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Original Article

New proposed tumor-node-metastasis staging system for medullary thyroid carcinoma based on the Surveillance, Epidemiology, and End Results database

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Abstract: Background: Medullary thyroid carcinoma (MTC) has been separated into its own chapter in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. However, controversies still exist for the staging of MTC. This study aimed to identify prognostic differences among patients with MTC to define a more accurate staging system. Methods: Data on cancer-specific survival from the Surveillance, Epidemiology, and End Results database between 2010 and 2014 were used for this study. Kaplan-Meier (K-M) curves, Cox proportional hazards regression analysis, and mortality per 1000-person-years were used to evaluate the mortality rate to create the new staging system. Results: A total of 960 cases were included in this analysis. The mortality rates of 24 different groups, which were classified using T stage (T1-4), N stage (N0-1b), and M stage (M0-1) were assessed using K-M curves. Cox proportional hazards regression analysis and mortality per 1000-person-years were used to classify patients, as stage I (T1-3N0-1aM0, 654, 68.34%), stage II (T1-3N1bM0, 181, 18.91%), stage III (T4N0-1bM0, 58, 6.06%), and stage IV (T1-4N0-1bM1, 64, 6.69%). The hazard ratios of stages II, III, and IV, using stage I as a reference, were 5.281 (95% confidence interval [CI], 1.236-22.562), 20.603 (95% CI, 4.400-96.467), and 55.717 (95% CI, 14.307-216.988), respectively. The mortality rates per 1000-person-years of stages I, II, III, and IV were 2.036 (95% CI, 0.657-6.312), 14.867 (95% CI, 6.679-33.092), 98.287 (95% CI, 54.432-177.478), and 224.199 (95% CI, 146.180-343.860), respectively. Conclusions: Compared with the current AJCC tumor-node-metastasis (TNM) staging system for MTC, this new proposed TNM staging system, which is based on cancer-specific mortality rate analysis, provides more accurate risk stratification and can ensure more rational treatment measures.

Keywords: Medullary thyroid carcinoma, SEER, TNM staging system, AJCC staging system

Introduction

Medullary thyroid carcinoma (MTC), a rare neuroendocrine tumor, derives from the neuroendocrine parafollicular calcitonin-producing cells of the thyroid [1, 2]. MTC accounts for approximately 13% of all thyroid cancer related deaths, although it accounts for only 5% of all thyroid cancers [3]. According to a previous study, the biological behavior of MTC is highly variable; it can be an indolent neoplasm that dose not progress for decades, or it can undergo fatal malignant neoformation within several months [4]. Therefore, assessing the prognosis of MTC remains challenging and inexact.

The American Joint Committee on Cancer (AJCC) published the revised 8th edition of the tumor-node-metastasis (TNM) cancer staging system in 2017 [5]. For MTC, the most important change is the separation into its own chapter [6]. Although MTC now has its own discrete stand-alone chapter in the 8th edition, the detailed definitions of the T, N, and M categories are not different from those in the 7th edition [5, 7]. Furthermore, because of the rarity of MTC and the overall paucity of data, the AJCC TNM staging system for MTC is largely extrapolated from the staging for differentiated thyroid cancer (DTC) [7]. However, MTC differs from DTC in terms of histology and biological behav-

Table 1. Demographics and clinical characteristics of 960 patients with MTC

Variable	N (%)
Gender	
Female	568 (59.17)
Male	392 (40.83)
Race	
White	814 (84.79)
Black	75 (7.81)
Other	71 (7.40)
Age at diagnosis, mean (SD), years	54.29 (17.39)*
Year of diagnosis	
2010-2012	574 (59.79)
2013-2014	386 (40.21)
Tumor size (mm)	
<10 (including 10)	270 (28.39)
10-20 (including 20)	227 (23.87)
20-40 (including 40)	270 (28.39)
>40	184 (19.35)
Number of tumor foci	
1	671 (71.54)
≥2	267 (28.46)
Extension	
No	796 (84.68)
Yes	144 (15.32)
T category	
T1	454 (47.44)
T2	223 (23.31)
T3	199 (20.79)
T4	81 (8.46)
N category	
N0	574 (59.79)
N1a	124 (12.92)
N1b	262 (27.29)
M category	
M0	889 (92.60)
M1	71 (7.40)
Surgical procedure	
Biopsy	45 (4.75)
Lobectomy	67 (7.07)
Subtotal or near-total thyroidectomy	14 (1.48)
Total thyroidectomy	822 (86.71)

Abbreviations: MTC, medullary thyroid carcinoma; SD, standard deviation; *Standard deviation.

ior, and therefore requires different treatment management and prognosis tools.

Although the incidence of thyroid cancer is rising steadily, mortality rates have only minimally changed over the past five decades because of ongoing research on thyroid cancer and continuous optimization of treatment and management [8]. The challenge is to balance the therapeutic approach to allow for adequate treatment while minimizing the risk of overtreatment. In this study, we aim to create an accurate staging system based on cancer-specific survival status for patients with MTC, in order to balance the therapeutic approach.

Materials and methods

Patients and the Surveillance, Epidemiology, and End Results (SEER) database

The present study used data, collected between 2010 and 2014, on disease-specific survival from patients with medullary carcinoma (code: 8510/3) from the Surveillance, Epidemiology, and End Results Program (SEER 18), an openly accessible database from the National Cancer Institute. A data use agreement was signed for this project. Because SEER is a publicly available database with anonymized data, no ethical review was required.

The following demographic information and clinical characteristics were collected: age at diagnosis, year of diagnosis, sex, race, tumor size, number of tumor foci, extension, T category, N category, M category, and surgical method. To ensure the accuracy of the results, user missing value was performed for missing or unknown data.

Experimental process

We divided the 960 patients into 24 groups according to the T, N, and M category. Kaplan-Meier (K-M) curves were used for survival analysis. Based on the results of the survival analysis, we divided the 24 groups into four stages, and we then adjusted this distribution combined with clinical consideration. Because some controversies remain regarding the staging of T1N0M1, T1N1bM1 and T2N0M1 cases, we categorized them as stage III for analysis. Because there were only three T0N1bM1 and T0N0M1 cases, they were excluded from the analysis.

We performed Cox proportional hazards models to assess variables associated with prognosis in the four stages, adjusting for age at diagnosis, year of diagnosis, sex, race, tumor size,

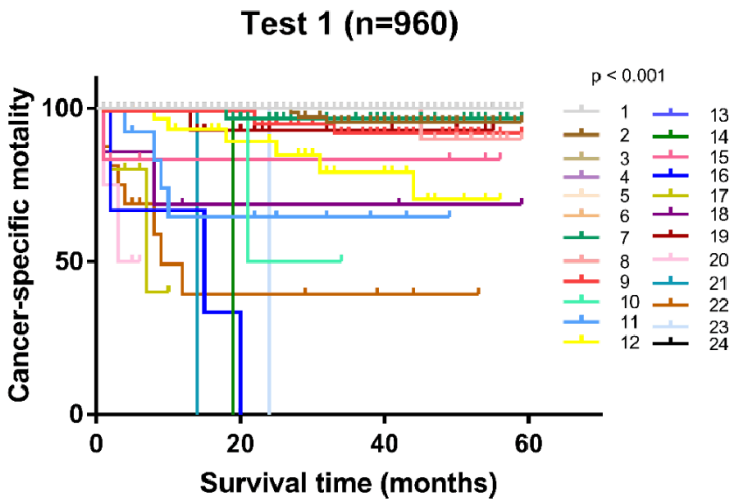

Figure 1. Kaplan-Meier cancer-specific survival curves in medullary thyroid carcinoma patients divided into 24 group by T, N, and M categories. Note: 1, T1N0M0; 2, T2N0M0; 3, T3N0M0; 4, T1N1aM0; 5, T2N1aM0; 6, T3N1aM0; 7, T1N1bM0; 8, T2N1bM0; 9, T3N1bM0; 10, T4N0M0; 11, T4N1aM0; 12, T4N1bM0; 13, T0N1bM1; 14, T0N0M1; 15, T1N1bM1; 16, T1N0M1; 17, T2N1bM1; 18, T2N0M1; 19, T3N1bM1; 20, T3N0M1; 21, T3N1aM1; 22, T4N1bM1; 23, T4N1aM1; 24, T4N0M1.

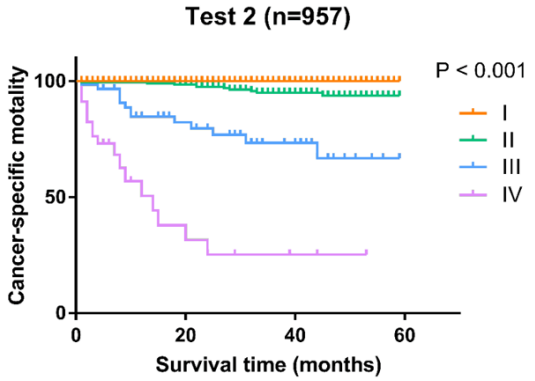

Figure 2. Kaplan-Meier survival curves for the distribution, based on the cancer-specific survival trends of the 24 groups that are based on T, N, and M categories. Note: I, T1N0M0, T1N1aM0, T2N1aM0, T3N0M0, T3N1aM0, T0N1bM1, T4N0M1; II, T1N1bM0, T2N0M0, T2N1bM0, T3N1bM0, T1N-1bM1, T3N1bM1; III, T4N0M0, T4N1aM0, T4N-1bM0, T2N0M1; IV, T0N0M1, T1N0M1, T2N1bM1, T3N0M1, T3N1aM1, T4N1aM1, T4N1bM1.

number of tumor foci, extension, and surgical modality. The mortality probability was calculated using 1000-person-years.

Statistical analysis

Variables are reported as proportions or means ± standard deviation (SD). All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, USA), Stata/SE version 12 (Stata Corp, College Station, TX, USA), Matlab version 2018a (MathWorks, Cambridge University Press, England, UK) and GraphPad Prism version 6 (GraphPad Software Inc., La Jolla, CA, USA). All Pg-values <0.05 were considered statistically significant.

Results

Demographic and clinical features

Demographic and clinical characteristics of the 960 MTC patients included in this study are shown in **Table 1**. The average age at diagnosis was 54.29±17.39 years, and the female:male ratio was 1.45:1. There were 454, 223, 199, and 81 patients with T1, T2, T3, and T4 disease, respectively; 574, 124, and 262 patients with N0, N1, and N1b disease, respectively; 889 patients with M0 disease and 71 patients with M1 disease.

Proposed TNM staging system

We divided the 960 patients into 24 groups, shown in Table S1. Based on survival trends (**Figure 1**), we then classified the 24 groups into four stages (**Figure 2**). Taking clinical issues into consideration, the stages were determined as follows: stage I included T1N0M0, T2N0M0, T3N0M0, T1N1aM0, T2N1aM0, and T3N1aM0; stage II included T1N1bM0, T2N1bM0, and T3N1bM0; stage III included T4N0M0, T4N1-aM0, and T4N1bM0; and stage IV included T2N1bM1, T3N0M1, T3N1aM1, T3N1bM1, T4N0M1, T4N1aM1, and T4N1bM1 (**Table 2**).

After further analysis, we categorized T1N0M1, T1N1bM1 and T2N0M1 as stage III (**Table 2**). Survival curves are shown in **Figure 3**. Compared with the new proposed staging system (**Figure 5**), in which T1N0M1, T1N1bM1 and T2N0M1 are considered stage IV (**Table 2**), there was less distinguishability between stage III and IV in this present analysis.

Finally, the proposed staging system defined T1-3N0-1aM0 as stage I, T1-3N1bM0 as stage II, T4N0-1bM0 as stage III, and T1-4N0-1bM1

Table 2. Comparison of the different distribution of the 24 groups

Stage	Test 2*	Test 3*	New Proposed*
I	T1N0M0	T1N0M0	T1N0M0
	T3N0M0	T2N0M0	T2N0M0
	T1N1aM0	T3N0M0	T3N0M0
	T2N1aM0	T1N1aM0	T1N1aM0
	T3N1aM0	T2N1aM0	T2N1aM0
	T0N1bM1	T3N1aM0	T3N1aM0
	T4N0M1		
II	T2N0M0	T1N1bM0	T1N1bM0
	T1N1bM0	T2N1bM0	T2N1bM0
	T2N1bM0	T3N1bM0	T3N1bM0
	T3N1bM0		
	T1N1bM1		
	T3N1bM1		
III	T4N0M0	T4N0M0	T4N0M0
	T4N1aM0	T4N1aM0	T4N1aM0
	T4N1bM0	T4N1bM0	T4N1bM0
	T2N0M1	T1N0M1	
		T1N1bM1	
		T2N0M1	
IV	T0N0M1	T2N1bM1	T1N0M1
	T1N0M1	T3N0M1	T1N1bM1
	T2N1bM1	T3N1aM1	T2N0M1
	T3N0M1	T3N1bM1	T2N1bM1
	T3N1aM1	T4N0M1	T3N0M1
	T4N1bM1	T4N1aM1	T3N1aM1
	T4N1aM1	T4N1bM1	T3N1bM1
			T4N0M1
			T4N1bM1
			T4N1aM1

*: Test 2, proposed based on test 1 without adjustment; Test 3, treating T1N0M1, T1N1bM1, and T2N0M1 as stage III based on *New proposed*; New proposed, adjusted based on the results of test 2 and clinical experience.

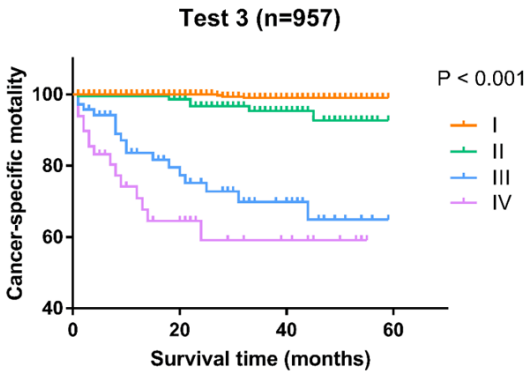

Figure 3. Kaplan-Meier cancer-specific survival curves for the new proposed distribution with the disputed groups of T1N0M1, T1N1bM1, and T2N0M1 considered as stage III. Note: I, T1N0M0, T1N1aM0, T2N0M0, T2N1aM0, T3N0M0, T3N1aM0; II, T1N1bM0, T2N1bM0, T3N1bM0; III, T4N0M0, T4N1aM0, T4N1bM0, T1N0M1, T1N1bM1, T2N0M1; IV, T2N1bM1, T3N0M1, T3N1aM1, T3N1bM1, T4N0M1, T4N1aM1, T4N1bM1.

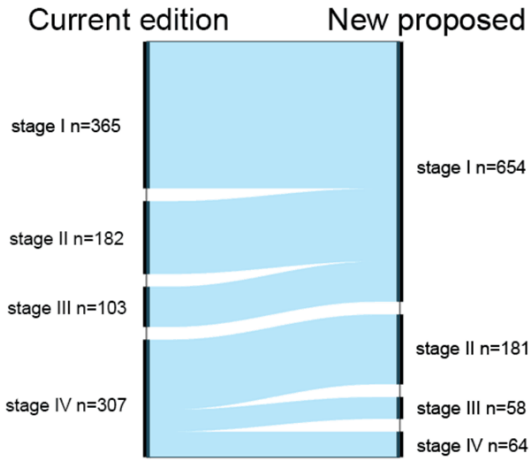

Figure 4. Alluvial flow diagram representing restaging of patients in the Surveillance, Epidemiology, and End Results (SEER) database from the current edition to the new proposed staging system.

as stage IV. A comparison with the current staging system is shown in **Table 3**, and **Figure 4** depicts the alluvial flow diagram showing changes between the current edition and the new proposed staging system.

Predictive ability of the new proposed TNM staging system

To verify the accuracy of the proposed staging system, we assessed survival using K-M analysis. As shown in **Figure 5**, which is based on cancer-specific survival data, the new proposed TNM staging system (**Figure 5**) better stratified patients with different survivals times than did the current edition (**Figure 5**). This new model could better distinguish patients with different prognoses. **Figure 6** shows overall mortality based on the current and proposed models. The mortality rates per 1000-person-years for the new stages I, II, III, and IV were 2.036 (95% confidence interval [CI], 0.657-6.312), 14.867 (95% CI, 6.679-33.092), 98.287 (95% CI, 54.432-177.478), and 224.199 (95% CI, 146.180-343.860), respectively (**Table 4**). The mortality rates per 1000-person-years for the

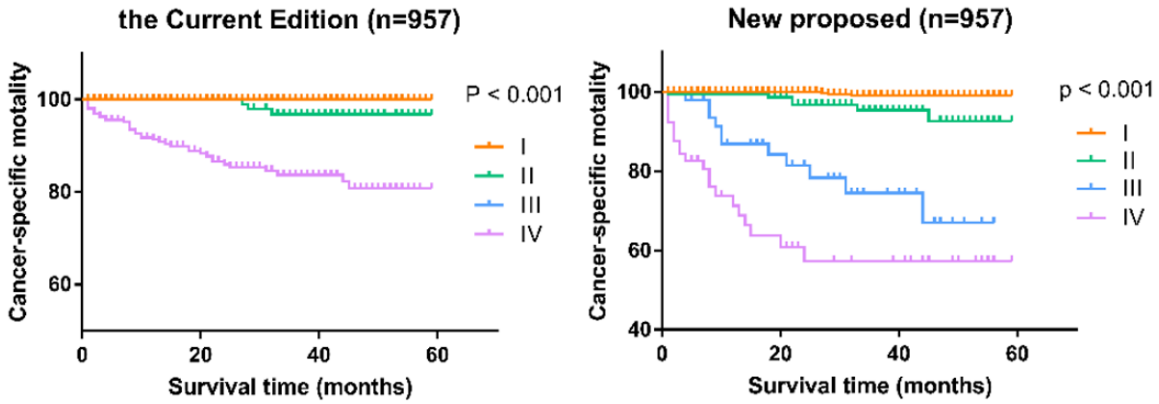

Figure 5. Comparison of Kaplan-Meier curves of the new proposed TNM staging system and the current edition based on data on cancer-specific survival; T, tumor; N, node; M, metastasis. Note: I, T1N0M0; II, T2-3N0M0; III, T1-3N1aM0; IV, T1-3N1bM0, T4N0-1bM0, T1-4N0-1bM1. Note: I, T1-3N0-1aM0; II, T1-3N1bM0; III, T4N0-1BM0; IV, T1-4N0-1bM1.

Table 3. Comparison of the differences in distribution of patients with medullary thyroid carcinoma between the current edition * and the new proposed TNM staging system

Stage	the current edition*		New proposed	
	Distribution	N (%)	Distribution	N (%)
I	T1N0M0	365 (38.14)	T1-3N0-1aM0	654 (68.34)
II	T2-3N0M0	182 (19.02)	T1-3N1bM0	181 (18.91)
III	T1-3N1aM0	103 (10.76)	T4N0-1bM0	58 (6.06)
IV	T1-3N1bM0	307 (32.08)	T1-4N0-1bM1	64 (6.69)
	T4N0-1bM0			
	T1-4N0-1bM1			

Abbreviations: T, tumor; N, node; M, metastasis; *: staging was based on the American Joint Committee on Cancer 7th and 8th editions.

24 groups based on cancer-specific survival are shown in Table S2.

The adjusted hazard ratios of the new proposed staging system for stages II, III, and IV, with stage I as reference, were 5.281 (95% CI, 1.236-22.562), 20.603 (95% CI, 4.400-96.467), and 55.717 (95% CI, 14.307-216.988), respectively. We also performed Cox proportional hazards analysis for overall mortality (**Table 5**), and the results indicated that the new proposed staging system was more suitable than the current edition. Adjusted Cox proportional hazards analysis of cancer-specific survival based on the new proposed staging system is shown in Table S3.

Discussion

The AJCC staging system is used by clinicians to predict prognosis in clinical oncology, and it is largely based on the TNM staging system [9]. One of the main prognostic factors for survival in MTC is disease stage [10]. Unlike other thyroid malignancies, MTC is resistant to radioactive iodine therapy because the tumors do not concentrate radioactive iodine [11]. Therefore, surgery is the primary curative therapy for MTC, and the extent of surgical resection is mainly dictated by the size of the primary tumor and the extent of nodal and distant metastases. Hence, an appropriate TNM staging system is highly important for MTC [12]. Therefore, our present work aims to improve the predictive ability of the current AJCC staging system.

We used the SEER database, which is recognized annually by the North American Association of Central Cancer Registries for its completeness and accuracy [13] and analyzed survival using K-M curves and Cox proportional hazards models. This new proposed staging system was based on the survival of previous patients and provides a more accurate prognosis for MTCs. In the final proposed staging system, stage I includes T1-3N0-1aM0, stage II includes T1-3N1bM0, stage III includes T4N0-1bM0, and stage IV includes T1-4N0-1bM1.

Compared with the current staging system, the significant change in our new proposed staging system is the downgrading of high-level stages. This would have a significant effect on the treat-

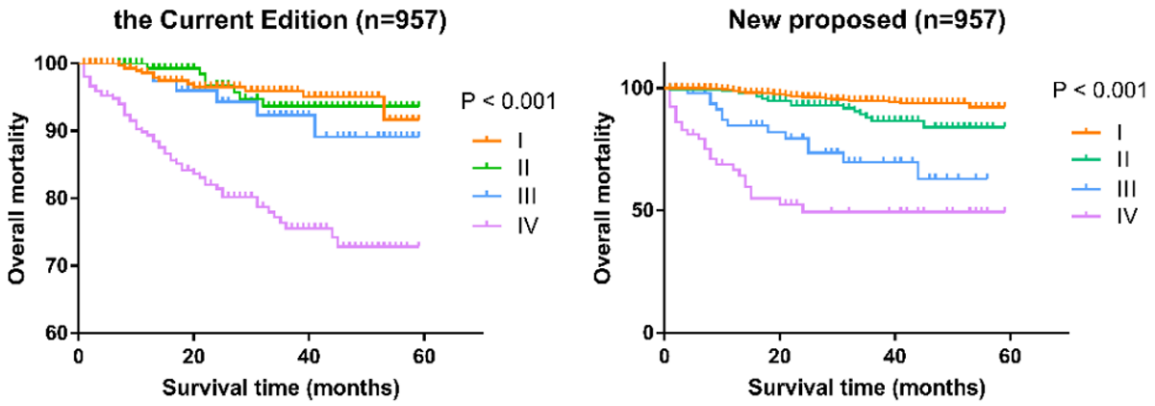

Figure 6. Comparison of Kaplan-Meier curves of the new proposed TNM staging system and the current edition based on data on overall mortality; T, tumor; N, node; M, metastasis. Note: I, T1N0M0; II, T2-3N0M0; III, T1-3N1aM0; IV, T1-3N1bM0, T4N0-1bM0, T1-4N0-1bM1. Note: I, T1-3N0-1aM0; II, T1-3N1bM0; III, T4N0-1bM0; IV, T1-4N0-1bM1.

Table 4. Comparison of mortality (per 1000-person-years) between the current edition and the new proposed TNM staging system based on cancer-specific survival

Stage	the current edition			New proposed		
	Fail	Rate	95% CI	Fail	Rate	95% CI
I	0	-	-	3	2.036	0.657-6.312
II	3	6.879	2.219-21.330	6	14.867	6.679-33.092
III	0	-	-	12	98.287	54.432-177.478
IV	40	62.380	45.390-85.730	22	224.199	146.180-343.860

Abbreviation: T, tumor; N, node; M, metastasis; CI, confidence interval.

Table 5. Comparison of the differences in the adjusted * Cox analyses of cancer-specific mortality and overall mortality in patients with medullary thyroid carcinoma between the current edition and new proposed TNM staging system

Stage	Cancer-specific survival						Overall mortality					
	The current edition			New proposed			The current edition			New proposed		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
I	Ref			Ref			Ref				Ref	
II	NA	-	0.888	5.281	1.236-22.562	0.025	0.452	0.140-1.458	0.184	1.699	0.832-3.471	0.146
III	NA	-	0.994	20.603	4.400-96.467	<0.001	1.248	0.400-3.889	0.702	3.273	1.223-8.755	0.018
IV	NA	-	0.866	55.717	14.307-216.988	<0.001	2.279	0.909-5.715	0.079	10.218	4.756-21.955	<0.001

Abbreviation: T, tumor; N, node; M, metastasis; HR, hazard ratio; CI, confidence interval; *: adjusted for age at diagnosis, year of diagnosis, gender, race, tumor size, extension, multifocality, and surgical method.

ment of MTC patients, as it has been reported that patients who underwent more extensive surgery showed a worse prognosis than patients who underwent only central neck nodal dissection [14]. Furthermore, in the process of statistical analysis, we also found that the current edition was unable to explain the varying prognoses of patients with different stages. For example, in the current edition, stage IV included 40 patients who died of MTC, whereas no patients with stage I and III, and only 3 patients with stage II disease died of MTC.

In addition to considering distant metastasis, we also considered tumor size and lymph node metastasis. In a study by Adam et al., recursive partitioning analysis was used to propose a new staging system [15]. In that model, they emphasize the prognostic significance of distant metastasis in MTC, and stage IV included only patients with distant metastases. In addition, patients with T4 and/or N1b disease were no longer classified as stage IV but were downstaged to stage II or stage III. Furthermore, Park et al. [16] and Mathiesen et al. [17], adopted

that staging system in Korean and Danish cohorts, respectively, and showed that it was superior to the current staging system. However, Momin et al. showed that larger tumor size and cervical metastases were poor prognostic factors [18]. Further, Scollo et al. found that MTC readily invaded the intraglandular lymphatics and regional lymph nodes. Indeed, lymph node involvement was found in more than 80% of cases, and lymph node metastasis was more common in patients with larger tumors [19]. Machens et al. found that N staging was an important prognostic instrument in that the number of metastatic lymph nodes showed power in distant metastasis and survival analysis, suggesting that N staging should be evaluated in MTC treatment decisions for optimal assessment [20]. Therefore, these three factors (tumor size, lymph node involvement, and distant metastasis) interact with each other to affect the TNM staging system.

There were some limitations to the present study. There was inadequate data for disputed stages, such as T1N0M1, T1N1bM1 and T2N0M1, and too little data for stages T1N1aM1 and T2N1aM1, which might affect the distribution of the staging system we proposed. On this point, we defer to previous models until there is enough evidence to prove a better allocation. Additionally, in recent years, cytokines levels (particularly serum calcitonin) have also been used to determine medical treatment, prognosis, and recurrence of MTC to a greater extent than that of TNM, but the appropriate cut-off level is controversial [21, 22]. In addition, age at diagnosis appears to be one of the most important factors in multivariate analysis, but its exact impact is still unclear [23, 24]. Patient management should be adjusted for these factors after their impact on MTC is clarified.

In recent decades, significant medical advances have been made in the management of MTC. These advances demonstrate that MTC is being better recognized and treated, leading to significant improvements in cure and survival rates. However, questions remain that require clarification. For our staging system, we have taken tumor size and lymph node metastasis into account and used scientific statistical methods to propose a new staging system. We expect single-center data or larger trials to verify our conclusion.

Disclosure of conflict of interest

None.

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Table S1. Patients distribution and events of 24 groups

Group	Distribution	No.	CSS (%)	OS (%)
1	T1N0M0	365	0 (0)	12 (3.29)
2	T2N0M0	128	3 (2.34)	6 (4.69)
3	T3N0M0	54	0 (0)	1 (1.85)
4	T1N1aM0	41	0 (0)	1 (2.44)
5	T2N1aM0	33	0 (0)	3 (9.09)
6	T3N1aM0	29	0 (0)	2 (6.90)
7	T1N1bM0	39	1 (2.56)	1 (2.56)
8	T2N1bM0	49	1 (2.04)	4 (8.16)
9	T3N1bM0	93	4 (4.30)	1 (10.75)
10	T4N0M0	7	1 (14.29)	2 (28.57)
11	T4N1aM0	15	4 (26.67)	5 (33.33)
12	T4N1bM0	36	7 (19.44)	7 (19.44)
13	T0N1bM1	1	0 (0)	0 (0)
14	T0N0M1	2	1 (50.00)	1 (50.00)
15	T1N1bM1	6	1 (16.67)	1 (16.67)
16	T1N0M1	3	3 (100)	3 (100.00)
17	T2N1bM1	6	2 (33.33)	2 (33.33)
18	T2N0M1	7	2 (28.57)	3 (42.86)
19	T3N1bM1	16	2 (12.50)	3 (18.75)
20	T3N0M1	4	2 (50.00)	3 (75.00)
21	T3N1aM1	3	1 (33.33)	1 (33.33)
22	T4N1bM1	16	8 (50.00)	9 (56.25)
23	T4N1aM1	3	1 (33.33)	1 (33.33)
24	T4N0M1	4	0 (0)	1 (25.00)
Total	-	960	44 (4.58)	81 (8.46)

Abbreviation: No., number; CSS, cancer-specific survival; OS, overall survival.

Table S2. Comparison of mortality per 1000-person-years in the 24 groups by cancer specific mortality

Group	Distribution	No.	CSS (%)	Rate	95% CI
1	T1N0M0	365	0 (0)	-	-
2	T2N0M0	128	3 (2.34)	9.531	3.074-29.553
3	T3N0M0	54	0 (0)	-	-
4	T1N1aM0	41	0 (0)	-	-
5	T2N1aM0	33	0 (0)	-	-
6	T3N1aM0	29	0 (0)	-	-
7	T1N1bM0	39	1 (2.56)	9.772	1.377-69.372
8	T2N1bM0	49	1 (2.04)	9.050	1.275-64.245
9	T3N1bM0	93	4 (4.30)	20.970	7.870-55.872
10	T4N0M0	7	1 (14.29)	127.660	17.983-906.264
11	T4N1aM0	15	4 (26.67)	173.913	65.273-463.375
12	T4N1bM0	36	7 (19.44)	73.998	33.244-164.711
13	T0N1bM1	1	0 (0)	-	-
14	T0N0M1	2	1 (50.00)	352.941	49.717-2505.555
15	T1N1bM1	6	1 (16.67)	71.429	10.062-507.077
16	T1N0M1	3	3 (100)	972.973	313.805-3016.77
17	T2N1bM1	6	2 (33.33)	827.586	206.977-3309.052
18	T2N0M1	7	2 (28.57)	181.818	45.472-726.989
19	T3N1bM1	16	2 (12.50)	29.851	4.205-211.913
20	T3N0M1	4	2 (50.00)	1600	400.156-6397.501
21	T3N1aM1	3	1 (33.33)	600.000	84.518-4259.443
22	T4N1bM1	16	8 (50.00)	417.391	208.736-834.620
23	T4N1aM1	3	1 (33.33)	387.097	54.529-2748.028
24	T4N0M1	4	0 (0)	-	-

Abbreviation: No., number; CSS, cancer-specific survival; CI, confidence interval.

Table S3. Adjusted Cox analysis of cancer specific mortality of patients with medullary thyroid carcinoma

Variable		HR	95% CI	*P*-value
Gender		0.890	0.437-1.813	0.748
Race White		Ref		
Black		1.466	0.471-4.560	0.509
Other		1.631	0.461-5.766	0.448
Age at diagnosis		1.025	1.001-1.051	0.041
Year of diagnosis		1.050	0.422-2.612	0.916
Tumor size (mm)	<10 (including 10)	Ref		
	10-20 (including 20)	19861.101	0-?	0.884
	20-40 (including 40)	21939.567	0-?	0.883
	>40	21972.371	0-?	0.883
Number of tumor foci		1.107	0.513-2.390	0.795
Extension		1.625	0.711-3.719	0.250
Staging	I	Ref		
	II	5.281	1.236-22.562	0.025
	III	20.603	4.400-96.467	<0.001
	IV	55.717	14.307-216.988	<0.001
Surgical procedure	Biopsy	Ref		
Lobectomy		0.702	0.138-3.575	0.670
Subtotal or near-total thyroidectomy		2.899	0.314-26.764	0.348
Total thyroidectomy		0.470	0.195-1.131	0.092

Abbreviation: HR, hazard ratio; CI, confidence interval.