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Refinement of the 8th AJCC Staging System for Medullary Thyroid Cancer: Integrating Tumor Size and Lymph Node Characteristics with SEER and Multicenter Validation

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Abstract

The 2018 release of the 8th edition of the AJCC staging system for medullary thyroid cancer (MTC) aimed to standardize prognosis assessment. However, its effectiveness in predicting patient outcomes is still debated. Patient records were extracted from both the SEER database and multicenter cohorts. The study's main endpoint was overall survival (OS). Prognostic performance of different staging models was evaluated using the concordance index (C-index). A total of 1450 MTC cases were included from SEER, along with 349 cases from the multicenter cohort. No significant OS difference was observed between T4a and T4b groups according to the AJCC criteria (P = .299). Therefore, the T4 group was redefined based on tumor size into T4a' (≤3.5 cm) and T4b' (>3.5 cm), which provided better discrimination of survival outcomes (P = .003). Additional analyses revealed that the T stage was closely linked to both lymph node (LN) location and total number (P < .001). Based on these findings, the N stage was revised to integrate LN location with LN count. Finally, the modified T and N categories were used to update the 8th AJCC system via recursive partitioning analysis, resulting in improved prognostic accuracy (C-index 0.811 vs. 0.792). Refining the 8th AJCC staging system by considering the relationship between T stage, LN location, and LN count enhances its prognostic performance, supporting better clinical decision-making and follow-up strategies.

Keywords: Medullary thyroid cancer, AJCC, Staging, SEER, Prognosis

Introduction

Medullary thyroid cancer (MTC) is a neuroendocrine tumor originating from para-follicular C cells in the thyroid gland. It accounts for around 2% of thyroid cancers [1]. Surgery remains the primary therapeutic approach [2]. Despite the introduction of targeted therapies and immunotherapies [3–6], survival outcomes remain poor, with MTC responsible for up to 13% of thyroid cancer deaths [7]. Accurate staging is therefore essential to guide treatment and follow-up.

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The UICC/AJCC TNM system is the most commonly used method for classifying MTC [8], yet its prognostic reliability is questioned. Adam *et al* [9] reported that the 8th AJCC edition did not significantly distinguish survival for stages I, II, and III (P > .05) based on the NCDB and SEER datasets. In contrast, stage IV patients had markedly worse outcomes, with a 5-year OS of 33%, while stages I–III exceeded 90%. Chen *et al* [10] incorporated the metastatic lymph node ratio (LNR) to enhance N staging, improving prognostic ability, though LNR is affected by factors such as total resected nodes, pathology review, and patient variability [11, 12]. Other attempts, like integrating mortality per 1000-person-years, caused substantial stage imbalance, with 835 patients (87.25%) in stages I–II and 122 (12.25%) in stages III–IV [13]. Additionally, this approach has not been widely adopted clinically. Previous strategies to

improve AJCC staging were still limited in effectiveness [14, 15].

Previously, we proposed a modification incorporating LN count rather than location [16]. In the present study, we further examined how T and N stages interact and their prognostic value using SEER and multicenter cohorts, offering a potential framework for more accurate MTC staging.

Materials and Methods

Data

Patient information was sourced from the SEER database, a major clinical registry in the United States. Inclusion criteria included: (1) age ≥18 years; (2) MTC diagnosis confirmed via histology; (3) MTC as the first or only primary tumor; (4) complete TNM data according to the 8th AJCC edition, with N1a indicating metastasis to level VI or VII lymph nodes (LNs) and N1b indicating metastasis to lateral or retropharyngeal LNs; (5) at least one LN surgically removed; (6) documented number and location of both removed and positive LNs; (7) tumor size available for T4NanyM0 patients; (8) available follow-up information. Patients with M0 disease but nonspecific staging information (NOS) for T4 or N1 were excluded. For cases with distant metastases, T and N details were unnecessary because all were classified as stage IV. Maximum follow-up was 143 months.

Data from four Chinese hospitals—Shanghai Tenth People's Hospital, Xuzhou Central Hospital, Yueyang Hospital, and Changhai Hospital—collected between 2010 and 2018, were used as a multicenter cohort. All patients were of Chinese descent. Inclusion and exclusion criteria mirrored those applied to the SEER cohort. Maximum follow-up in this cohort was 94 months. Written informed consent was obtained from each participant. This study adhered to STROBE reporting guidelines [17] and was approved by the Bioethics Committee of Shanghai Tenth People's Hospital, Tongji University School of Medicine, P.R. China.

Statistical analysis

Categorical variables were compared using Chi-square tests. Survival differences were assessed using Kaplan-Meier curves and reported as hazard ratios (HR) with 95% confidence intervals (CI). The concordance index (C-index) evaluated the prognostic performance of different models. All analyses were conducted using R software (v3.6.2). Optimal cutoff points for tumor size and LN count were determined using X-tile software, which systematically evaluates all possible cutoffs and selects the best-performing threshold. A P-value < .05 was considered statistically significant.

Results and Discussion

Baseline characteristics

Following application of inclusion and exclusion criteria, 1450 MTC patients from SEER (2004–2017) were included **(Table 1)**. Ages ranged from 18 to 99 years, with a median of 53. Females slightly predominated (58.7% vs. 41.3%), and over 80% of patients were White. Tumor sizes varied between 1 and 150 mm, with a median of 24 mm. Stage distribution showed T1 as the most common (38.8%) and T4 as the least (9.8%). Among T4 patients, 95 were T4a and 47 were T4b. Positive LN counts ranged from 0 to 73, with a median of 1. Of patients with LN metastases, 224 were N1a and 532 were N1b; 395 had 1–8 positive LNs, and 358 had more than 9. Distant metastases occurred in 117 patients (8.1%). Tumor grade data were largely missing (90.9%), but this did not impact the analysis or conclusions.

Table 1. Baseline features of the study cohort

Variables	Multicenter (%)	SEER (%)
Total number	349	1450
Age (years)		
Median(range)	56(19-76)	53 (18-99)
Gender		
Male	154 (44.1%)	599 (41.3%)
Female	195 (55.9%)	851 (58.7%)
Race/ethnicity		
White	0	1204 (83.0%)
Black	0	131 (9.0%)
Others*	349 (100%)	115 (8.0%)
Grade		
I+II	/	78 (5.4%)
III+IV	/	53 (3.7%)
Unknown	/	1319 (90.9%)
TNM (8th)		
I	65 (18.7%)	392 (27.1%)
II	46 (13.2%)	277 (19.1%)
III	87 (24.9%)	192 (13.2%)
IV		
IVA	95 (27.2%)	447 (30.8%)
IVB	19 (5.4%)	25 (1.7%)

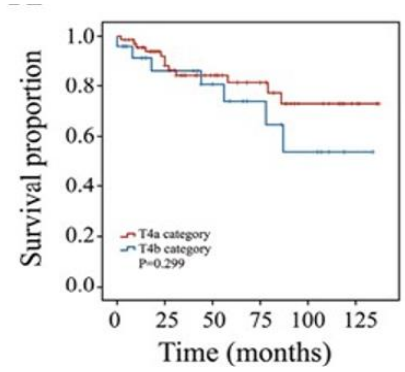
IVC	37 (10.6%)	117 (8.1%)
T category		
T1	93 (26.7%)	563 (38.8%)
T2	72 (20.6%)	376 (26.0%)
T3	90 (25.8%)	359 (24.7%)
T4a	43 (12.3%)	95 (6.6%)
T4b	23 (6.6%)	47 (3.2%)
TX	28 (8.0%)	10 (0.7%)
Tumor size (mm)**		
Median(range)	20 (3-85)	24 (1-150)
N category		
N0	133 (38.1%)	679 (46.8%)
N1a	102 (29.2%)	224 (15.4%)
N1b	92 (26.4%)	532 (36.8%)
N1 NOS	0	10 (0.7%)
NX	22 (6.3%)	5 (0.3%)
Number of positive LNs		
Median(range)	2 (0-42)	1 (0-73)
0	133 (38.1%)	679 (46.8%)
1-8	104 (29.9%)	395 (27.3%)
≥9	86 (24.6%)	358 (24.7%)
Unknown	26 (7.4%)	18 (1.2%)
M category		
M0	312 (89.4%)	1333 (91.9%)
M1	37 (10.6%)	117 (8.1%)

*Includes American Indian/Alaska Native, Asian/Pacific Islander/Unknown in the SEER cohort and Chinese patients in the multicenter cohort.
**Twenty-six cases were unavailable in the SEER dataset.

Revision of the T4 category

In the existing AJCC framework, T4 tumors are divided into T4a—defined by extension into subcutaneous tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve—and T4b—defined by invasion of the prevertebral fascia or encasement of the carotid artery or mediastinal vessels. However, survival analysis excluding M1 patients indicated no meaningful difference between T4a and T4b groups **(Figure 1a)**, (P = .299).

To further explore prognostic significance, tumor size within the T4 category was assessed using X-tile software. Patients with tumors exceeding 3.5 cm had markedly worse outcomes than those with tumors ≤3.5 cm **(Figure 1b)**, (P = .003, HR = 3.941, 95% CI, 1.493–10.401). Consequently, the T4 category was redefined: tumors ≤3.5 cm were designated as T4a', while tumors >3.5 cm were designated as T4b'.



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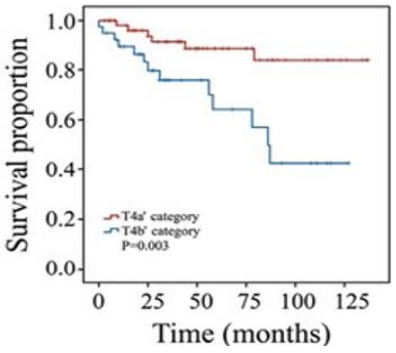

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Figure 1. Kaplan-Meier survival plots based on the T4 classification. (a) Survival comparison of T4a versus T4b in the SEER cohort; (b) survival curves for the redefined T4a' and T4b' groups in the SEER cohort.

Redefining the N category considering T stage, LN location, and LN number

Kaplan-Meier analysis indicated that, among M0 patients, those classified as N1b had significantly worse overall survival compared with N1a patients **(Figure 2a)**, (P = .003, HR = 2.271, 95% CI, 1.289–4.002). A Chi-square test further revealed that patients in the N1b category tended to have a higher number of metastatic lymph nodes than those in the N1a group **(Table 2)**; (P < .001).

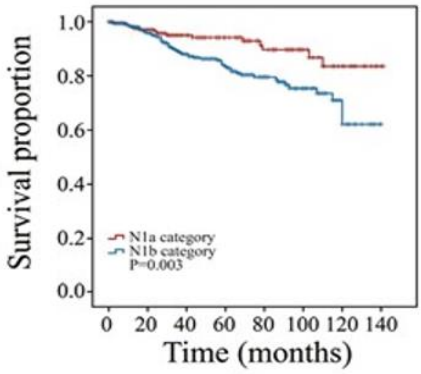
To explore the prognostic relevance of LN count, the optimal cutoff for positive LNs was determined using X-tile software, aiming to maximize survival discrimination **(Figure 2b)**; (P = .001). M0 patients with LN metastases were initially divided into three groups: 1–8 LNs, 9–16 LNs, and ≥17 LNs. No significant survival difference was found between the 9–16 LNs and ≥17 LNs groups (P = .339), so these were combined into a single ≥9 LNs group for subsequent analysis. Patients in the ≥9 LNs group exhibited poorer survival than those with 1–8 LNs

(Figure 2c), (P < .001, HR = 2.331, 95% CI, 1.457–3.729).

These findings suggest that incorporating both the anatomical location and the number of positive lymph nodes can effectively stratify prognosis in MTC patients.

Table 2. Distribution of LN location and LN count.

Lymph Node count	N1a category: metastasis to level VI or VII (paratracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) Lymph Nodes. This can be unilateral or bilateral disease	N1b category: metastasis to unilateral, bilateral, or contralateral lateral neck LNs (levels I, II, III, IV, or V) or retropharyngeal LNs	N1′ category: N1a with 1-8 LNs	N2′ category: N1b with 1-8 LNs, N1a with ≥9 LNs	N3′ category: N1b with ≥9 LNs
1-4	149	93	149	93	—
5-8	34	85	34	85	—
9-12	17	77	—	17	77
13-16	6	58	—	6	58
17-20	1	46	—	1	46
21-24	3	27	—	3	27
≥25	3	62	—	3	62



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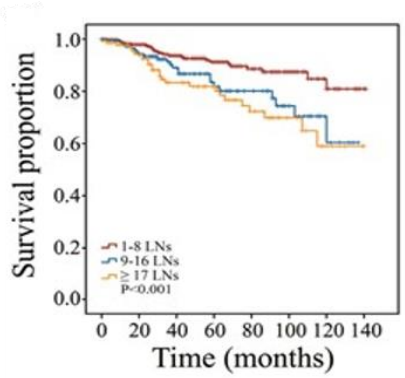

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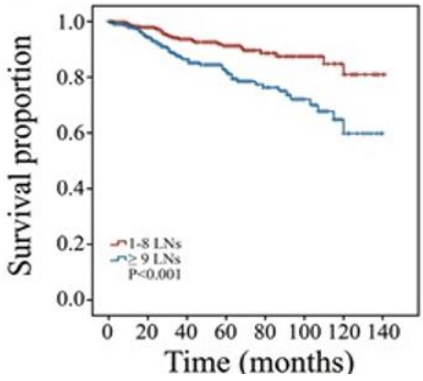

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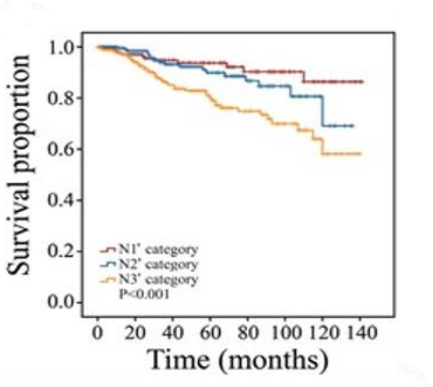

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Figure 2. Kaplan-Meier survival analyses by N category. (a) Survival of patients with N1a versus N1b in the SEER cohort; (b) survival of three LN count-based groups: 1–8 LNs, 9–16 LNs, and ≥17 LNs; (c) survival for two LN count groups: 1–8 LNs and ≥9 LNs;

(d) survival of patients stratified into the new N1′, N2′, and N3′ categories.

We examined the interplay between T stage, LN anatomical site, and LN number. With progression from T1 to T4, the frequency of N1b classification increased. Chi-square testing revealed that patients with higher T stages (T3 + T4) were more likely to have N1b disease compared with those at lower T stages (T1 + T2) ($P < .001$), suggesting a strong correlation between T stage and LN location. Additionally, the proportion of N1b patients with ≥9 positive LNs in advanced T stages nearly doubled that of early T stages (54.38% vs. 27.44%, $P < .001$), indicating that T stage is linked to both the location and quantity of metastatic LNs.

Based on these associations, the N category was revised by combining the LN site and count:

- N1a patients with 1–8 LNs → N1′
- N1a patients with ≥9 LNs and N1b patients with 1–8 LNs → N2′
- N1b patients with ≥9 LNs → N3′

Patients without LN metastasis remained in the N0' group. Kaplan-Meier analysis demonstrated clear survival differences across these new categories **(Figure 2d)**; reference N1′, $P < .001$, HR for N3′ = 3.062, 95% CI, 1.620–5.787), indicating that this revised N classification provides stronger prognostic discrimination.

Revision of the TNM staging system

Analysis using the original 8th AJCC TNM system revealed no significant differences in survival among stages I, II, and III **(Figure 3a)**; $P = .911$). Stage IVB patients had shorter survival than stage IVA patients, but the difference did not reach statistical significance **(Figure 3a)**; $P = .130$).

To improve prognostic accuracy, the newly defined T and N categories were integrated to adjust the AJCC TNM system via recursive partitioning. The modified stage definitions were:

- Stage I: T1N0′–2′M0, T2N0′M0
- Stage II: T1N3′M0, T2N1′–2′M0, T3N0′–1′M0
- Stage III: T2N3′M0, T3N2′–3′M0, T4a′N0′–3′M0
- Stage IVA: T4bN0′–3′M0
- Stage IVB: TanyNanyM1 **(Table 3)**

The modified AJCC (mAJCC) system showed statistically significant survival differences between each pair of adjacent stages **(Figure 3b and Table 4).** Its C-index was 0.811 (95% CI, 0.762–0.860), compared with 0.792 (95% CI, 0.743–0.841) for the original AJCC system, demonstrating enhanced prognostic performance.

Table 3. Comparison of T, N, and M criteria between the 8th AJCC and the modified AJCC staging system.

8th Edition Staging		**Modified Staging System**	
T Category	**T Criteria**	**T Category**	**T Criteria**
T0	Absence of detectable primary tumor	T0	Identical to 8th edition
T1	Tumor measuring ≤2 cm at its largest diameter, restricted within the thyroid gland	T1	Identical to 8th edition
T2	Tumor measuring >2 cm but ≤4 cm at its largest diameter, restricted within the thyroid gland	T2	Identical to 8th edition
T3	Tumor exceeding 4 cm but still confined to the thyroid, or with macroscopic extrathyroidal spread involving only the strap muscles	T3	Identical to 8th edition
T4	Encompasses any tumor showing macroscopic extrathyroidal spread	T4	Identical to 8th edition

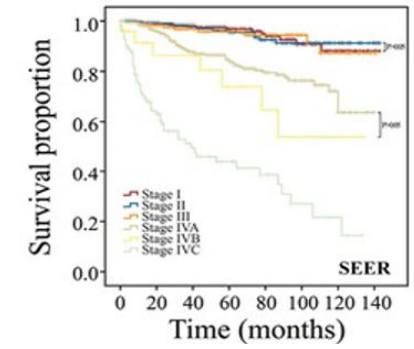
T4a	Macroscopic extrathyroidal spread into subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve (regardless of tumor size)	T4a′	Macroscopic extrathyroidal spread into subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia, carotid artery, or mediastinal vessels (when primary tumor is ≤3.5 cm)
T4b	Macroscopic extrathyroidal spread into prevertebral fascia or wrapping around the carotid artery or mediastinal vessels (regardless of tumor size)	T4b′	Macroscopic extrathyroidal spread into subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, prevertebral fascia, carotid artery, or mediastinal vessels (when primary tumor is >3.5 cm)
N Category	**N Criteria**	**N Category**	**N Criteria**
N0	Absence of locoregional lymph node metastases	N0	Identical to 8th edition
N1	Presence of metastases in regional lymph nodes	N1′	N1a subcategory involving 1–8 positive nodes
N1a	Metastases in Level VI or VII nodes (including paratracheal, prelaryngeal/Delphian, or upper mediastinal nodes); can be unilateral or bilateral	N2′	(1) N1a subcategory involving ≥9 positive nodes (2) N1b subcategory involving 1–8 positive nodes
N1b	Metastases in unilateral, bilateral, or contralateral lateral cervical nodes (Levels I–V) or retropharyngeal nodes	N3′	N1b subcategory involving ≥9 positive nodes
M Category	**M Criteria**	**M Category**	**M Criteria**
M0	Absence of distant metastases	M0	Identical to 8th edition
M1	Presence of distant metastases	M1	Identical to 8th edition

Abbreviation: AJCC, American Joint Committee on Cancer.

Table 4. Survival comparison between the 8th edition AJCC staging system and the modified AJCC (mAJCC) system.

Stage	AJCC Combinations	AJCC HR (95% CI) Reference	AJCC P-value Reference	mAJCC Combinations	mAJCC HR (95% CI) Reference	mAJCC P-value Reference
I	T1N0M0	- (baseline)	- (baseline)	T1N0′-2′M0 T2N0′M0	- (baseline)	- (baseline)
II	T2-3N0M0	1.020 (0.471-2.209) vs. stage I	.960 vs. stage I	T1N3′M0 T2N1′-2′M0 T3N0′-1′M0	2.280 (1.249-4.162) vs. stage I	.007 vs. stage I
III	T1-3N1aM0	1.176 (0.495-2.793) vs. stage II	.714 vs. stage II	T2N3′M0 T3N2′-3′M0 T4a′N0′-3′M0	2.248 (1.317-3.839) vs. stage II	.003 vs. stage II
IVA	T1-3N1bM0 T4aNanyM0	3.364 (1.667-6.789) vs. stage III	.001 vs. stage III	T4b′N0′-3′M0	2.417 (1.305-4.477) vs. stage III	.005 vs. stage III
IVB	T4bNanyM0	1.833 (0.837-4.013) vs. stage IVA	.130 vs. stage IVA	TanyNanyM1	2.107 (1.150-3.860) vs. stage IVA	.016 vs. stage IVA
IVC	TanyNanyM1	2.789 (1.264-6.158) vs. stage IVB	.011 vs. stage IVB	-	-	-

Abbreviations: AJCC, American Joint Committee on Cancer; HR: hazard ratio.



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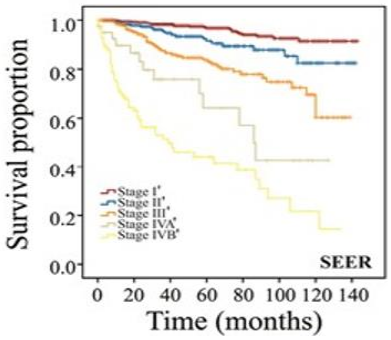

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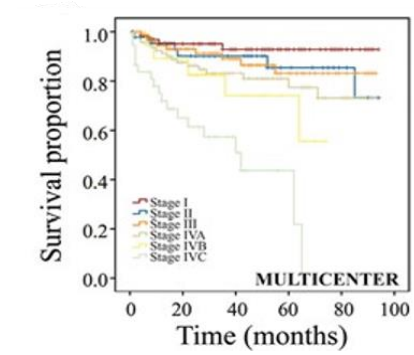

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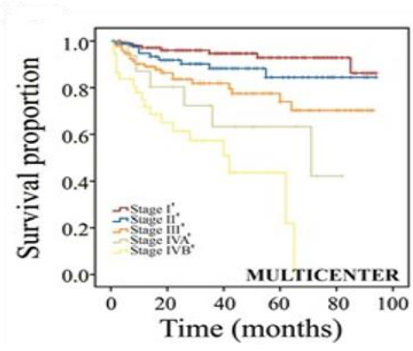

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Figure 3. Kaplan-Meier curves comparing prognoses under two staging systems. (a) SEER cohort patients according to the 8th AJCC system; (b) SEER cohort using the modified AJCC (mAJCC) system; (c) multicenter cohort with 8th AJCC; (d) multicenter cohort under mAJCC.

Validation in multicenter cohort

The multicenter dataset included 349 MTC patients collected between 2010 and 2018 **(Table 1)**, all of Chinese ethnicity. According to the 8th AJCC TNM staging system, 65 patients were stage I, 46 stage II, 87 stage III, 95 stage IVA, 19 stage IVB, and 37 stage IVC. Tumor sizes ranged from 3 mm to 85 mm, with a median of 20 mm. The number of metastatic lymph nodes varied from 0 to 42, with a median of 2. Survival analysis indicated that the mAJCC system more effectively differentiated prognosis **(Figure 3c and 3d)**. The C-index of mAJCC was 0.725 (95% CI, 0.629–0.821), outperforming the AJCC system, which had a C-index of 0.686 (95% CI, 0.588–0.784).

In the 8th AJCC system, T4 tumors are divided into T4a and T4b based on anatomical invasion. Our results, however, showed no statistically meaningful difference in survival between these categories. Although a study by Portugal *et al*. reported worse outcomes for T4b patients, the difference did not reach significance (P = .06) [18]. By subdividing the T4 category based on tumor size, we were able to better stratify mortality risk (P = .003), highlighting the prognostic value of tumor size even in advanced T4 tumors. This approach represents the first effort, to our knowledge, to refine the T4 classification and to distinguish stage IVA from IVB more effectively. Previous studies, such as Mohamed *et al*. [9], aimed to optimize TNM staging based on overall survival differences, and Mathiesen *et al*. [19] confirmed better discrimination using Danish registry data. However, there were limitations. First, their system performed well for stages I–III in the NCDB training cohort but did not generalize to the SEER validation cohort, limiting its universal applicability. Second, the T4 category was treated as a single entity, masking heterogeneity and reducing prognostic power, unlike the original AJCC subdivision. Our revision of T4 yielded clearer prognostic separation. Third, stage IV patients were not subdivided in previous proposals, complicating clinical management. In our analysis, dividing stage IV using the new T4 categorization reduced the survival gap between stages III and IV, producing a smoother survival curve distribution. **Table 4** demonstrates that the risk of death roughly doubled between each pair of consecutive stages,

supporting the mAJCC system's improved discriminatory ability.

Lymph node metastasis (LNM) is common in MTC, with over 50% of patients presenting with LNM at diagnosis [20, 21]. The anatomical location of LNs has been recognized as an independent prognostic factor and is incorporated as a criterion in the current AJCC staging system [8, 22]. Recent studies have increasingly highlighted that the total number of metastatic LNs is also independently associated with poorer outcomes in MTC patients [14, 23, 24], emphasizing the prognostic significance of LN count. A large retrospective analysis from Korea reported that the mean number of positive LNs in N1a patients was much lower than in N1b patients (0.3 vs. 12.8), reflecting a strong intrinsic relationship between LN location and count [25]. These findings are consistent with our results.

By integrating LN location and count, risk stratification becomes more precise, improving discrimination among stages I, II, and III. For instance, under the 8th AJCC system, T1–3N1aM0 cases were collectively assigned to stage III. In contrast, the mAJCC system classified T1N0′–2′M0 as stage I, T2N1′–2′M0 and T3N1′M0 as stage II, and T3N2′M0 as stage III. This refined classification demonstrated enhanced prognostic performance.

Several limitations of the present study should be noted. First, its retrospective design is a primary limitation, and prospective studies with larger cohorts are required to validate the accuracy and reliability of the mAJCC system. Second, the SEER database lacks information on key biomarkers such as calcitonin, carcinoembryonic antigen (CEA), RET mutation status, and details on disease recurrence and progression, preventing assessment of their impact on staging. Elevated CEA and calcitonin levels have been associated with larger tumors and greater LN involvement, suggesting the need for more extensive surgery [26, 27], and they also may predict MTC recurrence [28]. RET mutations play a critical role in MTC development, LNM, and post-surgical disease persistence [29], making their inclusion in future AJCC updates highly relevant. Third, the multicenter database may have lower data quality compared with SEER, possibly contributing to a lower C-index. Fourth, a subset of patients had small, incidentally detected tumors, which could lead to incomplete surgical resection and worse outcomes [30], and increase the risk of missed diagnoses of conditions such as pheochromocytoma and hyperparathyroidism [31].

Conclusion

In conclusion, we refined the 8th AJCC staging system by accounting for the relationship between T category, LN location, and LN count. The mAJCC system exhibited improved prognostic performance over the conventional 8th AJCC system, offering potential benefits for clinical decision-making and optimized patient surveillance.

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Conflict of Interest: None

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Ethics Statement: None

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