International Initiative on a Refined Staging System for Medullary Thyroid Cancer: A Multinational Multicenter Study

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ABSTRACT

PURPOSE To refine the suboptimal prognostic discrimination of the American Joint Committee on Cancer (AJCC) 8th edition TNM (TNM-8) staging system for medullary thyroid carcinoma (MTC).

METHODS This retrospective study enrolled patients with MTC from 43 centers across 15 countries under the framework of the International Medullary Thyroid Cancer Staging Consortium (IMTCSC). Pooled data were analyzed with disease-specific survival as the primary end point. With M1 disease fixed in stage IVC, we redefined the schema for stages I to IVB in M0 patients. Using exhaustive enumeration, all possible TN combinations were fitted into multivariable Cox models, with the lowest Akaike information criterion (AIC) defining the proposed system. Prognostic discrimination was assessed using adjusted hazard ratios (aHRs) and the concordance index (C-index).

RESULTS The IMTCSC cohort included 2,573 patients with MTC (female-to-male ratio: 1.25; median age 52 years [IQR, 41-62]; median follow-up 76.3 months [IQR, 37.3-121.0]). Level VII metastasis correlated with poorer survival, supporting its upgrade to N1c. Exhaustive search of 116,284 admissible stage-grouping schemas identified the optimal model (lowest AIC) defining stages I to IVB: I (T1N0-N1a/T2N0), II (T1N1b/T2N1a/T3N0), III (T1N1c/T2N1b/T3N1a/T4aN0-N1a), IVA (T2N1c/T3N1b-N1c/T4aN1b), and IVB (T4aN1c/T4b any N). Compared with AJCC TNM-8 (stage I as reference; stage II aHR, 0.84, $P = .652$; stage III aHR, 1.48, $P = .172$; stage IV aHR, 7.95, $P < .001$), the proposed system showed a clearer monotonic increase in disease-specific death risk (stage II aHR 2.22; stage III aHR, 4.81; stage IV aHR 15.75; all $P \leq .001$) and a higher C-index (0.892 *v* 0.856, $P < .001$), which was also evaluated in the SEER cohort (N = 1,909).

CONCLUSION The proposed MTC staging system confers an improved schema for prognostic stratification compared with AJCC TNM-8.

ACCOMPANYING CONTENT

Graphical Abstract
Appendix
Data Supplement

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INTRODUCTION

Medullary thyroid carcinoma (MTC) is a relatively rare neuroendocrine malignancy originating from thyroid parafollicular C cells, accounting for about 3% of all thyroid cancers yet contributing approximately 13% of all thyroid cancer–related mortality.[1,2] MTC exhibits a heterogeneous clinical course, with excellent survival when localized but a compromised prognosis once distant metastasis occurs.[2] Accurate staging is thus critical for risk stratification.

The American Joint Committee on Cancer (AJCC) TNM staging system serves as the universal language for clinicians, researchers, and cancer registries. However, its

CONTEXT

Key Objective

The AJCC 8th edition TNM (TNM-8) staging for medullary thyroid carcinoma (MTC) remains controversial regarding its prognostic discrimination and stage distribution. To address these limitations, we proposed a refined staging system using a global cohort spanning 15 countries (N = 2,573).

Knowledge Generated

Given the prognostic significance, we validated up-classifying level VII nodal metastasis to a new N1c category. By stage reconstruction, we proposed a refined staging system that demonstrated superior discriminatory power compared with AJCC TNM-8 and effectively mitigated its tendency for stage IV concentration. The proposed system was evaluated in the US SEER cohort (N = 1,909).

Relevance *(B.B.Y. Ma)*

Proposed refinements, particularly (1) a distinct category for level VII lymph nodes (N1c) that would upstage to stage III-IVa or IVb, and (2) N1b disease no longer automatically stage IVA, but also distributed between stages II and III have important implications on future revision of the TNM8 staging system, postoperative surveillance and management of MTC.*

*Relevance section written by *JCO* Associate Editor Brigette B.Y. Ma, MD, MBBS, FRACP, FHKAM, FHKCP.

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8th edition (TNM-8) for MTC faces challenges.[3,4] Due to the rarity of MTC, its staging framework is largely derived from differentiated thyroid cancer (DTC), potentially overlooking MTC's unique features. A significant point of contention is the N classification. Under AJCC TNM-8, any patient with lateral neck lymph node metastasis (LNM) is categorized as stage IV. Given that lateral neck metastasis is common in MTC,[5] this criterion assigns >30% of patients to stage IV,[3,4] thereby inducing unnecessary anxiety in many patients who often achieve favorable outcomes with curative-intent surgery. Therefore, concurrent with its initial release in 2017, a pivotal study by Adam et al[4] identified this flaw and proposed a modified staging strategy. Furthermore, the down-classification of superior mediastinal (level VII) LNM from N1b in TNM-7 to N1a in TNM-8 remains controversial, since emerging evidence suggests that metastases to this compartment confer a poorer prognosis.[3,6-10]

To address these shortcomings, we established the International Medullary Thyroid Cancer Staging Consortium (IMTCSC), which assembled the largest cross-national MTC cohort to date, aiming to develop a robust, MTC-specific staging system.

METHODS

Study Design and Participants

IMTCSC Cohort

This international multicenter cohort study analyzed data from consecutive patients with histologically confirmed MTC who were treated between May 1977 and June 2025 across 43 centers from 15 countries (China, United States, Australia, Italy, France, Germany, Korea, Russia, Portugal, Turkey, Egypt, Chile, Argentina, Colombia, and Vietnam, Table 1). Since the AJCC system applies to all ages, we set no age threshold for recruitment. This also allowed the inclusion of pediatric and adolescent patients, who constitute a significant population of hereditary MTC. Initially, this cohort enrolled 2,909 patients, of whom 336 were subsequently excluded for the following reasons: not undergoing lymph node dissection (n = 252), complete loss to follow-up (n = 58), unknown cause of death (n = 5), or incomplete staging data (n = 21; Data Supplement, Fig S1).

All study variables were harmonized across participating institutions using a standardized data dictionary, with central validation to ensure robustness. The diagnosis of hereditary MTC relied on two criteria: identification of a pathogenic germline *RET* variant via genetic testing, or meeting clinical criteria (MTC with family history, adrenal pheochromocytoma, or other associated symptoms) in the absence of genetic testing. Sporadic status necessitated a negative testing for pathogenic germline *RET* mutations. Patients who did not meet the above criteria were classified as Unknown. For staging variables, the T category was determined by integrating tumor size and extrathyroidal extension (ETE) status, and was reclassified according to the AJCC TNM-8 criteria. N staging was primarily based on the regions of LNM documented in surgical pathology. For unresectable nodal disease, staging was determined via biopsy or a consensus assessment by experienced radiologists using preoperative imaging (eg, computed tomography [CT], with representative images shown in the Data Supplement, Fig S2). Level VII LNM, located between the suprasternal notch and the superior border of the aortic arch, was

TABLE 1. Demographic Characteristics, AJCC TNM-8 Stage, and Follow-Up Time of Patients With Medullary Thyroid Cancer by Medical Center in the IMTCSC Cohort

Medical Center	Patients, No.	Female Patients, No. (%)	Male Patients, No. (%)	Age at Diagnosis, Years (IQR)	AJCC TNM-8 Stages I to III, No. (%)	AJCC TNM-8 Stage IV, No. (%)	Disease-Specific Mortality, No. (%)	Follow-Up Time, Months (IQR)
Ankara Bilkent City Hospital (Turkey)	67	38 (56.7)	29 (43.3)	55 (46-62)	48 (71.6)	19 (28.4)	1 (1.5)	28.00 (13.00-65.00)
Gustave Roussy Cancer Campus (France)	184	105 (57.1)	79 (42.9)	54 (44-66)	85 (46.2)	99 (53.8)	54 (29.3)	115.50 (54.00-178.50)
Ho Chi Minh City Oncology Hospital (Vietnam)	22	15 (68.2)	7 (31.8)	46 (40-62)	22 (100.0)	0 (0.0)	0 (0.0)	17.00 (9.45-26.98)
Hospital de Clínicas, University of Buenos Aires (Argentina)	33	15 (45.5)	18 (54.5)	51 (41-63)	1 (3.0)	32 (97.0)	9 (27.3)	37.20 (23.50-59.20)
Hospital del Salvador, Universidad de Chile (Chile)	64	36 (56.2)	28 (43.8)	38 (29-51)	26 (40.6)	38 (59.4)	16 (25.0)	122.75 (30.15-207.93)
Medical Center—University of Freiburg (Germany)	49	31 (63.3)	18 (36.7)	52 (45-65)	38 (77.6)	11 (22.4)	4 (8.2)	46.50 (16.60-95.70)
Memorial Sloan Kettering Cancer Center (United States)	189	88 (46.6)	101 (53.4)	54 (40-63)	90 (47.6)	99 (52.4)	15 (7.9)	68.20 (27.70-119.30)
Oncology Center, Mansoura University (Egypt)	51	31 (60.8)	20 (39.2)	39 (30-51)	8 (15.7)	43 (84.3)	3 (5.9)	41.60 (13.75-82.05)
Royal North Shore Hospital (Australia)	200	105 (52.5)	95 (47.5)	54 (38-67)	107 (53.5)	93 (46.5)	32 (16.0)	77.60 (28.90-162.47)
Saint Petersburg State University Hospital (Russia)	110	90 (81.8)	20 (18.2)	53 (41-61)	83 (75.5)	27 (24.5)	2 (1.8)	89.50 (74.62-98.88)
Seoul National University Hospital (Korea)	159	99 (62.3)	60 (37.7)	52 (39-60)	98 (61.6)	61 (38.4)	16 (10.1)	128.78 (68.89-181.32)
Unidade Local de Saúde de Coimbra (Portugal)	14	9 (64.3)	5 (35.7)	46 (37-58)	8 (57.1)	6 (42.9)	1 (7.1)	56.55 (43.55-115.58)
University of Bologna (Italy)	51	28 (54.9)	23 (45.1)	63 (52-70)	35 (68.6)	16 (31.4)	2 (3.9)	35.80 (18.85-104.10)
University of Milan (Italy)	125	81 (64.8)	44 (35.2)	57 (46-68)	90 (72.0)	35 (28.0)	7 (5.6)	48.30 (18.10-110.40)
University of Naples Federico II (Italy)	17	6 (35.3)	11 (64.7)	59 (43-61)	6 (35.3)	11 (64.7)	1 (5.9)	44.60 (9.20-77.80)
University of Pisa (Italy)	88	39 (44.3)	49 (55.7)	54 (46-63)	66 (75.0)	22 (25.0)	4 (4.5)	68.05 (28.00-81.25)
19 Medical Centers in China[a]	1,137	606 (53.3)	531 (46.7)	50 (41-59)	663 (58.3)	474 (41.7)	66 (5.8)	79.70 (46.90-118.70)
8 Medical Centers in Colombia[b]	13	9 (69.2)	4 (30.8)	50 (40-67)	8 (61.5)	5 (38.5)	0 (0.0)	25.20 (17.80-33.40)
Overall	2,573	1,431 (55.6)	1,142 (44.4)	52 (41-62)	1,482 (57.6)	1,091 (42.4)	233 (9.1)	76.30 (37.30-121.00)

[a]Including Affiliated Hospital of Jining Medical University (n = 28); Beijing Tsinghua Changgung Hospital (n = 12); Changzhou Second People's Hospital (n = 1); Fudan University Shanghai Cancer Center (n = 533); Jiangsu Taizhou People's Hospital (n = 1); Liaoning Cancer Hospital & Institute (n = 17); Peking University People's Hospital (n = 8); Peking University Shenzhen Hospital (n = 1); Renmin Hospital of Wuhan University (n = 28); Shanghai Electric Power Hospital (n = 1); Shanghai Sixth People's Hospital (n = 58); Sir Run Shaw Hospital, Zhejiang University School of Medicine (n = 43); The Affiliated Hospital of Qingdao University (n = 71); The First Affiliated Hospital of China Medical University (n = 19); The First Affiliated Hospital, Sun Yat-sen University (n = 7); The First Affiliated Hospital, Zhejiang University School of Medicine (n = 13); The Second Hospital of Dalian Medical University (n = 5); Tianjin Medical University Cancer Institute & Hospital (n = 272); and Zhejiang Cancer Hospital (n = 19), all in China.

[b]Including the following cities and health institutions, all in Colombia: Barranquilla, Clínica El Carmen (n = 1); Bogotá, Centro de Investigación sobre Cáncer (CTIC; n = 3) and Clínica Universitaria Colombia (n = 1); Bogotá/Ibagué, Clínica Iberoamérica (n = 2); Cali, Clínica Sebastián de Belalcázar (n = 1) and Clínica de Occidente (n = 1); Ibagué, Clínica Internacional de Alta Tecnología Clinaltec S.A.S. (n = 3); and Medellín, Clínica Colsanitas (n = 1).

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adjudicated primarily via pathological nodal mapping, supplemented by operative notes and, where available, re-evaluation of preoperative imaging.

The study received ethical approval from the Institutional Review Board (IRB) of the initiating center, Fudan University Shanghai Cancer Center, and from the local, regional, or national IRBs of participating centers, whenever required by regulations. Informed consent was waived due to the nature of this retrospective clinical study, anonymous measures for ensuring participants' privacy and adhering to data protection regulations, and no involvement of direct intervention or new medical procedures, posing minimal risk to participants.

US SEER Database

The SEER database was used for external validation. The data were sourced from the US SEER 17 Registries Custom Data Set (November 2024 Submission, released April 2025). Within this database, cases of MTC diagnosed between 2004 and 2015 were identified based on the ICD-O-3 Site code C73.9 and Histology/Behavior codes 8345 and 8510. Consistent with the IMTCSC cohort, we imposed no age restrictions on the SEER cohort, which also enrolled both pediatric and adult patients. The inclusion and exclusion criteria mirrored the IMTCSC cohort, except that nonsurgical patients were included to better capture advanced-stage disease. AJCC TNM-8 and modified N stages were reconstructed using SEER variables for tumor size, extension, lymph nodes, and metastases. As SEER provides publicly available deidentified data, its use was deemed exempt from IRB review.

Outcomes

Given the typically prolonged clinical course of MTC, it is essential to consider the impact of competing noncancer mortality on survival. Therefore, disease-specific survival (DSS) was selected as the primary end point, offering a more direct assessment of staging accuracy than overall survival. DSS, defined as time from initial surgery (IMTCSC cohort) or initial diagnosis (SEER cohort) to death due to MTC, was analyzed using the Kaplan-Meier method, and group differences were assessed with the log-rank test. The 10-year DSS rates were calculated separately to compare prognostic differences across stages.

Statistical Analysis

The proposed staging was derived in the IMTCSC cohort and externally validated in the SEER cohort in three sequential steps.

- **Step 1:** We first defined the candidate space for stage-group refinement. Metastatic (M1) disease was prespecified as stage IVC. For nonmetastatic (M0) disease, the number of stage groups was prespecified as five, corresponding to stages I, II, III, IVA, and IVB, thereby preserving the same number of nonmetastatic stage categories used in AJCC TNM-8. Under this framework, all admissible mappings of T1-T4b $\times$ modified N combinations to the five nonmetastatic stage groups were enumerated under clinical monotonicity constraints. A total of 116,284 candidate admissible staging schemas satisfied these constraints and were retained for subsequent model evaluation.
- **Step 2:** Each admissible candidate scheme was mapped back to the patient level and included into a multivariable Cox proportional hazards model together with the prespecified baseline covariates, including age, sex, geographic region, extent of surgery, heredity, and year-of-diagnosis. Akaike information criterion (AIC) was compared across all candidate Cox models, with a lower value indicating better relative model fit after accounting for model complexity. The candidate scheme with the lowest AIC was selected as the proposed staging schema.
- **Step 3:** We then evaluated the discriminatory ability of the proposed staging system regarding DSS in the IMTCSC cohort using Kaplan-Meier estimates and the log-rank test, and externally validated its performance in the SEER cohort. Patients in each cohort were restaged according to both AJCC TNM-8 and the proposed staging system. We then assessed the monotonic progression of adjusted hazard ratios (aHRs) across stages I to IV for both systems using multivariable Cox models adjusting for baseline covariates. The discriminative performance of the proposed staging system relative to AJCC TNM-8 was compared using Harrell's C-index derived from multivariable Cox models, with differences estimated by paired bootstrap resampling with 5,000 iterations. To account for the multi-institutional design, sensitivity analyses were performed by sequentially excluding centers meeting the thresholds of n ≥ 50 and events ≥10, thereby ruling out potential single-site bias.

Categorical variables were compared using the Pearson's chi-square test. Continuous variables were compared using the Student's t-test or the Mann-Whitney U test, depending on data normality. All statistical analyses were performed with R (version 4.5.2), and a two-sided $P < .05$ was defined as the threshold for statistical significance.

RESULTS

Baseline Characteristics

Of the 2,573 patients in the IMTCSC cohort, 1,431 (55.6%) were female and 1,142 (44.4%) were male. The median age was 52 years (IQR, 41-62), and the median follow-up time was 76.3 months (IQR, 37.3-121.0). Total thyroidectomy was performed as the initial surgical procedure in 2,108 patients (81.9%). Of the 2,186 patients evaluable for heredity, sporadic MTC (n = 1,765) represented about 4.2-fold the number of hereditary MTC cases (n = 421). According to the AJCC TNM-8 staging system, 797 (31.0%), 276 (10.7%), 409 (15.9%), and 1,091 (42.4%) patients were classified as stage

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I, II, III, and IV, respectively. During follow-up, 233 MTC-related deaths (9.1%) were recorded. Patient characteristics are summarized in the Data Supplement (Table S1).

Of the 1,909 patients included in the SEER cohort, 1,140 (59.7%) were female and 769 (40.3%) were male. The median age was 55 years (IQR, 43-66), and the median follow-up duration was 120 months (IQR, 88-160). According to the AJCC TNM-8 staging system, 729 (38.2%), 412 (21.6%), 240 (12.6%), and 528 (27.7%) patients were classified as stage I, II, III, and IV, respectively. By the end of follow-up, 541 patients (28.3%) had died from all causes, of whom 253 (13.3%) were attributable to MTC. Across most covariates, patient characteristics differed significantly between the SEER and IMTCSC cohorts (Data Supplement, Table S1).

Confirmation of the Prognostic Significance of the Proposed N1c Classification

We first aimed to further validate a previous study's proposal to upgrade level VII metastasis from N1a in AJCC TNM-8 to the highest-risk N1c category.[3] In the IMTCSC cohort, we found that patients with N1c disease exhibited significantly higher T stages and a greater proportion of distant metastasis (M1), indicating that metastasis to the superior mediastinum is associated with a heavier tumor burden (Data Supplement, Table S2). Furthermore, the 10-year DSS rates in the IMTCSC cohort were 98.32% (N0), 94.24% (N1a), 81.36% (N1b), and 68.37% (N1c), with N1c disease associated with significantly poorer survival than N1a or N1b (log-rank $P < .001$; Fig 1A), with consistent trends observed in the SEER cohort (Fig 1B). These findings support the modified N classification: N0 (no LNM), N1a (isolated level VI metastasis), N1b (lateral neck metastasis, levels I-V), and N1c (level VII metastasis).

Development of the Proposed Staging System

As stated in the Methods, an exhaustive enumeration of 116,284 admissible T-modified N stage-grouping schemas was performed; each fitted into a multivariable Cox model adjusting for baseline covariates. We found that the current AJCC TNM-8 staging (AIC = 2928.56) fell within the highest 2.5% of the AIC distribution, indicating substantial room for improvement (Fig 2A). The combination with the lowest AIC (2859.67) was defined as the new staging system, as detailed below: stage I: T1N0-N1a, T2N0; stage II: T1N1b, T2N1a, T3N0; stage III: T1N1c, T2N1b, T3N1a, T4aN0-N1a; stage IVA: T2N1c, T3N1b-N1c, T4aN1b; stage IVB: T4aN1c, T4b any N; stage IVC: any T any N M1 (Table 2). Further analysis revealed that within the proposed staging system, the aHR for every T-N combination in any given stage was lower than that for all T-N combinations in the subsequent stage (Data Supplement, Fig S3A). In contrast, AJCC TNM-8 exhibited significant inconsistencies within stages (Data Supplement, Fig S3B).

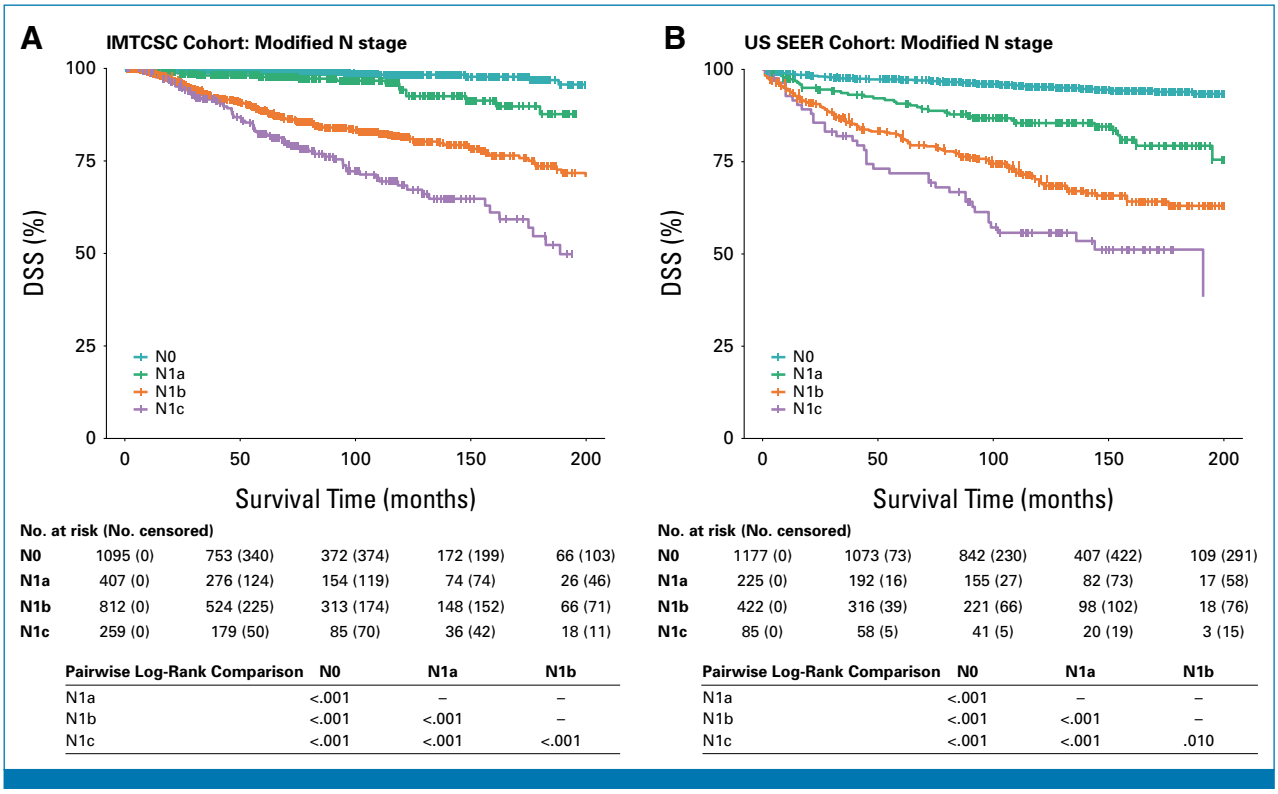

FIG 1. Kaplan-Meier survival curves for DSS according to the modified N classification in the (A) IMTCSC cohort and (B) US SEER cohort. DSS, disease-specific survival; IMTCSC, International Medullary Thyroid Cancer Staging Consortium.

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Alluvial plots demonstrated a marked downward stage migration with the proposed system, notably shifting cases from AJCC II-III to proposed stage I and from AJCC stage IVA to proposed stage II/III (Figs 2B and 2C). This proposed system also relieved AJCC TNM-8's overcategorization of stage IV patients, reducing proportions from 42.4% to 20.2% (IMTCSC) and 27.7% to 20.4% (SEER; Figs 2D and 2E).

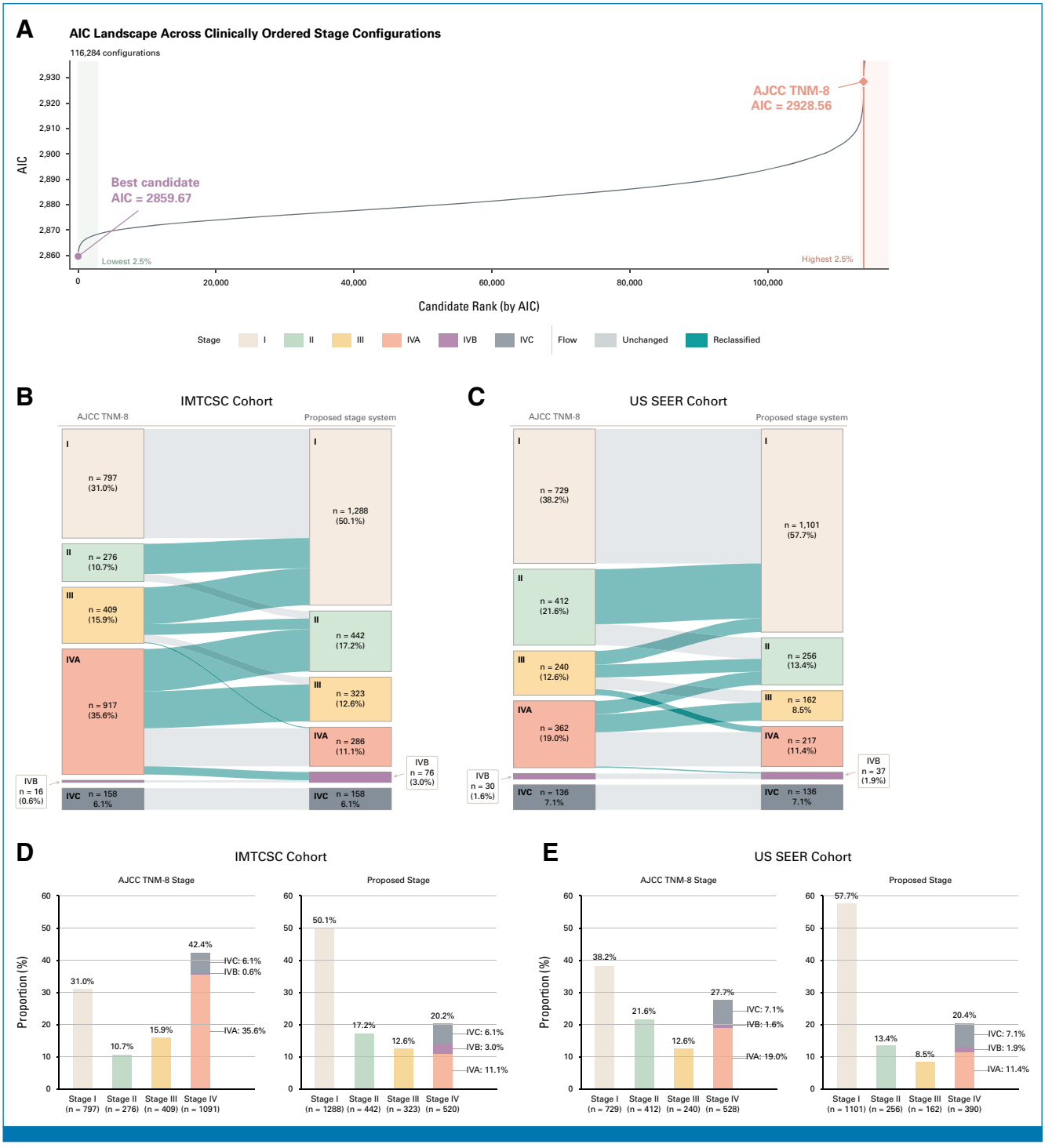

FIG 2. (A) AIC landscape of 116,284 clinically monotone nonmetastatic admissible stage-grouping schemas based on T category and modified N category. Candidates are ranked by AIC from the prespecified multivariable Cox model. The minimum-AIC candidate and AJCC TNM-8 are annotated. Alluvial plots showing patient-level reclassification from AJCC TNM-8 to the proposed staging system in the (B) IMTCSC cohort and (C) US SEER cohort. Bar plots showing the distribution of stages under the AJCC TNM-8 and proposed staging frameworks in the (D) IMTCSC cohort and (E) US SEER cohort. AIC, Akaike information criterion; AJCC, American Joint Committee on Cancer; IMTCSC, International Medullary Thyroid Cancer Staging Consortium.

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TABLE 2. Classification Criteria and Stage Grouping of the AJCC TNM-8 Staging System and Proposed Staging System

Category		AJCC TNM-8 Staging	Proposed Staging
T category: no change			
T1	T1a	Tumor ≤1 cm, confined to the thyroid	
	T1b	Tumor >1 cm and ≤2 cm, confined to the thyroid	
T2		Tumor >2 cm and ≤4 cm, confined to the thyroid	
T3		Tumor >4 cm limited to the thyroid, or gross ETE invading only strap muscles	
T4	T4a	Tumor of any size with gross ETE invading subcutaneous soft tissue, the larynx, trachea, esophagus, or recurrent laryngeal nerve	
	T4b	Tumor of any size with gross ETE invading the prevertebral fascia or encasing the carotid artery or mediastinal vessels	
N category: up-classification of level VII metastasis from N1a to N1c category			
N0		No evidence of locoregional LNM	No evidence of locoregional LNM
N1	N1a	Metastasis to level VI or VII lymph nodes	Metastasis to level VI lymph nodes
	N1b	Metastasis to level I-V or retropharyngeal lymph nodes	Metastasis to level I-V or retropharyngeal lymph nodes
	N1c	Non-existent	Metastasis to level VII lymph nodes
M category: no change			
M0		No distant metastasis	
M1		Distant metastasis	

Category	AJCC TNM-8 Staging Grouping Criteria	Proposed Staging Grouping Criteria
Stage I	T1 N0 M0	T1 N0-N1a M0, T2 N0 M0
Stage II	T2 N0 M0; T3 N0 M0	T1 N1b M0, T2 N1a M0, T3 N0 M0
Stage III	T1-3 N1a M0	T1 N1c M0, T2 N1b M0, T3 N1a M0, T4a N0-N1a M0
Stage IV	IVA: T4a any N M0 or T1-3 N1b M0 IVB: T4b any N M0 IVC: Any T any N M1	IVA: T2 N1c M0, T3 N1b-N1c M0, T4a N1b M0 IVB: T4a N1c M0, T4b any N M0 IVC: Any T any N M1

Abbreviations: AJCC, American Joint Committee on Cancer; ETE, extrathyroidal extension; LNM, lymph node metastasis.

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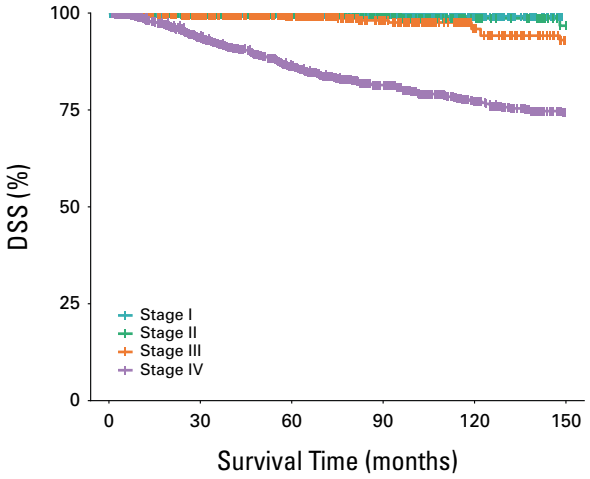
Prognostication on Disease-Specific Survival of AJCC TNM-8 and Proposed Staging

In the IMTCSC cohort, AJCC TNM-8 showed limited discrimination for stages I to III (10-year DSS: 99.17%, 98.63%, 95.89%), but identified significantly poorer survival for stage IV (10-year: 77.13%; overall log-rank χ^2 = 224.52, Fig 3A). Notably, subclassification of stage IV revealed that stage IVA had a favorable 10-year DSS of 83.54%, significantly outperforming stages IVB (45.94%) and IVC (41.48%) (Fig 3B). In contrast, the proposed staging system revealed better prognostic discrimination. Stratifying into stages I to IV yielded 10-year DSS of 99.49%, 94.33%, 86.42%, and 60.63%, respectively (log-rank χ^2 = 481.96, Fig 3C). Stage IV subdivision refined risk assessment, yielding 10-year DSS rates of 73.27% (IVA), 54.95% (IVB), and 41.48% (IVC; Fig 3D).

Mirroring IMTCSC findings, AJCC TNM-8 showed relatively limited discrimination for stages I to III in the SEER cohort (10-year DSS: stages I to III: 98.60%, 94.21%, and 86.20%) but identified poorer survival in stage IV (10-year DSS: 64.08%; log-rank χ^2 = 367.19, Fig 4A). Subclassification revealed that survival of stage IVA (10-year DSS: 76.77%) aligned closely with that of stage III, diverging markedly from IVB (54.20%) and IVC (31.46%; Fig 4B). In contrast, our proposed system provided clearer stratification, stratifying stages I to IV with 10-year DSS of 97.45%, 89.62%, 81.37%, and 55.58% (log-rank χ^2 = 523.29, Fig 4C). Notably, following stage IV subdivision, survival of stage IVA (69.40%) was balanced between stage III (81.37%) and stage IVB (59.97%; Fig 4D), thereby addressing the misalignment observed in AJCC TNM-8.

Subgroup Kaplan-Meier analyses showed qualitatively similar stage-risk patterns across the displayed geographic (Data Supplement, Figs S4 and S5) and hereditary strata (Data Supplement, Fig S6).

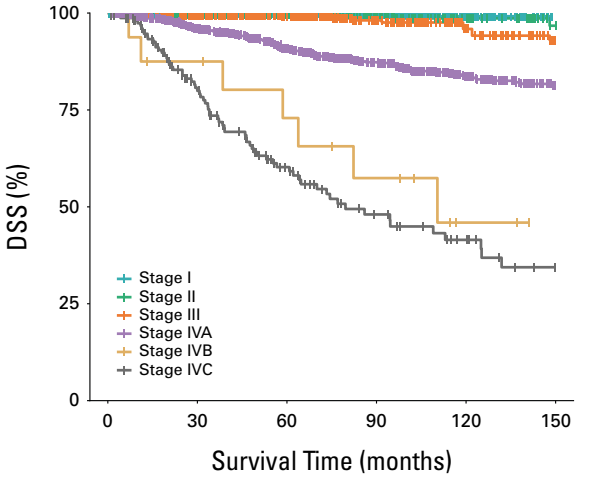
Multivariable Cox models revealed a consistent pattern. In both the IMTCSC and SEER cohorts, the proposed staging system demonstrated a clearer, stepwise increase in aHRs from stages I to IV (Data Supplement, Tables S3 and S4), with the C-index increasing from 0.856 to 0.892 (ΔC-index, 0.035 [95% CI, 0.022 to 0.048]; P < .001) in the IMTCSC cohort and slightly increasing from 0.852 to 0.860 (ΔC-index, 0.007 [95% CI, −0.090 to 0.020]; P = .280) in the SEER cohort. Furthermore, the leave-one-center-out sensitivity analyses indicated that after sequentially excluding any major contributing center (n ≥ 50 and events ≥10) in the IMTCSC cohort, the proposed staging system retained a monotonic increase in event rates and aHRs across stages, and its C-index



No. at risk (No. censored)

Stage I	797 (0)	644 (153)	502 (141)	328 (174)	192 (136)	120 (70)
Stage II	276 (0)	225 (50)	177 (48)	118 (59)	71 (46)	50 (21)
Stage III	409 (0)	336 (71)	261 (77)	182 (74)	113 (66)	78 (32)
Stage IV	1091 (0)	852 (176)	633 (159)	450 (151)	287 (144)	182 (95)

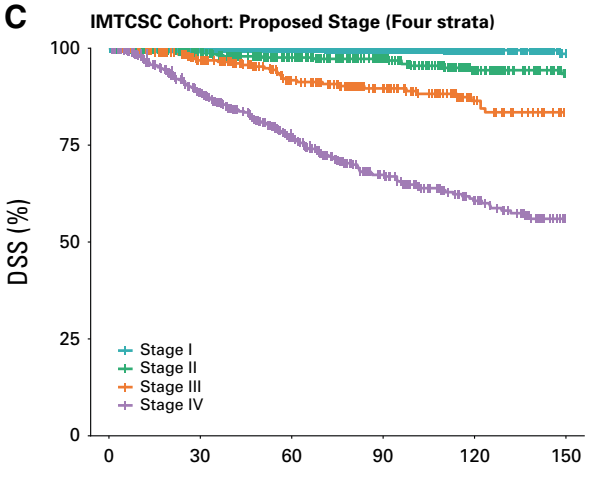
Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III
Stage II	.03	–	–
Stage III	<.001	.18	–
Stage IV	<.001	<.001	<.001



No. at risk (No. censored)

Stage I	797 (0)	644 (153)	502 (141)	328 (174)	192 (136)	120 (70)
Stage II	276 (0)	225 (50)	177 (48)	118 (59)	71 (46)	50 (21)
Stage III	409 (0)	336 (71)	261 (77)	182 (74)	113 (66)	78 (32)
Stage IVA	917 (0)	737 (146)	566 (137)	411 (135)	264 (133)	171 (86)
Stage IVB	16 (0)	13 (1)	10 (1)	7 (1)	2 (4)	0 (2)
Stage IVC	158 (0)	102 (29)	57 (21)	32 (15)	21 (7)	11 (7)

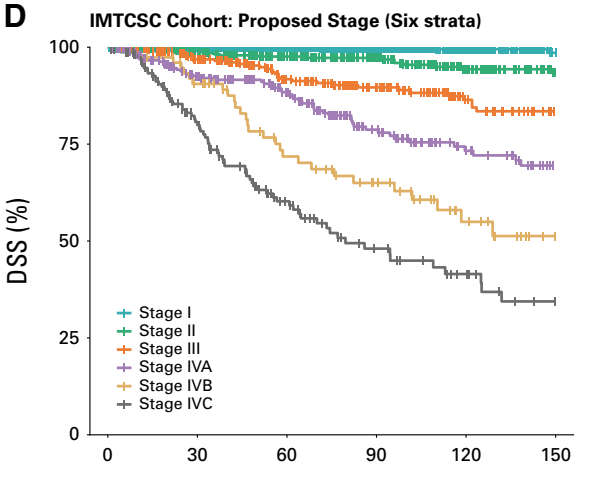
Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III	Stage IVA	Stage IVB
Stage II	.03	–	–	–	–
Stage III	<.001	.18	–	–	–
Stage IVA	<.001	<.001	<.001	–	–
Stage IVB	<.001	<.001	<.001	<.001	–
Stage IVC	<.001	<.001	<.001	<.001	.45



No. at risk (No. censored)

Stage I	1288 (0)	1050 (238)	813 (238)	537 (274)	318 (219)	208 (107)
Stage II	442 (0)	368 (70)	301 (63)	231 (68)	152 (73)	97 (54)
Stage III	323 (0)	261 (53)	200 (49)	143 (53)	89 (50)	64 (22)
Stage IV	520 (0)	378 (89)	259 (75)	167 (63)	104 (50)	61 (35)

Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III
Stage II	<.001	–	–
Stage III	<.001	<.001	–
Stage IV	<.001	<.001	<.001



No. at risk (No. censored)

Stage I	1288 (0)	1050 (238)	813 (238)	537 (274)	318 (219)	208 (107)
Stage II	442 (0)	368 (70)	301 (63)	231 (68)	152 (73)	97 (54)
Stage III	323 (0)	261 (53)	200 (49)	143 (53)	89 (50)	64 (22)
Stage IVA	286 (0)	211 (56)	158 (45)	102 (41)	65 (32)	44 (17)
Stage IVB	76 (0)	65 (4)	44 (9)	33 (7)	18 (11)	6 (11)
Stage IVC	158 (0)	102 (29)	57 (21)	32 (15)	21 (7)	11 (7)

Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III	Stage IVA	Stage IVB
Stage II	<.001	–	–	–	–
Stage III	<.001	<.001	–	–	–
Stage IVA	<.001	<.001	<.001	–	–
Stage IVB	<.001	<.001	<.001	.003	–
Stage IVC	<.001	<.001	<.001	<.001	.04

FIG 3. Kaplan-Meier curves comparing DSS based on the AJCC TNM-8 staging system (A and B, A: stage IV as a single category; B: stage IV separated into stages IVA, IVB, and IVC) and proposed staging system (C and D, C: stage IV as a single (continued on following page)

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FIG 3. (Continued). category; D: stage IV separated into stages IVA, IVB, and IVC) in the IMTCSC cohort. See Table 2 for the descriptions of the definitions of T, N, and M categories and stage grouping schema in different staging systems. AJCC, American Joint Committee on Cancer; DSS, disease-specific survival; IMTCSC, International Medullary Thyroid Cancer Staging Consortium.

remained higher than that of AJCC TNM-8 (Data Supplement, Fig S7). This confirms that the better performance of the proposed staging is not driven by a key contributing institution.

DISCUSSION

Since its introduction in 2017, the AJCC TNM-8 has served as the official staging system for MTC, although its adoption has raised immediate concerns about excessive stage IV categorization. In the same year, a landmark study using the National Cancer Database proposed a new staging strategy, which was successfully validated using SEER data.[4] Later corroborated by a Danish cohort,[11] the proposed system in this pivotal work not only significantly reduced the proportion of stage IV but also inspired subsequent efforts, including the present study, to address this issue through staging reorganization.[3,12,13] Additionally, other studies focused on refining the N category based on the number, ratio, or log odds of LNM.[14-17] In contrast, a multicenter study by the Chinese component of IMTCSC retained the AJCC's location-based principle of N staging and upgraded level VII metastasis to N1c,[3] which was validated through an expanded global cohort in this study. We then refined the staging system using AJCC T category and this modified N category.

In this study, we excluded all patients who did not undergo lymphadenectomy (NX) in the IMTCSC derivation cohort. This strictly adheres to the AJCC Staging Manual,[18] which specifically omits NX from the MTC staging matrix, unlike DTC/anaplastic thyroid cancer (ATC) where NX is combined with N0 in their stage grouping schema. This distinction arises from fundamental clinical standards: standardized MTC surgery mandates at least level VI dissection, whereas early DTC does not universally require prophylactic neck dissection and ATC often involves only palliative tumor resection. Consequently, despite representing a non-negligible proportion, 8.7% (252/2,909) of patients in the IMTCSC cohort were appropriately excluded to maintain alignment with both AJCC criteria and standardized disease management (Methods, and Data Supplement, Fig S1).

A key difference between the IMTCSC and SEER cohorts was a higher proportion of hemithyroidectomy in the IMTCSC cohort (18.1% *v* 8.9%). Although the greater number of Chinese centers partly explains this disparity, it also somewhat underscores a shift in clinical perception. Accumulating evidence has explored the anatomical feasibility or oncologic safety of hemithyroidectomy in selected patients with sporadic MTC.[19-29] The IMTCSC cohort partly reflects regional variations in practice patterns and may also reflect this increasing acceptance.

An additional key difference is the observation that patients in the IMTCSC cohort presented at more advanced stages, characterized specifically by higher rates of superior mediastinal and lateral cervical LNM. Although multifactorial, this discrepancy may be partly attributable to the inclusion of a substantial number of cases from high-volume Chinese centers within the IMTCSC, where routine preoperative CT coverage of the superior mediastinum is widely adopted.[30] The SEER database, being population-based, tends to include institutions of all practice levels, thereby capturing a wider variety of health care settings. From this perspective, the inclusion of both specialized and general hospitals within SEER reflects a more macro-level representation of real-world clinical practice. Consequently, the validation of the new staging system within the SEER cohort provides evidence supporting its generalizability.

It should be noted that the anatomical continuity between level VI and VII may blur their distinction, as dissection of the pretracheal nodes often extends just below the suprasternal notch, potentially misclassifying borderline nodes as level VI. However, this distinction is of limited clinical consequence, given that the true concern lies with deeper superior mediastinal nodes that are inaccessible via a standard cervical incision. Since prophylactic level VII dissection is rarely performed in MTC due to the morbidity associated with sternotomy, pathological identification of level VII disease predominantly reflects therapeutic intent for confirmed or suspected metastases. This arguably improves the specificity of a Level VII–positive designation, although some residual misclassification at the VI/VII junction likely persists and represents a source of bias we cannot fully quantify.

This study has several limitations. First, the IMTCSC cohort included only surgically treated patients, excluding non-surgical cases receiving systemic therapy or supportive care for advanced disease. This selection bias likely underestimates advanced-case proportions and limits generalizability across the full MTC spectrum. Second, although preoperative CT improves detection of level VII LNM, its use varies widely by year of diagnosis, region, and institution due to differences in guidelines, economics, and resources, thus introducing bias. Third, because tumor grading was introduced in 2022 and adopted globally later,[31-34] it was unavailable for patients treated before its implementation. Fourth, although calcitonin is a pivotal biomarker for MTC,[9,35-37] integration of calcitonin levels was precluded by drastic, unstandardized variations in assays and reference

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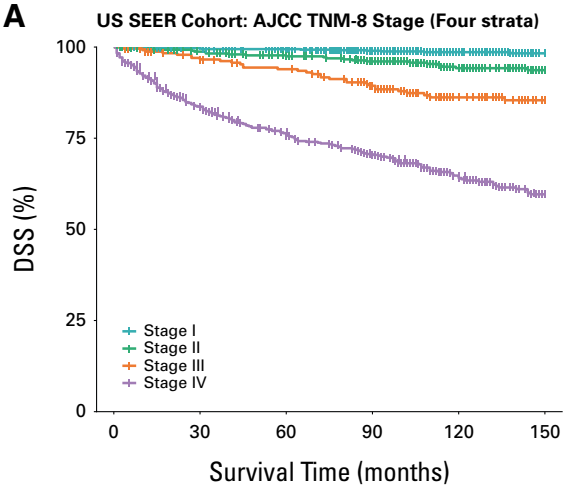
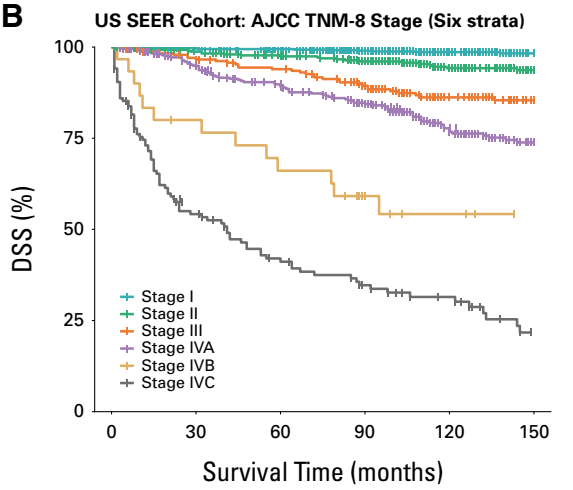


No. at risk (No. censored)

Stage I	729 (0)	699 (28)	674 (24)	596 (85)	407 (183)	249 (158)
Stage II	412 (0)	388 (19)	362 (23)	323 (37)	236 (79)	154 (80)
Stage III	240 (0)	225 (10)	211 (5)	188 (16)	129 (51)	91 (41)
Stage IV	528 (0)	414 (31)	356 (23)	298 (34)	193 (82)	113 (68)

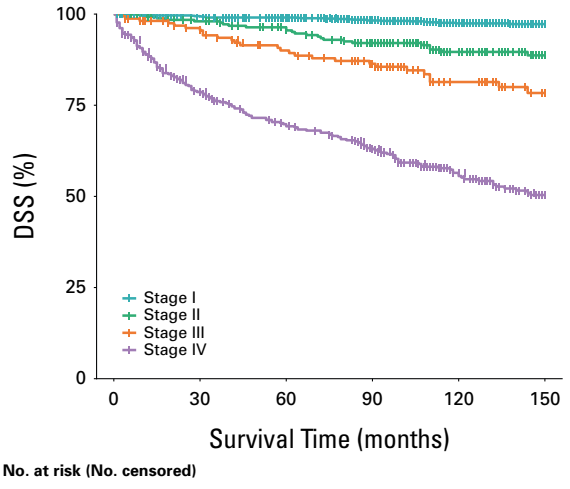
Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III
Stage II	<.001	–	–
Stage III	<.001	<.001	–
Stage IV	<.001	<.001	<.001



No. at risk (No. censored)

Stage I	729 (0)	699 (28)	674 (24)	596 (85)	407 (183)	249 (158)
Stage II	412 (0)	388 (19)	362 (23)	323 (37)	236 (79)	154 (80)
Stage III	240 (0)	225 (10)	211 (5)	188 (16)	129 (51)	91 (41)
Stage IVA	362 (0)	325 (20)	290 (18)	250 (25)	160 (72)	97 (57)
Stage IVB	30 (0)	23 (1)	19 (0)	13 (5)	9 (2)	6 (3)
Stage IVC	136 (0)	66 (10)	47 (5)	35 (4)	24 (8)	10 (8)

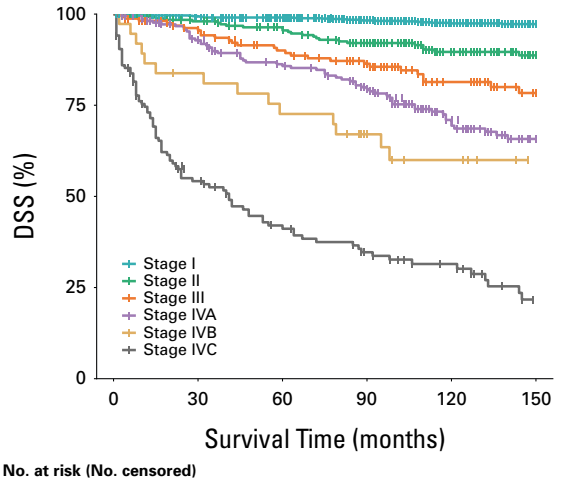
Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III	Stage IVA	Stage IVB
Stage II	<.001	–	–	–	–
Stage III	<.001	<.001	–	–	–
Stage IVA	<.001	<.001	.03	–	–
Stage IVB	<.001	<.001	<.001	.001	–
Stage IVC	<.001	<.001	<.001	<.001	.007



No. at risk (No. censored)

Stage I	1101 (0)	1052 (43)	1009 (41)	904 (111)	635 (256)	406 (229)
Stage II	256 (0)	243 (8)	227 (13)	195 (23)	132 (59)	82 (49)
Stage III	162 (0)	145 (12)	127 (8)	107 (17)	69 (31)	45 (24)
Stage IV	390 (0)	286 (25)	240 (13)	199 (21)	129 (49)	74 (45)

Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III
Stage II	<.001	–	–
Stage III	<.001	.006	–
Stage IV	<.001	<.001	<.001



No. at risk (No. censored)

Stage I	1101 (0)	1052 (43)	1009 (41)	904 (111)	635 (256)	406 (229)
Stage II	256 (0)	243 (8)	227 (13)	195 (23)	132 (59)	82 (49)
Stage III	162 (0)	145 (12)	127 (8)	107 (17)	69 (31)	45 (24)
Stage IVA	217 (0)	190 (14)	167 (8)	144 (12)	90 (39)	54 (32)
Stage IVB	37 (0)	30 (1)	26 (0)	20 (5)	15 (2)	10 (5)
Stage IVC	136 (0)	66 (10)	47 (5)	35 (4)	24 (8)	10 (8)

Pairwise Log-Rank Comparison	Stage I	Stage II	Stage III	Stage IVA	Stage IVB
Stage II	<.001	–	–	–	–
Stage III	<.001	.006	–	–	–
Stage IVA	<.001	<.001	.04	–	–
Stage IVB	<.001	<.001	.01	.26	–
Stage IVC	<.001	<.001	<.001	<.001	<.001

FIG 4. Kaplan-Meier curves comparing DSS based on the AJCC TNM-8 staging system (A and B, A: stage IV as a single category; B: stage IV separated into stages IVA, IVB, and IVC) and proposed staging system (C and D, C: stage IV as a (continued on following page)

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FIG 4. (Continued). single category; D: stage IV separated into stages IVA, IVB, and IVC) in the US SEER cohort. See Table 2 for the descriptions of the definitions of T, N, and M categories and stage grouping schema in different staging systems. AJCC, American Joint Committee on Cancer; DSS, disease-specific survival.

ranges across participating centers, thereby preventing a reliable pooled analysis.

In conclusion, our proposed MTC staging schema improves upon AJCC TNM-8 regarding prognostic discrimination and balance across stage groups, providing a more rational framework for clinical management. This underscores the need for continuous, evidence-based refinements to maintain global relevance. Independent external validation is warranted.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

International Initiative on a Refined Staging System for Medullary Thyroid Cancer: a Multinational Multicenter Study

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Research Funding: Novartis (Inst), Lilly (Inst)
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APPENDIX

TABLE A1. List of International Medullary Thyroid Cancer Staging Consortium Collaborators

Location	Investigator
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Chile	Javiera Arancibia, Jesus Veliz, Nelson Wohllk, Pablo Guzman
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Colombia	Ana Patricia Estrada-Florez, Anggi Vélez-Bohórquez, Carlos Eduardo Jiménez-Canizales, Mabel E. Bohórquez
Egypt	Omar Hamdy
France	Benjamin Houot, Julien Hadoux, Martin Schlumberger, Mohamed-Amine Bani
Germany	Andreas Spörlein, Christoph Becker, Mira Fink
Italy	Andrea Repaci, Antonio Matrone, Cosimo Durante, Cristina Luongo, Domenico Salvatore, Gabriele Materazzi, Giovanni Tallini, Laura Fugazzola, Leonardo Rossi, Matteo Trevisan, Rossella Elisei, Simone De Leo
Korea	Moon Young Oh, Young Joo Park
Portugal	João Martins Gama, Maria João Martins
Russia	Arseny A Semenov, Ilya V. Sleptsov
Turkey	Bekir Cakir, Berna Evranos Ogmen, Ekin Yigit Koroglu
United States	Bin Xu, Brian R. Untch, Ian Ganly, Lori Wirth, Louise Davies, Luis G. Carvajal-Carmona, Ronald A. Ghossein
Vietnam	Anh Tu Thai, Quoc Dat Ngo, Quoc Thang Pham

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