TERT Genetic Polymorphism rs2736100 Was Associated With Papillary Thyroid Carcinoma Aggressive Manifestation

Xilin Nie

Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital

Jinbiao Shang

Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital

Wendong Wang (✉ wangwd@zjcc.org.cn)

Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, Cancer Hospital of University of Chinese Academy of Sciences, Zhejiang Cancer Hospital

Research Article

Keywords: Papillary Thyroid Carcinoma, TERT, Rs2736100, Manifestation, Polymorphism

Posted Date: September 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-904123/v1>

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Abstract

Background: The *TERT rs2736100* genetic polymorphism was commonly found in human malignancies, indicated its key role in cancer cell transformation. The aim of this study was to investigate the effects of the functional *TERT rs2736100* genetic polymorphism in papillary thyroid carcinoma (PTC) patients' outcomes.

Methods: We had performed a retrospective study of the relationship between *rs2736100* and clinicopathological outcomes of PTC in 500 patients (378 female and 122 male) aged 43.8 ± 11.4 years (rang 15-74 years) with median follow-up of 60 months (range, 1 to 455 months).

Results: The *TERT rs2736100* genetic polymorphism (TG/GG versus TT) were significantly associated with several high risk clinicopathological features such as tumor spread, extra-thyroidal extension, central/lateral lymph node metastases, stage T III or IV disease. However, in the Kaplan-Meier survival analyses, the *rs2736100* mutation was unrelated to the overall disease-free survival with a log-rank $p > 0.05$. In the Cox-regression analyses, the overall survival rate of recurrence/neo-metastasis was related with lager size of tumor, younger age and tumor spread, but unrelated with *rs2736100* mutation.

Conclusion: The *TERT rs2736100* genetic polymorphism positive was more likely to manifest with aggressive clinicopathological characteristics but cannot worse prognosis much in PTC.

Background

The incidence of thyroid carcinoma increased by 4% per year, of which papillary thyroid carcinoma (PTC) accounts for approximately 80%, and accounts 1% for all human malignant [1]. All thyroid malignancies metastasize to the cervical lymph nodes mostly, with 18%-90% of patients developing metastasis to the cervical region, and which was associated with a higher rate of loco-regional recurrence and distant metastasis [2–4]. Despite the high metastasis rate, PTC still has an excellent prognosis as an indolence disease for majority [5]. However, the cervical lymph node metastasis was very common in PTC and was associated with an increased risk of loco-regional recurrence and overall mortality in selected patients' population [6–8]. As a result, controlling loco-regional recurrence has become a major challenge for most thyroid surgeons [9].

Accumulated evidence demonstrated that the ch 5p15.33 region (*TERT-CLPTM1L*) was a common susceptibility locus of multiple cancers. The Genome-wide association studies (GWAS) declared that many independent susceptibility single nucleotide polymorphisms (SNPs) in 5p15.33 were identified in different malignancies, including lung cancer [10, 11], melanoma and non-melanoma skin cancer [12], etc. Therefore, it was plausible that several functional DNA elements might exist in this region and influence cancer etiology. There were two known oncogenes, *TERT* and *CLPTM1L*, in this locus. Activated *TERT* (telomerase reverse transcriptase) transcription enhances telomerase activities and accelerates malignant transformation [13, 14]. In lung cancer, oncogene *CLPTM1L* (cleft lip and palate-associated transmembrane 1 like protein) plays a pro-tumorigenic role and is critical for RAS-driven lung cancers [15,

16]. In pancreatic cancer, *CLPTM1L* functions as a growth-promoting gene and its overexpression might lead to an abrogation of normal cytokinesis and enhance aneuploidy in pancreatic cancer cells [17].

However, the involvement of this locus in papillary thyroid carcinoma (PTC) etiology was still largely unknown. We had systematically evaluated PTC susceptibility genetic variants in the *TERT-CLPTM1L* locus and their regulatory role in *TERT* gene expression *ex vivo* and *in vivo*. *Ex vivo* luciferase gene assays demonstrated that the PTC susceptibility *rs2736100* polymorphism locates in a potential *TERT* intronic enhancer and had a genotype-specific impact on *TERT* expression. Additionally, correlation between *rs2736100* genotype and tissue-specific *TERT* gene expression level supported the regulatory function of this genetic variant *in vivo*[18].

Based on our experiment results, the functional *TERT rs2736100* genetic polymorphism may be deemed as a novel genetic component of the PTC etiology in Chinese populations. In the neoplasia development, how the *TERT rs2736100* genetic polymorphism effect on the progress in clinical? In this research, we retrospectively analyze the clinicopathological features of these patients from our hospital in order to find the effects of the functional *TERT rs2736100* genetic polymorphism on PTC patients' outcome.

Methods

At the last report, then all the patients' clinicopathological features and outcomes were retrieved from medical records and were analyzed to explore the relationship between the *TERT rs2736100* genetic polymorphism's mutation and none mutations. Those patients were treated for PTC or clinical observed between OCT 2013 and DEC 2013 at Zhejiang Cancer Hospital. This study included 500 patients (378 female and 122 male) age 43.8 ± 11.4 years (Mean $\pm$ SD, rang 15–74 years, age of initial diagnosis) with median follow-up of 60 months (range, 1 to 455 months) after initial surgery. There were 20 patients coexisting with other malignancies like breast carcinomas (4), nasopharyngeal carcinomas (10) and esophagus carcinomas (6) was excluded before the Genome-wide association studies (GWAS). At same time, part of those patients had received external radiation therapy at neck included thyroid gland before the thyroid surgery also excluded before the Genome-wide association studies (GWAS). All subjects gave written consent and the study was approved by the regional ethical committee of Zhejiang Cancer Hospital in accordance with the Helsinki Declaration.

The clinicopathological features were retrospectively analysed, including gender, age (≤ 45 years or >45 years), tumor size (≤ 1 cm or >1 cm), tumor spread, tumor multifocality, extra-thyroidal extension (ETE), central lymph node metastases, and lateral lymph node metastases, pTNM stage, recur and/or distant metastasis. When multiple lesions were found in the specimen, the largest tumor or the most suspicious nodule was analyzed. The TNM staged of the tumor is according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) classification system [19].

Statistical analysis

Categorical data were summarized with frequencies and percentages. Continuous data were summarized with Means $\pm$ Standard deviations (if normally distributed) or medians and interquartile ranges (if not normally distributed). Comparisons of categorical variables were performed using the χ^2 test, or Fisher's exact test for small cell sizes. The independent t and Wilcoxon-Mann-Whitney tests were used for normally and non-normally distributed continuous variables, respectively. We used Kaplan-Meier survival curves with long-rank test to present either overall survival (considering only disease-related deaths) or disease-free survival (where "disease" was defined as persistent or recurrent lymph nodal or distant metastases, or disease-related death). The associations between TERT and PTC risk were estimated by odds ratios (ORs) and their 95% confidential interval (CIs) computed by logistic regression models. All ORs were adjusted for age or sex, where it was appropriate. Follow-up time was defined as the time interval from the initial thyroidectomy to the discovery of disease recurrence and/or distant metastases. If no recurrence, the time of last follow-up visit (around OCT 2016) interval, were used to calculate recurrence-free survival rates by mutation status. Independent associations of mutations with PTC recurrence were examined by Cox regression analyses. All P values were two sides, and a P value of <0.05 was treated as statistically significant. The analyses were performed using Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL, USA).

Results

TERT rs2736100 genetic polymorphism in PTC

The study cohort has been previously described [18]. The rs2736100 polymorphism variants distribution (TT 136, TG 238, GG 126) was shown in the Table 1. The diameter of tumor ranged from 0.1cm to 7.2cm with a median diameter 1.5cm. Among all patients, 163 patients show tumor spread in the thyroid gland, 325 patients have more than one lesion, and 226 patients show ETE. There were 346 patients demonstrated central lymph node metastases and 196 patients demonstrated lateral lymph node metastases, the number of positive lymph nodes range from 1 to 21. In addition, there were 14 patients have metastases to distance sites like lung or bone at the initial diagnosis. Overall, 111 patients experienced recurrence for lymph nodes at central compartment or lateral compartment of the neck and 39 patients experience distance metastasis at lung or bone, etc. (14 patients have metastases at the initial diagnosis were not included, simplified as neo-distance metastasis), only one patient metastases to brain. There were 363 patients disease-free at the end of the follow-up period. Only two patients had died from PTC, one with tumor size of 7.2cm and refuse any treatment consequence with trachea constrict and apnea, the other one with local advanced disease (larynx, trachea and esophagus invasion) and untreated. Baseline characteristics of the cohort according to the presence or absence of TERT rs2736100 genetic polymorphism mutations were presented in Table 1.

Table 1
Demographic clinicopathological features of 500 patients

Clinicopathological features		<i>rs2736100</i> Wild	<i>rs2736100</i> Mutation			Univariate analysis <i>p</i> -value
		TT	TG	GG	Total	
Total No. of cases		136	238	126	364	
Gender	Female	98	179	101	280	0.260
	Male	38	59	25	84	
Age at diagnosis, years	M ± SD	43.2 ± 11.9	44.1 ± 11.2	43.8 ± 11.4	44.0 ± 11.2	0.492
	≤ 45y	68	129	68	197	0.411
	> 45y	68	109	58	167	
Tumor size, cm	M ± SD	1.5 ± 1.0	1.6 ± 1.1	1.7 ± 1.3	1.6 ± 1.2	0.218
	≤ 1cm	63	104	52	156	0.487
	> 1cm	73	134	74	208	
Tumor Spread	Absent	101	157	79	236	0.045*
	Present	35	81	47	128	
Tumor multifocality	Single	55	76	44	120	0.119
	Multi	81	162	82	244	
ETE	Absent	89	137	48	185	0.002*
	Present	47	101	78	179	
CLNM	Absent	52	71	31	102	0.028*

*symbol for $p < 0.05$; ETE, extra-thyroidal extension; CLNM, central lymph node metastases; LLNM, lateral lymph node metastasis; pT pathological tumor stage; pN pathological lymph node metastasis stage; pM pathological distant metastasis stage

In the univariate analyses, the *rs2736100* mutations TG and GG were combined as mutation positive like in the last report. The four pathological T stages were re-categorized as I + II and III + IV. In the overall analysis was found to be significantly associated with several high risk clinicopathologic features, including tumor spread, ETE, CLNM, LLNM and pathological T stages. The others don't demonstrate any significantly association including gender, age, tumor size, tumor multifocality, distant metastasis at diagnosis, recurrence and neo-distant metastasis ($p > 0.05$).

In the multivariate analyses for *TERT rs2736100* genetic polymorphism, ETE was the only one risk factor related to the *TERT rs2736100* genetic polymorphism ($p = 0.004$ OR = 1.832 95% C.I. 1.217–2.757). (Table 2)

Clinicopathological features		<i>rs2736100</i> Wild	<i>rs2736100</i> Mutation			Univariate analysis <i>p</i> -value
		TT	TG	GG	Total	
LLNM	Present	84	167	95	262	0.011*
	Absent	95	162	47	209	
pT	Present	41	76	79	155	0.029*
	1	85	132	66	210	
	2	8	7	5		
	3	32	73	37	154	
	4	11	26	18		
pN	0	47	62	28	90	0.028*
	1	89	176	98	274	
pM	Absent	134	231	121	352	0.370
	Present	2	7	5	12	
Recurrence	Absent	104	189	96	285	0.662
	Present	32	49	30	79	
Neo-distant Metastasis	Absent	127	212	111	323	0.257
	Present	7	19	10	29	
End-points Event	Absent	99	175	89	264	0.953
	Present	37	63	37	100	
*symbol for p < 0.05; ETE,extra-thyroidal extension; CLNM, central lymph node metastases; LLNM, lateral lymph node metastasis; pT pathological tumor stage; pN pathological lymph node metastasis stage; pM pathological distant metastasis stage						
In the univariate analyses, the <i>rs2736100</i> mutations TG and GG were combined as mutation positive like in the last report. The four pathological T stages were re-categorized as I + II and III + IV. In the overall analysis was found to be significantly associated with several high risk clinicopathologic features, including tumor spread, ETE, CLNM, LLNM and pathological T stages. The others don`t demonstrate any significantly association including gender, age, tumor size, tumor multifocality, distant metastasis at diagnosis, recurrence and neo-distant metastasis (p > 0.05).						
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Table 2
Factors associated with presence of *TERT rs2736100* genetic polymorphism (TT versus TG/GG) in multivariate analysis

Items	Risk factors	p	OR	95% C.I. of OR	
				lower	upper
rs2736100 mutation					
	ETE(present versus absent)	0.004*	1.832	1.217	2.757
*symbol for p < 0.05; ETE,extra-thyroidal extension					

Relationship of *TERT rs2736100* genetic polymorphism with clinicopathological outcomes of PTC

Tumor recurrence on lymph nodes was 78 of 285 in mutation positive patients versus 32 of 104 in mutation negative patients. The recurrence was related with large size ($p = 0.000$ OR = 2.426 95% C.I. 1.520–3.871) and younger age ($p = 0.008$ OR = 0.544 95% C.I. 0.348–0.850 for AGE > 45y) after logistic regression for multivariate analysis. In the analysis for distant metastasis, 14 patients were excluded because for diagnosed distant metastasis at initial diagnosis. Tumor neo-distant metastases was 29 of 323 in mutation positive patients versus 7 of 127 in mutation negative patients, the metastases were related with large size only after logistic regression ($p = 0.001$ OR = 4.375 95% C.I. 1.786–10.716). The overall recurrence (recurrence of lymph node and neo-distant metastasis was combined as an end-point event) was 100 of 264 in mutation positive patients versus 37 of 99 in mutation negative patients. The overall recurrence was related with large size ($p = 0.000$ OR = 3.039 95% C.I. 1.955–4.724) and younger age ($p = 0.046$ OR = 0.656 95% C.I. 0.434–0.992 for AGE > 45y) after logistic regression. However, in these analyses, the *TERT rs2736100* mutation was unrelated to the recurrence, neo-distant metastasis and end-point event. (Table 3)

Table 3
Multivariate analyses for recurrence and/or neo-distant metastasis

Items	Risk factors	p	OR	95% C.I. of OR	
				lower	upper
Recurrence					
	AGE(> 45y versus ≤ 45y)	0.008*	0.544	0.348	0.850
	SIZE(> 1cm versus ≤ 1cm)	0.000*	2.426	1.520	3.871
Neo-Distant Metastasis					
	SIZE(> 1cm versus ≤ 1cm)	0.001*	4.375	1.786	10.716
End-Point Event					
	AGE(> 45y versus ≤ 45y)	0.046*	0.656	0.434	0.992
	SIZE(> 1cm versus ≤ 1cm)	0.000*	3.039	1.955	4.724
*symbol for p < 0.05; OR, odds ratio; C.I., confidence interval					
We performed Kaplan-Meier and log-rank analyses for disease-free survival rates of patients by genotype. In analyses of all PTC patients, the overall recurrence and metastasis free probability was unrelated to the <i>TERT rs2736100</i> genetic polymorphism with log-rank analysis p = 0.542 and p = 0.242 respectively (p = 0.989 for combined) (Fig. 1 (A, B, C)).					

In the Cox-regression analysis, the overall survival rate of recurrence was related with larger size of tumor (p = 0.002 RR = 1.983 95% C.I. 1.296–3.034), younger age (p = 0.050 OR = 0.671 95% C.I. 0.451-1.000 for AGE > 45y) and tumor spread (p = 0.023 RR = 1.582 95% C.I. 1.064–2.352) and unrelated with *rs2736100* mutation and the others. (Table 4)

Table 4
Cox-regression analysis result of the overall recurrence (recurrence of lymph nodes and neo-distant metastases were combined)

Items	Risk factors	p	RR	95% C.I. of RR	
				lower	upper
End-Point Event					
	AGE(> 45y versus ≤ 45y)	0.050	0.671	0.451	1.000
	SIZE(> 1cm versus ≤ 1cm)	0.002*	1.983	1.296	3.034
	Tumor spread(present versus absent)	0.023*	1.582	1.064	2.352
*symbol for p < 0.05; RR, Risk Ratio; C.I., confidence interval.					

Discussion

TERT is the catalytic subunit of telomerase, which plays an important role in cell immortalization and tumorigenesis. The two *TERT* promoter mutations were shown to be mutually exclusive and able to increase *TERT* expression [20, 21]. They were also shown to be associated with aggressiveness of other human cancers, such as melanoma, brain tumor, bladder cancer and papillary thyroid carcinoma [22–26]. The prevalence of *TERT* promoter mutations in PTC varied between 7.5–27% in previous studies [26–33]. In our last report about *rs2736100*, the *TERT rs2736100* genetic variant (TG/GG versus TT) is significantly associated with elevated PTC risk. Correlations between *rs2736100* genotypes and tissue-specific *TERT* expression supported the regulatory function of this genetic variant *in vivo*. Our data demonstrated that the functional *TERT rs2736100* SNP was a novel genetic component of PTC etiology [18]. However, whether genetic variants of *TERT-CLPTM1L* are associated with the increased risk of PTC in clinical is unknown.

Some studies showed an association between *BRAF V600E* and *TERT* promoter mutations. In Xing's study, coexistence of the two mutations was associated with the worst clinicopathological outcomes of PTC [29]. The *TERT C228T* alone was significantly associated with lymph node metastasis, and there was an insignificantly association with other clinicopathological characteristics. In contrast, the coexistence of *BRAF V600E* and *TERT C228T* was strongly associated with virtually all the high-risk characteristics as well as distant metastasis recurrence. In the survival analysis, similar result demonstrated that *TERT* mutation only cannot affect the disease-free survival over than the coexistence of *BRAF V600E* and *TERT C228T*. The similar results were demonstrated in several reports; the coexistence of *BRAF V600E* and *TERT* promoter mutations was particularly associated with high-risk clinicopathological features [28, 34–38]. Those reports that implied the effects of *TERT C228T* mutation fell short of significant when it was separated from the *BRAF* mutation and have been examined alone, suggested that the *TERT* mutation needs additional genetic alteration to cooperate to promote the aggressive of PTC. However, in Melo's reports which detected an association between *TERT* mutations and aggressive clinicopathological features and had enough evidence to state that *TERT* promoter mutations with or without *BRAF V600E* was major indicator of poor prognosis in differentiated thyroid cancer and notably in PTC, due to its association with distant metastasis and increased disease specific mortality [26, 39, 40]. Unfortunately, the *BRAF* status was not assessed in this research. Additionally, the *TERT rs2736100* mutations coexistence with/without the *BRAF V600E* is particularly associated with some high-risk clinicopathological features, but unassociated with prognosis much on PTC patients in this research.

Additionally, the overall recurrence (recurrence of lymph nodes and neo-distant metastases were combined as an end-point event) was 100 of 264 in mutation positive patients versus 37 of 99 in mutation negative patients. The recurrence was related with large size ($p = 0.000$ OR = 3.039 95% C.I. 1.955–4.724) and younger age ($p = 0.046$ OR = 0.656 95% C.I. 0.434–0.992 for AGE > 45y) after logistic regression. However, the *TERT rs2736100* genetic polymorphism was unrelated to the recurrence, neo-distant metastasis and end-point event in this study.

There were several reports focus on the *SNP rs2736100*. In Liu's study, only *rs2736100* was significantly ($P = 0.034$) associated with an increased risk of lung cancer and suggested that *rs2736100* on *TERT-CLPTM1L* indicates a poor prognosis for lung cancer in the Chinese Han population [41]. In Bae's report, The single-nucleotide polymorphisms (SNP) at 5p15 (*rs2736100*, adjusted odds ratio 1.32, 95% confidence interval [CI] 1.03–1.67, $P = 0.025$) were significantly associated with lung cancer risk [42]. In Simon's report indicated that the *SNP rs2736100* risk genotypes were highly correlated with high-grade disease ($P < 0.001$), but the *rs2736100* unrelated with prognosis of tumor grade in glioma independently [43]. In Choi's study, there was no significant difference between the patients with gastric cancer and healthy controls in the genotype and allele frequencies of the *rs2736100* polymorphism. The *rs2736100* polymorphism of the *hTERT* gene is involved in the regulation of *hTERT* expression and telomere length, but not in the risk of gastric cancer [44]. In Chen's report, for *rs2736100*, the G variant and the GG genotype were more frequent, whereas the TT genotype was less frequent in patients with lung adenocarcinoma than in controls. They suggested that multiple variants at 5p15.33 contribute to susceptibility to lung adenocarcinoma [45]. In those reports, only Liu's report demonstrate the *SNP rs2736100* significantly related with poor prognosis, the others show that the *SNP rs2736100* was only related with several high risk clinicopathological features excluding poor prognosis. Our result agrees well with those report with the overall recurrence-free (recurrence of lymph nodes and neo-distant metastases were combined as an end-point event) survival un-affected significantly of patients with PTC.

In our recent study, we observed that the *TERT rs2736100* mutation (either TG or GG) were significantly associated with some high risk clinicopathological features such as tumor spread, extra-thyroidal extension, central/lateral lymph node metastases, stage T III and IV disease. In the multivariate analysis, the *TERT rs2736100* mutation was significantly associated with extra-thyroidal extension only ($p = 0.004$ OR = 1.832 95% C.I. 1.217–2.757). However, in the Kaplan-Meier survival analysis, the *rs2736100* mutation was unrelated to the overall disease-free survival with log-rank $p > 0.05$. In the Cox-regression analysis, the overall survival rate of recurrence was related with larger size of tumor ($p = 0.002$ RR = 1.983 95% C.I. 1.296–3.034), younger age ($p = 0.050$ OR = 0.671 95% C.I. 0.451-1.000 for AGE > 45y) and tumor spread ($p = 0.023$ RR = 1.582 95% C.I. 1.064–2.352) and unrelated with *rs2736100* mutation and the others.

The *TERT* mutation result is similar with Myung's report [46]. No significant difference in the frequency of the *TERT* promoter mutation was observed between the recurrence/metastasis group and the non-recurrence/metastasis group. These results suggest that the prognostic implications of the *TERT* promoter mutation are dependent on clinicopathological features. Additional, In Gong's report, the *hTERT* gene polymorphism at *rs10069690 C/T* is associated with the risk and prognosis of thyroid cancer, but *hTERT* gene polymorphism at *rs2736100G/T* is not [47]. Our results agree well with these reports.

The papillary thyroid carcinoma histotypes carries in general a good or even an excellent prognosis[5]. The *TERT rs2736100* mutation-positive PTC is more likely to manifest with aggressive clinicopathological characteristics. In appropriate clinical settings, testing for the *TERT rs2736100* mutation-positive is likely to be useful in assisting the risk stratification and management of PTC, but not

to predict prognosis in clinical practices [48]. These recent findings on *TERT rs2736100* mutation-positive in thyroid cancer are exciting, but they remain to be confirmed and generalized by further and high-power studies, ideally in different ethnic populations.

Conclusions

In the recent study, we observed that the *TERT rs2736100* mutation (either TG or GG) were significantly associated with some high risk clinicopathological features such as tumor spread, extra-thyroidal extension, central/lateral lymph node metastases, stage T III and IV disease. However, in the Kaplan-Meier survival analysis, the *rs2736100* mutation was unrelated to the overall disease-free survival with log rank $p > 0.05$. In the Cox-regression analysis, the overall survival rate of recurrence was related with larger size of tumor ($p = 0.002$ RR = 1.983 95% C.I. 1.296–3.034), younger age ($p = 0.050$ RR = 0.671 95% C.I. 0.451–1.000 for AGE > 45y) and tumor spread ($p = 0.023$ RR = 1.582 95% C.I. 1.064–2.352) and unrelated with *rs2736100* mutation and the others. Additionally, they remain to be confirmed and generalized by further and high-power studies, ideally in different ethnic populations.

Abbreviations

PTC, papillary thyroid carcinoma; *TERT*, telomerase reverse transcriptase; *CLPTM1L*, cleft lip and palate-associated transmembrane 1 like protein; GWAS, Genome-wide association studies; SNP, single nucleotide polymorphisms; ETE, extrathyroidal extension; CLNM, central lymph node metastases; LLNM, lateral lymph node metastases; AJCC, The American Joint Committee on Cancer; UICC, The Union for International Cancer Control; SPSS, Statistical Package for Social Sciences; OR, Odds Ratio; C.I., confidence interval; RR, Risk Ratio.

Declarations

Acknowledgements:

We thank all patients and their families for their precious medical records and cooperation.

Ethics approval and consent to participate:

Institutional review board approval was waived by the responsible Ethics Committee of Zhejiang Cancer Hospital, Hangzhou, PRC, given the retrospective study design and analysis of clinical data. Patient records and information were anonymized and de-identified prior to analysis in all working stages. For this type of research, a formal consent is not required.

Consent for publication:

Not applicable.

Availability of data and materials

The data that support the finding of this study are included within the article. Primary data is available upon request from the corresponding author.

Competing interests

The authors declare that they have no competing interests

Funding

This research was supported by Natural Science Foundation of Zhejiang Province (No. LY20H160007).

Authors' contributions

XL Nie has contributed mainly in conducting this research and papering the manuscript. JB Shang has contributed in research protocol designing and clinical theoretical guiding. WD Wang has contributed in outstanding assistance and guild in all working stages. All authors read and approved the final manuscript. All the authors declare that each contributed to the preparation of the manuscript submitted. All the authors accept responsibility for the article.

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Figures

Figure 1

Result of Kaplan-Meier analyses of the impacts of TERT rs2736100 genetic polymorphism on (A) The recurrence-free survival of patients with PTC; (B) The Neo-Metastasis-free survival of patients with PTC, 14 patients were excluded because for present distant metastasis at initial diagnosis; (C) The overall recurrence-free (recurrence of lymph nodes and neo-distant metastases were combined as an end-point event) survival of PTC.