Risk-stratified Distant Metastatic Thyroid Cancer with Clinicopathological Factors and *BRAF*/*TERT* Promoter Mutations

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ABSTRACT

Objective To assess the prognostic value of clinicopathological factors as well as *BRAF* and *TERT* promoter mutations in predicting distant metastasis in patients with papillary thyroid cancer.

Design The status of *BRAF* and *TERTp* mutations were available in 1,208 thyroid cancer patients who received thyroidectomy at Jiangyuan Hospital Affiliated to Jiangsu Institute of Nuclear Medicine from January 2008 to December 2021. Based on inclusion criteria, 99 distant metastasis thyroid cancers (DM-TCs) and 1055 patients without DM (Non-DM-TCs) were retrospectively reviewed.

Results After univariate and multivariate analyses, a risk model was established for DM prediction based on factors: T3/T4 stage, lymph node metastasis (LNM) number over 5, and *BRAF*/*TERT* mutations (TLBT). It was defined based on the number of TLBT factors: low risk (no risk factor, n = 896), intermediate risk (1 risk factor, n = 199), and high risk (≥ 2 risk factors, n = 59). Notably, compared with patients with low and intermediate risks, patients assigned to high TLBT risk have a shorter time of DM disease-free survival. Except for gene mutation, other factors were also included in the 2015 American Thyroid Association (ATA) risk guideline. Comparing with the ATA risk category, this risk model showed a better performance in predicting DM-TCs.

Conclusions This study proposes a TLBT risk classifier consisting of T3/T4 stages, LNM (n > 5), and *BRAF + TERTp* mutations for predicting DM-TCs. TLBT risk stratification may help clinicians make personalized treatment management and follow-up strategies.

Introduction

Distant metastasis (DM) is the leading cause of differentiated thyroid cancer (DTC) related morbidity and death [1]. The most common sites of DM in DTC are the lungs and bones, followed by the brain and liver [1]. Most DM-TCs are present at diagnosis and some develop during follow-up [2]. The presence of DM often impairs the patients' life quality due to a need for secondary surgery and gained doses of radioiodine therapy (RAIT). Thus, DM is usually tied with advanced DTC and poor prognosis. Early prediction of DM permits accurate staging and risk stratification of the disease and

guides more precise long-term surveillance for disease progression.

To enable early identification of patients with DM risks, several clinic-pathological features have been proposed. Older age [3], male sex [4], and pathologic factors like T stage [5], lymph node metastasis (LNM) [6], and extrathyroidal extension (ETE) [7] were reported to predict DM. Besides, genetic alterations among candidate genes were also postulated to improve the risk stratification of TC in recent years. So far, more and more studies point out that *TERTp* mutations only or with BRAF V600E mutations are frequently found in patients with aggressive histopathologic variants of thyroid cancer [8], recurrence [9], and non-RAI-avidity [10, 11]. One study tried a companion use of *TERTp* mutations and TNM stratification in improving the prediction of TC recurrence [12]. Whether *TERTp* mutations only or with BRAF V600E mutations could predict DM occurrence remains to be further confirmed.

Here, we propose a risk stratification according to the factors: T3/T4 stage, LNM number over 5, and *BRAF*/*TERT* mutations (TLBT). Subjects were classified into different risk groups based on the number of factors that distinguish TC with DM.

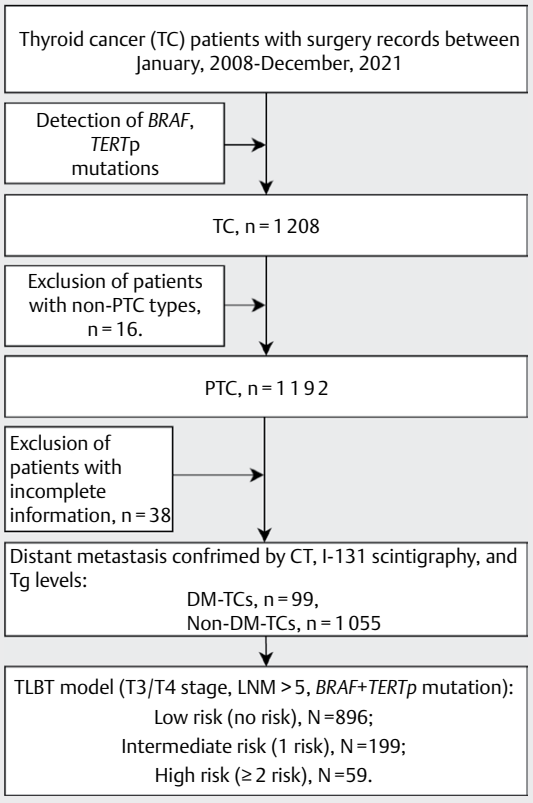
Materials and Methods

Study participants

All the procedures described in this study were in accordance with the national and institutional ethical standards of Jiangyuan Hospital, Affiliated with Jiangsu Institute of Nuclear Medicine (YL202144).

Primary thyroid tumors were obtained from papillary thyroid carcinoma (PTC) patients (age > 18) after the initial surgery. Patients with follicular thyroid carcinoma (FTC) and poorly differentiated thyroid carcinoma (PDTC), including tall cell, columnar cell, diffuse sclerosing, and hobnail variants of PTC, Hürthle cell carcinoma, or medullary thyroid carcinoma were excluded. Gross extrathyroidal extension (gETE) was referred to as widespread extrathyroidal spread into strap muscles, trachea, recurrent laryngeal nerve, and blood vessels.

DMs were identified by computed tomography (CT) scan, I-131 whole body scan, and post-RAIT thyroglobulin (Tg) levels [1]. DM was observed in 60 patients at diagnosis and in 39 patients during follow-up. Lung metastasis was observed in 83 DMs, and 11 patients of them were found in combination with bone metastasis. Single bone metastasis was found in 5 DMs, and hip metastasis was observed in 1 DM. The other 10 patients were determined as DM due to a high level of Tg levels. The procedure for the selection of patients is summarized in ▶ **Fig. 1**.



▶ **Fig. 1** Flow chart of the study. The cohort included 99 patients with DM and 1055 patients with non-DM. (DM: distant metastasis)

Detection of BRAF and TERTp mutations

Molecular data concerning BRAF and TERT mutation was successfully acquired from 99 DMs and 1,055 non-DMs between January 2008 and December 2021. Cases were identified based on clinical history followed by confirmation in fine needle aspiration (FNA) cytology or paraffin-embedded tissue examination. In FNA samples, gene mutation was measured by allele-specific fluorescent probe-quantative polymerase chain reaction (qPCR) analysis. DNA was extracted from the paraffin-embedded tissue section using an FFPE DNA kit (AmoyDx, Xiamen, China) following the manufacturer's instructions. In brief, paraffin-embedded tissues were dewaxed using xylene and washed twice with ethanol. After the ethanol was volatilized, tissues were lysed with lysis I and proteinase K at a final concentration of 1 µg/mL. Extracted DNA was then enriched using spin columns. Collected DNA was PCR amplified with *TERT* promoter primers: *TERTp* forward: 5′-ATCATGGCCCCTCCCTCGGGTTACC-3′; *TERTp* reverse: 5′-AGGGCTTCCCACGTGCGCAGCAGGA-3′. A PCR product of 440 bp length was then purified with SanPrep Column PCR Product Purification Kit (Sangon Biotech, Shanghai, China) and sequenced by Tsingke Biotechnology.

Follow-up and study endpoint

Routine serological measurement of FT3, FT4, TSH, Tg, and TgAb levels and neck ultrasonography were performed every 3–6 months. A chest computed tomography (CT) scan was routinely performed once a year for at least 5 years after initial surgery. For patients with lung metastasis, chest CT was performed every 6–12 months to evaluate the status of pulmonary metastatic foci. To assess the state of bone metastases and other extrapulmonary metastatic foci, imaging, including CT, MRI, or ^{18}F-FDG-PET/CT, were conducted at least once per year. The median follow-up period of DMs was 55.6 months (range: 27.2–83.0 months). Meanwhile, the median follow-up period of non-DMs was 39.1 months (range: 35.2–43.1 months). The patients in radioiodine therapy after with-

drawal of thyroid hormone treatment received a routine administration of 4.4–5.5 GBq (120–150 mCi) of ^{131}I to obtain a TSH level over 30 mUI/L.

Distant metastasis-free survival (DMFS) was defined as the time (in months) from the date of initial surgery to the occurrence of any DM. In the case of no DM, the date of the last follow-up was the study endpoint for DMFS.

ATA staging of TC was performed according to the classification of the 2015 American Thyroid Association guideline [1]. The ATA risk category as well as our risk category "TLBT" model were defined at the time after initial surgery but before the first radioiodine therapy.

Statistical analysis

Chi-square and Fischer's exact methods were used to measure the significance in contingency tables. Non-normally distributed continuous variables were presented as median with interquartile range (IQR) and compared using the Mann-Whitney *U* test. Univariate and multivariate Cox regression were performed to compare demographic and pathologic variables. Jamovi statistical software (Version 2.2.5) was used to perform the receiver operating characteristic (ROC) curve, Kaplan-Meier plot, and other statistical analyses. Statistical differences between two ROC curves were analyzed by MedCalc software. A two-sided $P<0.05$ was considered as statistically significant.

Results

Independent risk factors for distant metastasis thyroid cancers

Baseline characteristics of 1055 non-DM-TCs and 99 DM-TCs at their first treatment are mentioned in ▶ **Table 1**. The median age was 42 y (range 33–52 y) in non-DM-TCs and 47 y (range 34.5–63.5 y) in DM-TCs ($P<0.001$). Patients over 55 y of age were observed in 19.6 % (207/1055) non-DM-TCs and 36.4 % (36/99) DM-TCs ($P<0.001$). Male sex, tumor size > 2 cm, multifocality, gETE, LNM (n > 5), bilaterality, T3/T4 stage, N1 stage, and TNM III/IV stage were found to be associated with DM-TCs ($P<0.001$). Concomitant BRAF V600E and *TERT* promoter (*BRAF + TERTp*) mutations were detected in 18.7 % (17/99) DM-TCs and in 1.1 % (10/1055) non-DM-TCs ($P<0.001$). However, BRAF V600E mutation was identified in 84.8 % (895/1055) non-DM-TCs and 51.5 % (51/99) DM-TCs ($P<0.001$).

Then, the independent factors for DM-TCs were determined by a 5-year DMFS as follows: tumor size (> 2 cm) (HR: 2.446, CI: 1.251–4.784, $P=0.009$), T3/T4 stages (HR: 4.142, CI: 1.055–16.263, $P=0.042$), and LNM (n > 5), HR: 7.041, CI: 2.961–16.743, $P<0.0001$) (▶ **Table 2**).

Risk stratification with T stage/LNM/BRAF + TERTp mutations in thyroid cancer

Considering *BRAF + TERTp* mutations can be detected pre-surgery, risk stratification was performed according to the factors: T3/T4 stage, LNM number over 5, and *BRAF*/*TERT* mutations (TLBT). Subjects were classified into three groups based on the number of factors. A total of 45/99 (45.5 %) DM-TCs were assigned to the high

▶ **Table 1** Clinicopathological characteristics of the PTCs with or without distant metastasis.

Variables	Non-DM-TCs	DM-TCs	*P* value[f]
Number of cases	1055	99	
Median age (y)[a]	42 (33–52)	47 (34.5–63.5)	< 0.001
Age at diagnosis (y), ≥ 55	207 (19.6)	36 (36.4)	< 0.001
Sex			< 0.001
Female	787 (74.6)	58 (58.6)	
Male	268 (25.4)	41 (41.4)	
Maximum tumor size (cm)			< 0.001
≤ 2	948 (89.9)	27 (27.3)	
> 2	107 (10.1)	72 (72.7)	
< 4	103	50	
≥ 4	4	22	
Multifocality			< 0.001
Yes	342 (32.4)	50 (50.5)	
No	713 (67.6)	49 (49.5)	
Gross ETE			< 0.001
Yes	25 (2.4)	50 (50.5)	
No	1030 (97.6)	49 (49.5)	
LNM (n > 5)			< 0.001
Yes	144 (13.6)	62 (62.6)	
No	911 (86.4)	36 (36.4)	
Tumor laterality			< 0.001
Unilateral	814 (77.2)	49 (49.5)	
Bilateral	241 (22.8)	50 (50.5)	
Pathological T category[b]			< 0.001
T1/T2	1027 (97.3)	37 (37.4)	
T1a	681	4	
T1b	273	9	
T2	73	24	
T3/T4	28 (2.7)	62 (62.6)	
T3a	3	15	
T3b	13	9	
T4a	3	22	
T4b	9	16	
Pathological N category[c]			< 0.001
N0	569 (53.9)	26 (26.3)	
N1	486 (46.1)	73 (73.7)	
N1a	372	33	
N1b	114	40	
AJCC TNM stage[d]			< 0.001
I/II	1048 (99.3)	66 (66.7)	
I	984	3	
II	64	63	
III/IV	7 (0.7)	33 (33.3)	
III	3	0	
IVA	4	0	
IVB	0	33	
ATA risk category			< 0.001
Low	886 (84.0)	20 (20.2)	
Intermediate	144 (13.6)	33 (33.3)	
High	25 (2.4)	46 (46.5)	

▶ **Table 1** Continued.

Variables	Non-DM-TCs	DM-TCs	*P* value[f]
BRAF V600E			< 0.001
Yes	895 (84.8)	51 (51.5)	
No	160 (15.2)	48 (48.5)	
BRAF + *TERT* mutation[e]			< 0.001
Yes	10 (0.9)	17 (17.2)	
No	1045 (99.1)	82 (82.8)	

[a]Median age was presented with Median (interquartile range, IQR), Mann-Whitney *U* test.; [b]*P* value was compared between T1/T2 and T3/T4.; [c]*P* value was compared between N0 and N1.; [d]*P* value was compared between I/II and III/IV.; [e]*TERT* promoter mutation here included, collectively, *TERT* C228T and *TERT* C250T.; [f]Pearson Chi-Square χ^2 value.; AJCC: American Joint Committee on Cancer; ATA: American Thyroid Association; ETE: extrathyroidal extension; LNM: lymph node metastasis; PTC: papillary thyroid cancer; DM-TCs: distant metastasis thyroid cancers; TNM: Tumor, Node, Metastasis.

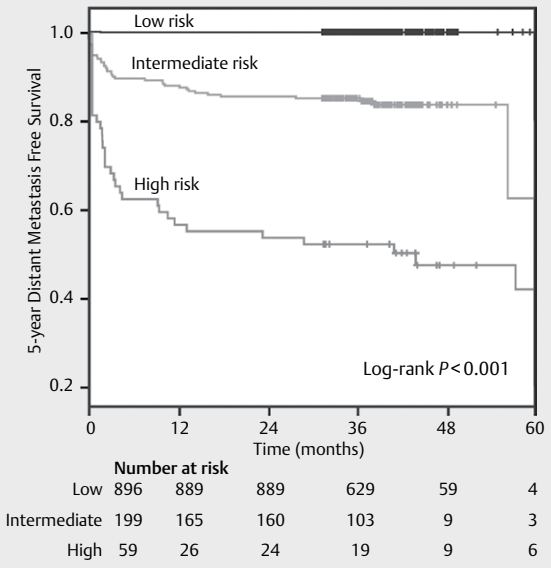
▶ **Table 2** Independent risk factors analysis related to worse distant-metastasis-free survival.

Variables	Hazard Ratio	95 % CI	*P* value
Age (y), ≥ 55	1.042	0.568–1.909	0.895
Sex, male	0.714	0.386–1.321	0.283
Surgical diagnosis, PDTC	1.967	0.988–4.686	0.636
Maximum tumor size, > 2 cm	2.446	1.251–4.784	**0.009**
Multifocality, yes	0.748	0.299–1.869	0.534
Gross ETE, yes	2.173	0.622–7.592	0.224
LNM (n > 5)	7.041	2.961–16.743	**< 0.001**
Tumor laterality, yes	1.608	0.605–4.275	0.341
Pathological T category, T3 + T4	4.142	1.055–16.263	**0.042**
Pathological N category, N1/Nx	0.648	0.244–1.721	0.384
BRAF V600E, wild type	1.848	0.982–3.472	0.057
BRAF + *TERTp* mutations, mutated	1.847	0.747–4.568	0.185
TLBT risk stratification			**< 0.001**
Low	//	//	
Intermediate	81.62	19.49–341.76	
High	386.67	92.50–1616.43	

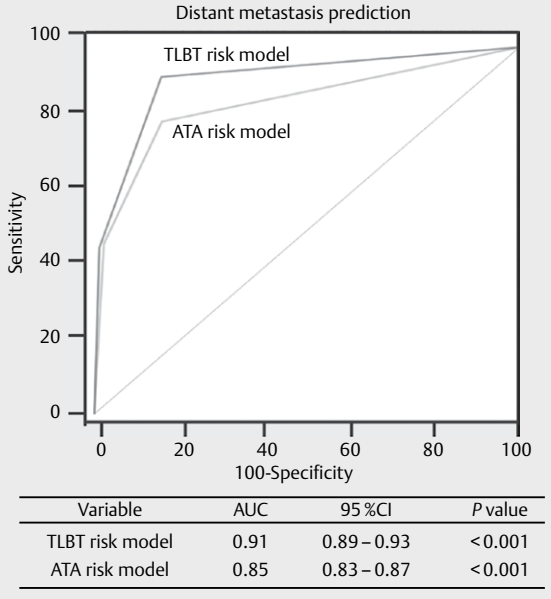
TLBT risk group (≥ 2 risks), and other 46/99 (46.5 %) and 8/99 (8.1 %) DM-TCs were classified into intermediate (1 risk) and low-risk group (no risk), respectively. The HR for intermediate-risk was 81.62 (CI: 19.49–341.76), and for high risk was 386.67 (CI: 92.50–1616.43) ($P < 0.001$). Further, the 5-year DMFS analysis showed that the time relapsed from DM was longer in individuals with low-risk and intermediate-risk when compared with those patients in the group with high-TLBT risk (▶ **Fig. 2**, Log-rank $P < 0.001$).

Prediction of distant metastasis thyroid cancers by TLBT and the ATA risk model

A statistically significant difference was observed between ROC curves predicted by TLBT (AUC: 0.85 [0.83–0.87], $P < 0.001$) and ATA category [AUC: 0.91 [0.89–0.92], $P < 0.001$], respectively ($P = 0.0017$, ▶ **Fig. 3**). Furthermore, the ORs for TLBT and ATA risk were 18.84 (CI: 12.13–29.25, $P < 0.001$) and 9.08 (CI: 6.55–12.58, $P < 0.001$), respectively (▶ **Table 3**).



▶ **Fig. 2** Distant Metastasis Free Survival curve stratified by TLBT risk model. Log-rank $P < 0.001$, Cox proportional hazards model. (TLBT: T3/T4 stage, LNM number over 5, and *BRAF*/*TERT* mutations)



Variable	AUC	95 %CI	*P* value
TLBT risk model	0.91	0.89 – 0.93	< 0.001
ATA risk model	0.85	0.83 – 0.87	< 0.001

▶ **Fig. 3** ROC curves for DM-TCs predicted by TLBT and ATA risk models. $P < 0.001$. (ROC: receiver operating characteristic; DM-TCs: distant metastasis thyroid cancers; TLBT: T3/T4 stage, LNM number over 5, and *BRAF*/*TERT* mutations; ATA: American Thyroid Association)

▶ **Table 3** Prediction of DM-TCs based on TLBT and ATA risk stratification.

Risk model	Odds Ratio	95 % CI	*P* value
TLBT risk	18.84	12.13–29.25	< 0.001
ATA risk	9.08	6.55–12.58	< 0.001

Discussion

To enable early detection of DM-TCs, *BRAF*/*TERT* mutations were combined with ATA risk factors: T3/T4 stage and LNM number over 5 (TLBT). Subjects were classified into three groups based on the number of TLBT factors, and the time period was significantly shorter in the TLBT high-risk group (≥ 2 risks) when compared with the low (no risk) and intermediate-risk (1 risk) groups.

The *BRAF*/*TERTp* mutations in our cohort have an adverse or merely no significant prognostic impact in patients with DM. However, the alternative classification system, which combines the *TERTp* mutation status with the pathologic factors of ATA risk, reflects DM prediction in PTC patients more accurately and keenly. A similar phenomenon was reported in predicting FTC prognosis using *TERTp* mutations [13, 14]. Only *TERTp* mutation cannot sufficiently predict cancer-specific survival of FTC [13, 14]. However, in the new model (the combination of *TERTp* mutation and the fourth edition of World Health Organization (WHO 2017) morphological classification), the proportions of variation explained (PVEs) and Harrell's C-index showed improvement when compared with models using WHO 2017 classification or *TERTp* mutation alone [13, 14]. The supplement of gene information like *BRAF*/*TERTp* in the classical ATA model markedly increased the prediction value for DTC prognosis.

Limitations

This study was conducted retrospectively and might have selection biases. Non-DM-TCs patients enrolled in the present study may face the lack of enough follow-up periods. These limitations may have some impacts on the explanation of our results, but other studies from different cohorts showed high consistency with the factors identified from our cohort. T stage was found in predicting lung metastasis in TC based on the Surveillance, Epidemiology, and End Results Program (SEER) database [5]. This report also pointed out a strong association of the clinical N1 (cN1) to lung metastasis, whereas the data considering LNM numbers were missing [5]. In our cohort, LNM numbers other than the N stage was an independent indicator for DM. Ho et al. (2021) further evaluated the prevalence of DM in well-differentiated thyroid carcinoma based on their lymph node (LN) burdens and found that the metastasis prevalence increased in a manner dependent on LN numbers [15]. Besides, the metastatic lymph node ratio has been found to be superior to N stage in predicting PTC recurrence [6].

Other than factors listed in the ATA risk guideline, epigenetic alterations like miRNA expression have also been examined to predict PTC metastasis [16, 17]. Inflammation markers like chemokines CCL22 and CCL26 have been reported in correlation with DM-TC poor prognosis [18]. Patients with metachronous metastasis had a worse prognosis compared to those with synchronous metastasis [19]. However, no differences were found between synchronous and metachronous metastases. Also, no differences were found in terms of gene mutations or risk models in subjects with different metastatic organs in our cohort (data not shown). Lastly, it cannot be overlooked that the low detection rate in *TERT* mutation examination may influence the implementation of the TLBT risk model.

Collectively, our results propose a TLBT model for the prediction of DM-TCs. Molecular testing, including *BRAF* and *TERTp,* in FNA samples or post-surgery specimens, can facilitate DM prediction.

Author Contribution

Xian Cheng, Ying Zhou, Huixin Yu, and Li Zhang contributed to the study conception and design. Data collection and analysis were performed by Xian Cheng, Ying Zhou, Huixin Yu, and Jiandong Bao. The first draft of the manuscript was written by Xian Cheng, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability

All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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