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ORIGINAL ARTICLE – ENDOCRINE TUMORS

A Novel N Staging System for Predicting Survival in Patients with Medullary Thyroid Cancer

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ABSTRACT

Introduction. Despite the crucially prognostic value of lymph node metastasis (LNM) in patients with medullary thyroid cancer (MTC), only the LNM compartment alone was reflected in the 8th edition of the American Joint Committee on Cancer (AJCC) system.

Objective. This study aimed to incorporate the metastatic lymph node number and metastatic lymph node ratio to generate a more accurate and appropriate N staging system for patients with MTC based on recursive partitioning analysis.

Design, Setting, and Patients. Two cohorts were included in the analysis, including 1374 MTC patients from the Surveillance, Epidemiology, and End Results database as the derivation cohort, and 164 patients from Fudan University Shanghai Cancer Center as the validation cohort. The predictive performance of the alternative proposed N staging system was compared with that of the 8th AJCC system by using the Harrell concordance index (C-index) and the area under the receiver operating characteristic curve (AUC).

Results. In the derivation cohort, the C-index and the AUC at 10 years were 0.778 and 0.789, respectively, for the novel N staging system, and 0.749 and 0.741, respectively, for the 8th AJCC N staging system. Similar trends were also observed in the validation cohort. The proposed N staging system had a better prognostic performance.

Conclusion. With some improvements, the novel N staging system for MTC suggested from this research may be assessed for potential adoption in the next edition of the AJCC N staging system.

Thyroid cancer is one of the most common malignant tumors in the endocrine system, with an increasing global incidence.[1] As the third most common histology of thyroid cancers, medullary thyroid cancer (MTC) is a rare neuroendocrine tumor that originates from parafollicular (C) cells.[2,3] The clinicopathological and biologic characteristics of MTC are intensively different from those of differentiated thyroid cancer (DTC). Currently, an increasing number of technical methods, such as advanced ultrasonography, fine needle aspiration biopsy, serum levels of calcitonin (Ctn) and carcinoembryonic antigen (CEA) measurements, and RET germline mutation analysis, have allowed MTC to be diagnosed much more accurately in the earlier stages of disease.[4–8] MTC only accounts for 1–2% of thyroid carcinomas of all types, but leads to 13.4% of all thyroid cancer-related deaths. Despite different biological features between MTC and DTC, the 8th edition of the American Joint Committee on Cancer (AJCC) N staging system of MTC is extrapolated from that of DTC and remains controversial in predicting patient survival.[9]

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Lymph node metastasis (LNM) status gradually appears to be an important predictor of outcome for many cancers, such as lung cancer, other head and neck cancers, and MTC.[10–14] For patients with hypopharyngeal cancer, the number of positive lymph nodes is an effective predictor of survival and has been demonstrated to further stratify prognoses.[13] In this study, we assumed that metastatic lymph node number (MLNN) and metastatic lymph node ratio (MLNR) could be prognostic metrics.[15,16] MLNR was defined as the ratio of MLNN to the examined LN number (ELNN). However, the impact of quantitative LNM (i.e. MLNN and MLNR) for predicting the survival of MTC patients has rarely been researched, and a modified N staging system of MTC is seldom proposed. Therefore, we believe that this study is necessary to some degree. We aimed to define a special N staging system for MTC through the population-based Surveillance, Epidemiology, and End Results (SEER) database and the Fudan University Shanghai Cancer Center (FUSCC) database. In this study, we developed and validated the N staging system for predicting the survival of MTC patients.

PATIENTS AND METHODS

Patients and Outcomes

Two large cohorts of patients with MTC, including a derivation cohort from the SEER database (1998–2014) and a validation cohort from FUSCC (2002–2015), were collected. In the derivation cohort, pathologically confirmed MTC patients whose primary site was limited to 'C73.9—thyroid gland' and codes 8345/3, 8510/3, and 8512/3 from the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology were included. The extent of operation was recognized according to the RX Summ–Surg Prim Site (1998 +) and regional nodes positive (1988 +). Only patients who received total thyroidectomy as their primary treatment were included. The exclusion criteria were patients with an unknown cause of death, distant metastasis, no LN resection or ELNN = 0, undetermined MLNN or ELNN, incomplete follow-up details, or those who received oncological therapy before surgery. In the validation cohort, all patients were also identified via pathological diagnoses. The primary treatment was limited to total thyroidectomy. All available data of these patients were collected. We used the same exclusion criteria from the derivation cohort for the validation cohort. Patients from both cohorts were followed for at least 1 year after the initial treatment, and were restaged according to the 8th AJCC staging system definitions.

In the SEER cohort, cancer-specific survival (CSS), which was calculated from the diagnosis date to the cancer-specific date of death or the last follow-up, was used as the primary endpoint for MTC patients. In the FUSCC cohort, the main endpoint was disease-free survival (DFS), the period from the first surgery to the recurrence, or the most recent follow-up visit. The MTC recurrence was confirmed by both histology and radiography.

This study was approved by the Ethics Committee of FUSCC.

Statistical Analyses

In the baseline characteristics, continuous variables are described as the means, and categorical variables are described as frequencies and percentages. Cut-off values of MLNN and MLNR with the highest sensitivity and specificity were calculated using the X-tile program (Yale University School of Medicine, New Haven, CT, USA). CSS curves and DFS curves were drawn using the Kaplan–Meier method and tested using the log-rank tests.

Recursive partitioning analysis (RPA), a method of building decision trees to model predictors,[17] was applied to develop a novel N staging system. A conditional inference tree was created using MLNN and MLNR, estimated by binary recursive partitioning.

Risk factors associated with CSS from the SEER database were enrolled in the Cox proportional hazards model. To judge the discriminatory ability of the novel N staging system and the 8th AJCC N staging system, we calculated the concordance index (C-index) and time-dependent receiver operating characteristic (td-ROC) curves for two cohorts. Analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) and R version 3.4.0 (Bell Laboratories, Murray Hill, NJ, USA; https://www.r-project.org/). Survival curves were generated using the R package survival and survminer, and C-indices were calculated using the R package Hmisc and survival. Td-ROCs were derived from R package survivalROC and Tidyverse (https://cran.r-project.org/src/contrib/Archive/). A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Patient Clinical Characteristics

Overall, 1179 patients with pathologically confirmed MTC were screened from the SEER database, approximately half of whom had LNM. The clinical features of MTC patients are shown in Table 1. The mean ELNN value was 21.53 (median 14). For MLNN, the mean value was 4.53 (median 0), and the MLNR was 0.19 (median 0.00). The mean age at diagnosis was 49.0 years (median

TABLE 1 Clinicopathologic characteristics of the SEER and FUSCC cohorts

Clinical characteristics	Total [1343 (100%)]	SEER cohort [1179 (87.8%)]	FUSCC cohort [164 (12.2%)]	*p* value
Age, years[a]				0.008
≤ 63	1076 (80.1)	932 (79.1)	144 (87.8)	
> 63	267 (19.9)	247 (20.9)	20 (12.2)	
Sex				0.002
Female	771 (57.4)	695 (58.9)	76 (46.3)	
Male	572 (42.6)	484 (41.1)	88 (53.7)	
Race				
White		999 (84.7)		
Black		92 (7.8)		
Others		88 (7.5)		
T stage				0.009
T1 + T2	963 (71.7)	843 (71.5)	120 (73.2)	
T3 + T4	304 (22.6)	261 (22.1)	43 (26.2)	
Unknown	76 (5.7)	75 (6.4)	1 (0.6)	
N stage				<0.001
N0	651 (48.5)	599 (50.8)	52 (31.7)	
N1a	192 (14.3)	166 (14.1)	26 (15.9)	
N1b	306 (22.8)	222 (18.8)	84 (51.2)	
NX	194 (14.4)	192 (16.3)	2 (1.2)	
Tumor size, cm				0.366
0–2	650 (48.4)	562 (47.7)	88 (53.7)	
2–4	454 (33.8)	400 (33.9)	54 (32.9)	
> 4	205 (15.3)	185 (15.7)	20 (12.2)	
Unknown	34 (2.5)	32 (2.7)	2 (1.2)	
Extracapsular extension				0.445
Yes	173 (12.9)	151 (12.8)	22 (13.4)	
No	1155 (86.0)	1013 (85.9)	142 (86.6)	
Unknown	15 (1.1)	15 (1.3)	0 (0)	

Data are expressed as *n* (%)

SEER Surveillance, Epidemiology, and End Results, *FUSCC* Fudan University Shanghai Cancer Center

[a]The age cut-off value was 63 years and was derived from the X-tile program

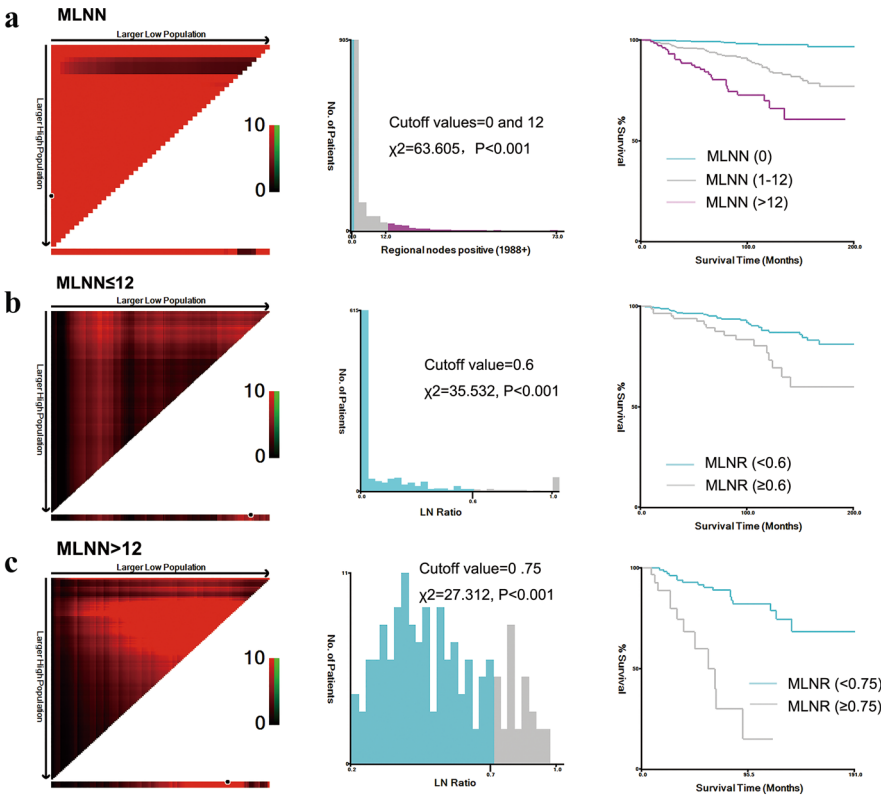
50 years). There were more female patients than male patients (female:male ratio of 1.3:1.0). The mean CSS value was 82.4 months (median 73.0 months).

Identification of Cut-Off Values for Metastatic Lymph Node Number and Metastatic Lymph Node Ratio

To discover the optimal cut-off values for MLNN and MLNR, an X-tile program was used to analyze the data of patients with MTC from the SEER database. The results showed that 0 and 12 were the best cut-off values for MLNN ($p < 0.001$) (Fig. 1a). When MLNN was ≤ 12, the optimal cut-off value for MLNR was 0.6 ($p < 0.001$) (Fig. 1b), and when MLNN was > 12, the optimal cut-off value for MLNR was 0.75 ($p < 0.001$) (Fig. 1c).

Proposed N Staging System

Using the RPA, we generated a novel N staging system (Fig. 1d) for patients from the SEER cohort. First, based on the MLNN, patients were divided into the following three groups: MLNN = 0, 1 ≤ MLNN ≤ 12, and MLNN > 12. Patients in the 1 ≤ MLNN ≤ 12 group were then divided into two subgroups as follows: MLNR < 0.6 and MLNR ≥ 0.6. In addition, patients in the MLNN > 12 group were divided into the following two subgroups: MLNR < 0.75 and MLNR ≥ 0.75. Kaplan–Meier estimates for the five subgroups (MLNN = 0; 1 ≤ MLNN ≤ 12 and MLNR < 0.6; 1 ≤ MLNN ≤ 12 and MLNR ≥ 0.6; MLNN > 12 and MLNR < 0.75; and MLNN > 12 and MLNR ≥ 0.75) indicated that there were no significances between patients from the two subgroups of 1 ≤ MLNN ≤ 12 and



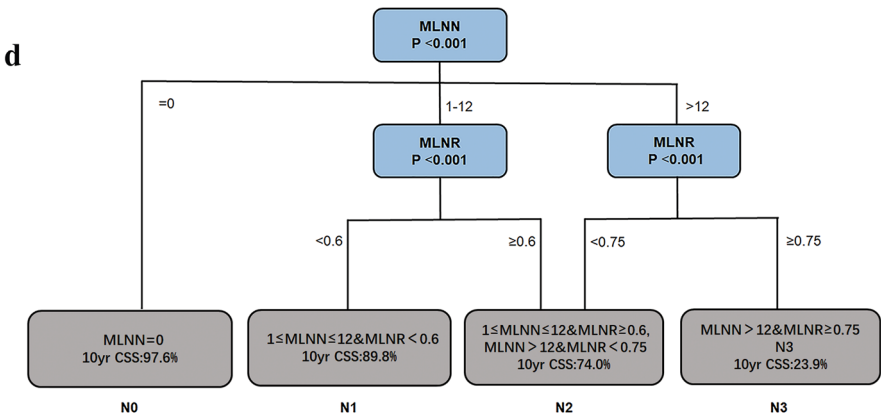


FIG. 1 X-tile analyses identifying optimal MLNN (**a**) and MLNR [**b** MLNN $\leq$ 12; **c** MLNN > 12] cut-off values based on cancer-specific survival. Defining a novel LN staging system for MTC by recursive partitioning analysis based on the MLNN and MLNR (**d**). The differences between the two systems are shown in (**e**). *LNs* lymph nodes, *MLNN* metastatic lymph node number, *MLNR* metastatic lymph node ratio, *MTC* medullary thyroid cancer, *CSS* cancer-specific survival, *AJCC* American Joint Committee on Cancer, *AUC* area under the receiver operating characteristic curve, *SEER* surveillance, epidemiology, and end results, *FUSCC* Fudan University Shanghai Cancer Center

e

Novel Nodal Staging System		
N-Category	**Criteria**	**10yr CSS**
N0	MLNN=0	97.6%
N1	1≤MLNN≤12 and MLNR < 0.6	89.8%
N2	1≤MLNN≤12 and MLNR≥0.6, MLNN > 12 and MLNR < 0.75	74.0%
N3	MLNN > 12 and MLNR≥0.75	23.9%

AJCC 8th Edition Staging System Nodal Staging System		
N-Category	**Criteria**	**10yr CSS**
N0	MLNN=0	97.6%
N1a	Metastasis to central neck LNs	93.8%
N1b	Metastasis to lateral neck LNs	71.2%
NX	Cannot be assessed	77.8%

N-staging system	SEER Cohort (n=1374)		FUSCC Cohort (n=164)	
	C-index	AUC (10yr)	C-index	AUC (10yr)
Novel	0.778 (0.775-0.781)	0.789	0.716 (0.712-0.720)	0.788
8th AJCC	0.749 (0.746-0.753)	0.741	0.670 (0.666-0.674)	0.735

MLNR $\geq$ 0.6, and MLNN > 12 and MLNR < 0.75. Therefore, we combined the two subgroups and then generated the following novel N staging system: N0: MLNN = 0; N1: 1 $\leq$ MLNN $\leq$ 12 and MLNR < 0.6; N2: 1 $\leq$ MLNN $\leq$ 12 and MLNR $\geq$ 0.6 or MLNN > 12 and MLNR < 0.75; and N3: MLNN > 12 and MLNR $\geq$ 0.75.

Impact of the Novel N Staging System on CSS Prediction

In the Cox model, univariate analysis showed that this novel N staging system was found to be a strong predictor of CSS ($p < 0.001$). Multivariate analysis implied that after adjusting for other clinical and demographic factors, the novel N staging system (N1: hazard ratio [HR] 2.889, 95% confidence interval [CI] 1.248–6.689, $p = 0.013$; N2: HR 7.005, 95% CI 3.033–16.182, $p < 0.001$; and N3: HR 29.162, 95% CI 8.316–102.263, $p < 0.001$) could still independently predict CSS (Table 2). Age > 63 years ($p < 0.001$) and larger tumor size ($p < 0.001$) were also independently associated with poorer prognosis.

Comparison of the Novel N Staging System Versus the 8th American Joint Committee on Cancer N Staging System

To identify whether the novel N staging system improved predictive ability compared with the 8th AJCC N staging system for MTC, Kaplan–Meier estimates of the novel system (Fig. 2a, c) and the AJCC system (Fig. 2b, d)

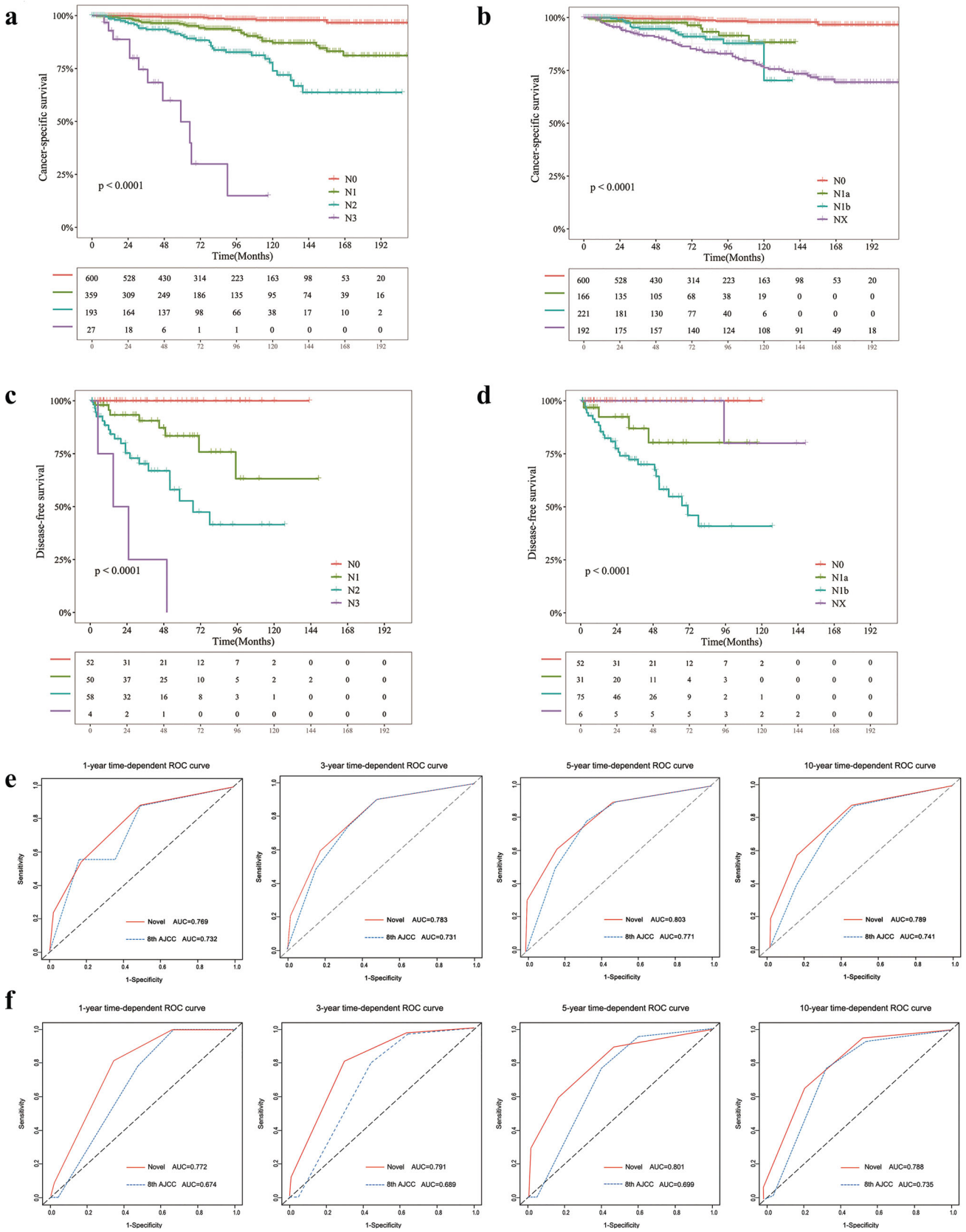
TABLE 2 Univariate and multivariate Cox analysis for cancer-specific survival in the SEER cohort

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, years[a]				
$\leq$ 63	1		1	
> 63	2.322 (1.479–3.645)	< 0.001	2.406 (1.405–4.119)	0.001
Sex				
Female	1		1	
Male	1.890 (1.202–2.970)	0.006	1.142 (0.663–1.968)	0.663
Year of diagnosis				
1998–2003	1		1	
2004–2009	0.601 (0.356–1.015)	0.057	0.742 (0.387–1.422)	0.368
2010–2014	0.547 (0.254–1.182)	0.125	0.553 (0.211–1.445)	0.227
T stage				
T1 + T2	1		1	
T3 + T4	5.037 (2.973–8.535)	< 0.001	1.316 (0.492–3.519)	0.585
Tumor size, cm				
0–2	1		1	
2–4	2.699 (1.447–5.036)	0.002	3.851 (1.1.787–8.300)	0.001
> 4	6.129 (3.259–11.524)	< 0.001	3.872 (1.388–10.798)	0.010
Extracapsular extension				
No	1		1	
Yes	4.767 (2.996–7.853)	< 0.001	1.323 (0.592–2.958)	0.496
ELNN[b]				
$\leq$ 14	1		1	
> 14	2.173 (1.352–3.492)	0.001	1.047 (0.581–1.887)	0.879
Novel N stage				
N0	1		1	
N1	4.562 (2.129–9.777)	< 0.001	2.889 (1.248–6.689)	0.013
N2	12.268 (5.581–25.725)	< 0.001	7.005 (3.033–16.182)	< 0.001
N3	76.100 (30.068–192.603)	< 0.001	29.162 (8.316–102.263)	< 0.001

HR hazard ratio, *CI* confidence interval, *ELNN* examined lymph node number, *SEER* surveillance, epidemiology, and end results

[a]The age cut-off value was 63 years and was derived from the X-tile program

[b]The ELNN cut-off value was 14 and was derived from the X-tile program


a
Cancer-specific survival
p < 0.0001
N0
N1
N2
N3
Time(Months)
b
Cancer-specific survival
p < 0.0001
N0
N1a
N1b
NX
Time(Months)
c
Disease-free survival
p < 0.0001
N0
N1
N2
N3
Time(Months)
d
Disease-free survival
p < 0.0001
N0
N1a
N1b
NX
Time(Months)
e
1-year time-dependent ROC curve
Novel AUC=0.769
8th AJCC AUC=0.732
3-year time-dependent ROC curve
Novel AUC=0.783
8th AJCC AUC=0.731
5-year time-dependent ROC curve
Novel AUC=0.803
8th AJCC AUC=0.771
10-year time-dependent ROC curve
Novel AUC=0.789
8th AJCC AUC=0.741
Sensitivity
1-Specificity
f
1-year time-dependent ROC curve
Novel AUC=0.772
8th AJCC AUC=0.674
3-year time-dependent ROC curve
Novel AUC=0.791
8th AJCC AUC=0.689
5-year time-dependent ROC curve
Novel AUC=0.801
8th AJCC AUC=0.699
10-year time-dependent ROC curve
Novel AUC=0.788
8th AJCC AUC=0.735
Sensitivity
1-Specificity

◀**FIG. 2** Kaplan–Meier survival curves for MTC patients using the modified N staging system and the 8th AJCC N staging system for the **a**, **b** SEER and **c**, **d** FUSCC cohorts. Time-dependent ROC curves of the novel and 8th AJCC N staging systems in the prognostic prediction of MTC patients at 1-, 3-, 5-, and 10-year points in the **e** SEER and **f** FUSCC cohorts. *MTC* medullary thyroid cancer, *AJCC* American Joint Committee on Cancer, *SEER* surveillance, epidemiology, and end results, *FUSCC* Fudan University Shanghai Cancer Center, *ROC* receiver operating characteristic curve, *AUC* area under the receiver operating characteristic curve

were illustrated. The novel system showed preferable discrimination of the survival curves for both the SEER and FUSCC cohorts. The same trend was found in the 10-year CSS of patients in each substage from the SEER cohort (Fig. 1e). According to the novel system, the 10-year CSS rates for N0, N1, N2, and N3 were 97.6%, 89.8%, 74.0%, and 23.9%, respectively. In contrast, the results for N0, N1a, N1b, and NX from the 8th AJCC system were 97.6%, 93.8%, 71.2%, and 77.8%, respectively. The results of the univariate Cox regression analysis also demonstrated that the novel system showed better discrimination in risk stratification than the AJCC system (Table 3).

The predictive metric C-indices of two different N staging systems are presented in Fig. 1e. The respective C-indices for the SEER cohort using the novel and AJCC systems were 0.778 (95% CI 0.775–0.781) and 0.749 (95% CI 0.746–0.753). For the FUSCC cohort, when predicting DFS, a similar result was obtained: the C-index of the novel system was 0.716 (95% CI 0.712–0.720) and the C-index of the AJCC was 0.670 (95% CI 0.666–0.674).

When analyzing the evaluation ability of the systems, the novel system performed better than the AJCC system in both the SEER cohort (5-year area under the curve (AUC) 0.803 vs. 0.771; 10-year AUC 0.789 vs. 0.741) (Fig. 2e) and the FUSCC cohort (5-year AUC 0.801 vs. 0.699; 10-year AUC 0.788 vs. 0.735) (Fig. 2f) for CSS (DFS).

DISCUSSION

This study was performed in the context that the 8th AJCC N staging system fails to fully use the state of LNM to reflect the prognosis of MTC. MTC differs from DTC in many aspects; however, the latest N staging system for MTC is still restricted to the same concepts that were initially developed for DTC.[3,4,18] It is very significant to propose a more accurate and appropriate N staging system for MTC. Based on the relatively large sample of patients from the SEER and FUSCC databases, this study proposed a novel N staging system. In this system, MLNN and MLNR were applied to predict patient prognosis. From our perspective, the joint use of MLNN and MLNR could potentially show two significant factors, i.e. regional metastasis [19,20] and surgical approach,[4,21] which were essentially regarded as prognostic factors. In addition, these two variables were easy to calculate, and it was convenient to classify patients based on these variables.[22,23] Therefore, we thought it was reasonable to use MLNN and MLNR for the new N staging system.

Notably, the number and ratio of LNM are important prognostic factors in many cancers.[16,24–26] However, owing to the low incidence and limited available data, there were few studies related to the connection between MTC prognosis and LNM. Either ≥ 16 or ≥ 10 positive LNs were identified as the optimal MLNN values in some studies that analyzed patients from the SEER database.[25,27] One study suggested a ratio of 0.5 as the optimal MLNR to predict the prognosis of MTC patients with stage IV disease.[28] Machens and Dralle demonstrated that MLNN was related to distant metastasis ($p = 0.003$) and proposed an N staging system that did not show the relationship between MLNN and CSS.[15] However, in all of the abovementioned studies, the validation methods were limited to the Kaplan–Meier analyses, patients were from a single center, and MLNN and MLNR were not jointly used. In this study, we collected patients with MTC from two databases (the SEER and FUSCC databases). The former database includes approximately 28% of the American population, and the latter is a high-volume cancer center in China. The X-tile program was used to choose the best cut-off values for MLNN and MLNR. Using RPA, we proposed a new MTC-specific N staging system based on MLNN and MLNR.

To assess whether the new system was better in predicting prognosis, several contrasts to the current system were implemented. Compared with the Kaplan–Meier survival curves obtained using the 8th AJCC N staging system, those obtained using the RPA-derived N staging system were sufficiently separated between the N substages of the SEER and FUSCC cohorts. The proposed system showed preferable discriminatory and predictive capacities (the C-index: SEER cohort 0.778 [novel] vs. 0.749 [8th]; FUSCC cohort 0.716 [novel] vs. 0.670 [8th]). Nevertheless, the LNM novel classification system seems to be better than the AJCC system in some ways. First, this novel classification system is a distinct system used for patients with MTC, rather than one extrapolated from a DTC system. In addition, a novel system abandoned the NX stage, which was defined as regional LNs that could not be assessed. Patients in the NX stage accounted for 16.3% of patients in the SEER database, and, although the location of LNM was unknown, the MLNN and MLNR values for these patients were easy to record and calculate. This result indicated that MLNN and MLNR were more useful in clinical practice. We believe that the novel N staging

TABLE 3 Comparison of the prognostic performances of different N staging systems in the derivation and validation cohorts

Cohort	Staging system	No. of patients	Death (recurrence) [*n* (%)]	CSS (DFS) 10-year (%) AUC	Cox analysis [HR (95% CI)]	C-index (95% CI)
SEER	Novel			0.784		0.778 (0.775–0.781)
	N0	600	9 (1.5)	97.6	1	
	N1	359	25 (7.0)	89.8	4.562 (2.129–9.777)	
	N2	193	32 (16.6)	74.0	12.268 (5.581–25.725)	
	N3	27	10 (37.0)	23.9	76.100 (30.068–192.603)	
	8th			0.743		0.749 (0.746–0.753)
	N0	600	9 (1.5)	97.6	1	
	N1a	166	8 (4.8)	93.8	4.209 (1.619–10.943)	
	N1b	221	14 (6.3)	71.2	6.111 (2.629–14.205)	
	NX	192	45 (23.4)	77.8	10.974 (5.326–22.500)	
FUSCC	Novel			0.788		0.716 (0.712–0.720)
	N0	52	0 (0.0)	100	1	
	N1	50	8 (16.0)	63.2	48085.126 (0.000–7.325E+71)	
	N2	58	20 (34.5)	41.5	142137.370 (0.000–2.225E+72)	
	N3	4	4 (100.0)	0.00	585403.168 (0.000–9.190E+72)	
	8th			0.735		0.670 (0.666–0.674)
	N0	52	0 (0.0)	100	1	
	N1	26	4 (15.4)	72.2	94663.868 (0.000–4.247E+79)	
	N1b	84	28 (33.3)	44.3	138092.231 (0.000–6.179E + 79)	
	NX	2	0 (0.0)	100	0.928 (0.000–4.259E + 271)	

CSS cancer-specific survival, *DFS* disease-free survival, *CI* confidence interval, *HR* hazard ratio, *AUC* area under the receiver operating characteristic curve, *SEER* surveillance, epidemiology, and end results, *FUSCC* Fudan University Shanghai Cancer Center

system will not only improve survival prognosis but will also more accurately recognize patients who need further treatment and close follow-up.

Limitations

This study has three limitations. First, the two cohorts are different in some aspects, such as race and sex ratios, and these clinicopathologic characteristics may affect the accuracy of the staging system. Second, the study is limited by its retrospective nature. It would be prudent to confirm our results in a prospective cohort study or by using another large, multi-institutional database, such as the National Cancer Database. Finally, although the SEER database maintains highly accurate records, incorrect coding or erroneous data are still possible.

CONCLUSIONS

The results of the Cox analysis demonstrated that the novel system predicts survival independently and significantly ($p < 0.001$). A standardized surgical strategy may account for this phenomenon. In addition, the collection method for specimens, and the method used by pathologists for verifying positive LNs could also affect the results; thus, there must be standards for surgeons and pathologists. Therefore, we must comply with standardized conditions for precisely using MLNN and MLNR values to predict survival, or the prognostic significance will be limited. Age and tumor size could also predict CSS. The T staging system has been considered in relation to the size of the tumor, and perhaps, in the future, we could explore the efficiency of age in stratifying different risk levels of MTC patients.

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