	–
	High, *TERT*(-)	2/131 (1.5)	1.00	–	1.00	–
	High, *TERT*(+)	4/14 (28.6)	27.24 (4.90–151.39)	<.001	94.50 (2.03–4406.31)	.020
	TNM stage					
	I-II	1/323 (0.3)	–	–	–	–
	III-IV, *TERT*(-)	2/96 (2.1)	1.00	–	1.00	–
	III-IV, *TERT*(+)	4/13 (30.8)	18.10 (3.29–99.66)	.001	15.27 (2.60–89.80)	.003
PTC >1 cm	ATA stage					
	Low	1/48 (2.1)	–	–	–	–
	Intermediate	0/76 (0.0)	–	–	–	–
	High, *TERT*(-)	2/109 (1.8)	1.00	–	1.00	–
	High, *TERT*(+)	3/13 (23.1)	18.03 (2.97–109.55)	.002	88.64 (1.80–4376.90)	.024
	TNM stage					
	I-II	1/165 (0.6)	–	–	–	–
	III-IV, *TERT*(-)	2/69 (2.9)	1.00	–	1.00	–
	III-IV, *TERT*(+)	3/12 (25.0)	10.53 (1.75–63.46)	.010	17.75 (2.00–157.41)	.010

Abbreviations: DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; CI, confidence interval.
[a]Adjusted for age at diagnosis, sex, tumor size, and mutational status of *BRAF* and *RAS* in ATA stage; age at diagnosis, sex, and mutational status of *BRAF* and *RAS* in TNM stage.

SUPPORTING FIGURE LEGEND

Figure S1. Additional prognostic effects of *TERT* promoter mutations on high-risk patients defined by AMES (A, C), and MACIS (B, D) scoring systems. Effects of *TERT* promoter mutations on disease-free (A, B) and disease-specific (C, D) survival.

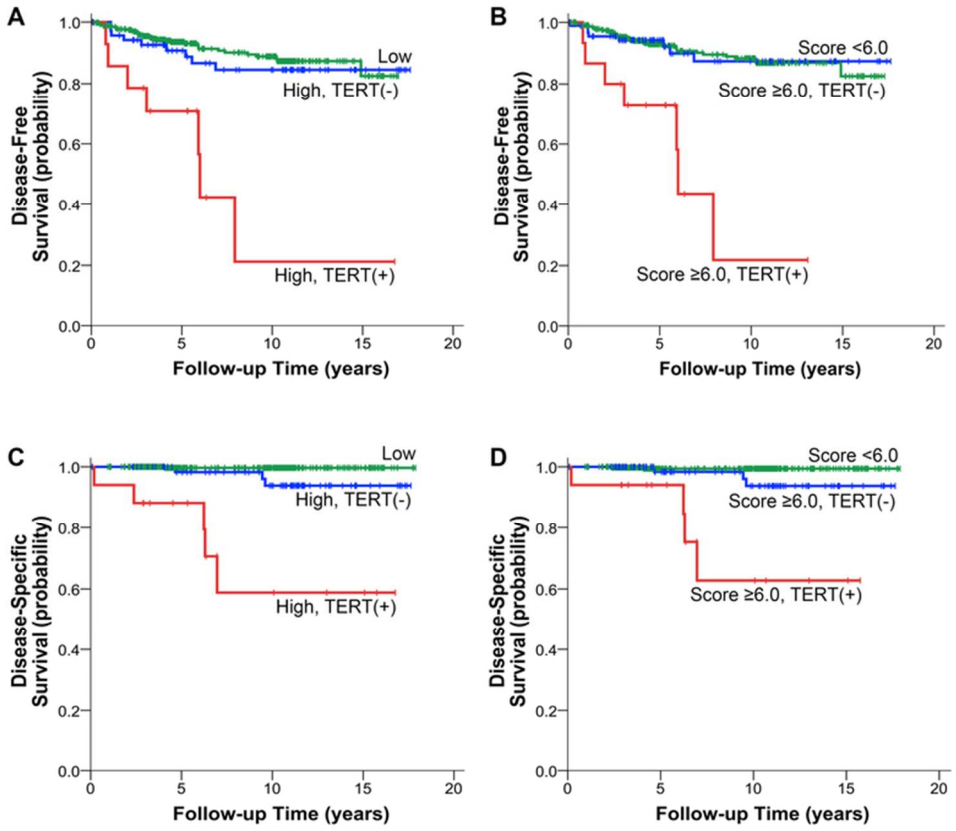

Figure S1. Additional prognostic effects of TERT promoter mutations on high-risk patients defined by AMES (A, C), and MACIS (B, D) scoring systems. Effects of TERT promoter mutations on disease-free (A, B) and disease-specific (C, D) survival.
34x29mm (600 x 600 DPI)