

# Prognostic value of numbers of metastatic lymph node in medullary thyroid carcinoma

## A population-based study using the SEER 18 database

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### Abstract

Lymph node (LN) metastases are widely considered as a vital assessment of disease progression, as well as an essential indicator for biochemical cure of medullary thyroid carcinoma (MTC). Prognostic effect of numbers of metastatic LN has not been fully studied and the optimal cut-point of LN numbers has not been established. This population-based study designed to investigate prognostic value of numbers of positive LN and determinate the prognostic factors.

Data were generated from Surveillance, Epidemiology, and End Results (SEER) database between 1998 and 2013. X-tile program was applied and cut points for division of LN numbers as low-, medium- and high-risk were 0, 1 to 10, and  $\geq 11$ . The relationship between numbers of metastatic LN, age, tumor size, extent of tumor, and radiotherapy on overall survival (OS) and disease-specific survival (DSS) were evaluated.

A total of 1466 diagnosed primary MTC patients without metastases were eligible for analysis in current study. 945 (64%) patients were classified as no positive LNs, 327 (22%) as 1 to 10 positive LNs, 194 (14%) as  $\geq 11$  positive LNs. Patients with older age, tumor size,  $\geq 11$  positive LN were associated with unfavorable OS. Those dispensed with radiation had statistically better prognosis than the others. When stratified by age, there was a significant difference in patients  $\geq 45$  years within LN categories (log-rank  $P < .001$ ). When stratified by tumor size, a significant correlation was noted between rising numbers of involved nodes and falling rates of OS in tumor measuring  $> 2$  cm setting (2–4 cm setting, log-rank  $P = .003$  and  $> 4$  cm setting, log-rank  $P = .014$ , separately). There was no statistical difference of the area under the curve (AUC) for OS and DSS prediction between LN group and N stage, suggesting the 2 LN systems had the same predictive power for OS and DSS.

Numbers of metastatic LN showed prognostic power in survival analysis and remained an independent survival predictor which can be evaluated in MTC treatment decisions for optimum assessment.

**Abbreviations:** AJCC = American Joint Committee on Cancer, AUC = under the curve, CI = confidence intervals, CT = calcitonin, DSS = disease-specific survival, HR = hazard ratio, LN = lymph node, MTC = medullary thyroid carcinoma, OS = overall survival, PTC = papillary thyroid carcinoma, ROC = receiver operating characteristic curve, SEER = Surveillance, Epidemiology, and End Results.

**Keywords:** disease-specific survival, extrathyroidal extension, lymph nodes metastases, medullary thyroid carcinoma, overall survival

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The authors declare no conflict of interests.

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## 1. Introduction

Medullary thyroid carcinoma (MTC) is a rare thyroid carcinoma. Due to the dramatically increased incidence of papillary thyroid carcinoma (PTC) in last three decades, the prevalence of MTC accounts for 1% to 2% of all thyroid malignancies according to recent Surveillance, Epidemiology, and End Results (SEER) data.<sup>[1]</sup> MTC originates from calcitonin-secreting parafollicular cells (C cells) of thyroid gland, and has completely disparate biologic and pathologic features compared with those of epithelial thyroid tumors. Thereby MTC exhibits more aggressive behavior than PTC which is responsible for up to 13.4% of all thyroid cancer-related deaths.<sup>[2]</sup>

Long term survival differs from patients with various disease courses. Age at diagnosis, stage of disease, thyroid capsule status and distant metastases have been consistently observed to be significant prognostic factors in patients with MTC.<sup>[3,4]</sup> As the full awareness of the utility of germline *RET* mutations, the role of *RET* mutations in predicting tumor outcome is well-established.<sup>[5]</sup>

It was reported that 54.8% to 64.3% MTC patients had lymph node (LN) metastases after diagnosis.<sup>[6]</sup> Nodal involvement is widely considered as a vital assessment of disease progression, as

well as an essential indicator of postoperative calcitonin (CT) normalization.<sup>[7]</sup> Adverse survival was detected in patients with rising numbers of involved LN from Esfandiari's study, suggesting the prognostic value of numbers of metastatic LN.<sup>[8]</sup> However, the current American Joint Committee on Cancer (AJCC) staging system for MTC identifies nodal status based on the cervical region where metastatic LN resected.<sup>[9]</sup> This nodal staging system gives insight into the extent of tumor spread through lymph vessels, whereas fails to take into account of the amount of LN involved. As a crucial instrument of prognosis prediction, current N categories have been challenging.<sup>[10]</sup>

However, prognostic effect of numbers of metastatic LN has not been fully studied and the optimal cut-point of LN numbers has not been established. In this population-based analysis, X-tile program was applied to investigate the cut points as high-, medium-, low-risk for division of LN numbers.<sup>[11]</sup> In order to further investigate prognostic value of numbers of positive LN and compare its survival prediction with current nodal classification in patients with MTC, we conducted this analysis based on SEER database.

## 2. Methods

We accessed the SEER database by SEER\*Stat version 8.3.5 and a patient list was generated for analysis. SEER is the only population-based database in the U.S. that provides information regarding tumor stage and survival information. Data released from the SEER database contains no identifiers and is publicly available. We obtained permission to access the research data file in the SEER program from the National Cancer Institute, USA (reference number 13493-Nov2017). We enrolled 2147 eligible patients between 1998 and 2013. All cases of histologically diagnosed primary MTC (ICD-O-3 8510/3) and atypical MTC (ICD-O-3 8513/3) were received surgical treatment of thyroid tumor. Patients were excluded if distant metastases were detected at the time of diagnosis. Follow-up durations were calculated from January 1, 1998 to December 31, 2015.

Numbers of positive LN were classified as a categorical variable, and categorized as low-, medium- and high-risk from X-tile program as follows:

1. no positive LNs;
2. 1–10 positive LNs;
3.  $\geq 11$  positive LNs.

Positive LNs were confirmed by dissection, sampling, aspiration or core biopsy. The tumor size was classified as categorical variable:  $\leq 2$  cm; 2 to 4 cm; and  $> 4$  cm. We also classified thyroid procedures into:

1. local excision;
2. lobectomy or lobectomy with isthmusectomy;
3. total/subtotal thyroidectomy.

The extent of tumor was classified as:

1. intrathyroidal disease (tumor confined to the thyroid, or invasion into thyroid capsule but not beyond, or localized tumor not otherwise specified);
2. minimal extrathyroidal disease (extension to sternothyroid muscle or perithyroid soft tissues);
3. moderately advanced extrathyroidal disease (invade to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve);
4. very advanced extrathyroidal disease (invade to prevertebral fascia or encases carotid artery or mediastinal vessels).

Patients with negative LN were used as a reference. The optimal cut-point for the number of involved LNs were analyzed using the X-tile program (<http://www.tissuearray.org/rimmlab/>), which identified the cut-point with the minimum  $P$  values from log-rank  $\chi^2$  statistics for the optimal division of positive LNs in terms of survival.<sup>[11]</sup> The demographic and clinical features of stratifying cases were compared between the 3 LN groups using one-way ANOVA (continuous variables) and Chi-squared test (categorical variable). The Kaplan–Meier method was performed to generate survival curves, and the log-rank test was performed to compare the unadjusted disease-specific survival (DSS) and overall survival (OS) rates of patients with different LN status. DSS was defined as the time from the date of diagnosis to the date of thyroid cancer death. OS was defined as the time from the date of diagnosis to the date of death due to any cause (including thyroid cancer) or the last follow-up. Univariate and multivariate analyses were carried out using Cox proportional hazards regression model to estimate the outcome-related factors. Hazard ratio (HR) and 95% confidence intervals (CI) were estimated by Cox regression analysis. In univariate analysis, variable with  $P$ -values  $< .2$  was entered into multivariate analysis. If the 95% CI of the HR did not cross 1.00, then the relationship was considered statistically significant for multivariable analysis.

All tests were two-tailed.  $P$ -values  $< .05$  were considered significant. All statistical analyses were performed using SPSS version 20.0 software (Chicago, IL, USA).

## 3. Results

### 3.1. Patient demographics and clinical features and optimal cut-point for the number of involved LNs identification

A total of 1466 patients met the eligibility criteria with information of LN status were analyzed in our study. LN metastases were presented in 521 patients (36%). Patient demographics and clinical features were listed in Table 1. Among these patients, 945 (64%) patients were classified as no positive LNs, 327 (22%) as 1 to 10 positive LNs, 194 (14%) as  $\geq 11$  positive LNs. The results obtained from clinical-pathologic variables demonstrated that patients with nodal involvement tended to be female ( $P < .001$ ), presented with a greater tumor size ( $P < .001$ ), and were more likely to extend beyond thyroid capsule into surrounding tissues ( $P < .001$ ).

X-tile identifies the optimal division of LNs into 3 populations (0, 1–10 and  $\geq 11$ ). The maximum of  $\chi^2$  log-rank values was 25.10, applying 11 and 1 as optimal cut point for the category into high, middle, and low subsets in terms of survival (Fig. 1).

### 3.2. Univariate and multivariate analysis

In univariate analysis of OS, age at diagnosis, gender, race, tumor size, extent of tumor, LN group and radiation were selected into Cox proportional hazard model for multivariate analysis (Table 2). Age at diagnosis was entered multivariate analysis as continuous variables. Patients with older age (HR 1.067 [95% CI, 1.054–1.081]), tumor size (HR 1.919 [95% CI, 1.272–2.896]),  $\geq 11$  positive LNs (HR 1.943 [95% CI, 1.144–3.303]) were associated with unfavorable OS (Table 3). Those dispensed with radiation had statistically better prognosis than the others (HR 0.616 [95% CI, 0.396–0.959]).

Age at diagnosis, gender, tumor size, extent of tumor, LN group and radiation had significant influences on DSS were

Characteristics	0 N = 945	1–10 N = 327	≥11 N = 194	P
Median follow-up duration (months)				.130
Age at diagnosis (years)	49.01	45.20	45.92	
Median	52.95	52.89	52.48	.942
<45	269	92	54	.981
≥45	676	235	140	
Gender				<.001
Male	290	147	119	
Female	655	180	75	
Race				.508
White	805	271	169	
Black	78	33	11	
Other	62	23	14	
Tumor size (cm)				<.001
≤2	603	136	63	
>2 and ≤4	251	121	66	
>4	91	70	65	
N stage				<.001
N0	942	0	0	
N1a	0	149	19	
N1b	2	150	165	
N1, NOS	1	28	10	
Extent of tumor				<.001
Intrathyroidal	916	236	86	
Minimal extrathyroidal	21	61	74	
Moderately advanced extrathyroidal	5	24	21	
Very advanced extrathyroidal	3	6	13	
Type of surgery				<.001
Local excision	3	0	0	
Lobectomy or lobectomy with isthmusectomy	94	7	4	
Total/subtotal Thyroidectomy	843	320	190	
Unknown	5	0	0	
Radiation				<.001
Yes	63	60	61	
No	866	256	131	
Unknown	16	11	2	

selected in univariate analysis. Finally, patients with older age (HR 1.040 [95% CI, 1.018–1.062]), tumor size (HR 3.505 [95% CI, 1.560–7.873]), LN metastases (HR 3.245 [95% CI, 1.392–7.566]) were correlated with poor DSS (Table 3). Those dispensed with radiation had statistically better DSS than the others (HR 0.471 [95% CI, 0.240–0.925]).

### 3.3. OS comparisons stratified by age, tumor size and radiation categories

Based on the aforementioned results, age at diagnosis, tumor size and radiation significantly affected OS rate. To further investigate this association, we analyzed the difference of OS broken down separately by age, tumor size and radiation classification to avoiding potential confounding factors. When stratified by age, there was a significant difference in patients ≥45 years within LN categories (log-rank  $P < .001$ ), as opposed to no statistical significant difference of OS in patient aged <45 years (Fig. 2).

When the effect of quantity of positive LNs in OS was compared stratified by tumor size, a similar correlation was noted

between rising numbers of involved nodes and falling rates of OS in tumor measuring >2cm setting (Fig. 3).

After comparison stratified by radiation, we found OS was significantly associated with LN numbers in patients did not receive any form of radiotherapy (Fig. 4).

### 3.4. Predictive accuracy of LN group and N stage

The predictive value of LN group and N stage systems was further studied by receiver operating characteristic curve (ROC) analysis. All of the factors predicted prognosis precisely ( $P < .05$ ). The area under the curve (AUC) for OS prediction was 0.798 and 0.788 in LN group and N stage ( $P = .0596$ ) (Fig. 5A), suggesting no statistically difference for OS predictive power between the 2 LN systems. The AUC for DSS prediction was 0.853 and 0.855 in LN group and N stage ( $P = .2234$ ) (Fig. 5B), suggesting the 2 indexes were both high-power markers for DSS.

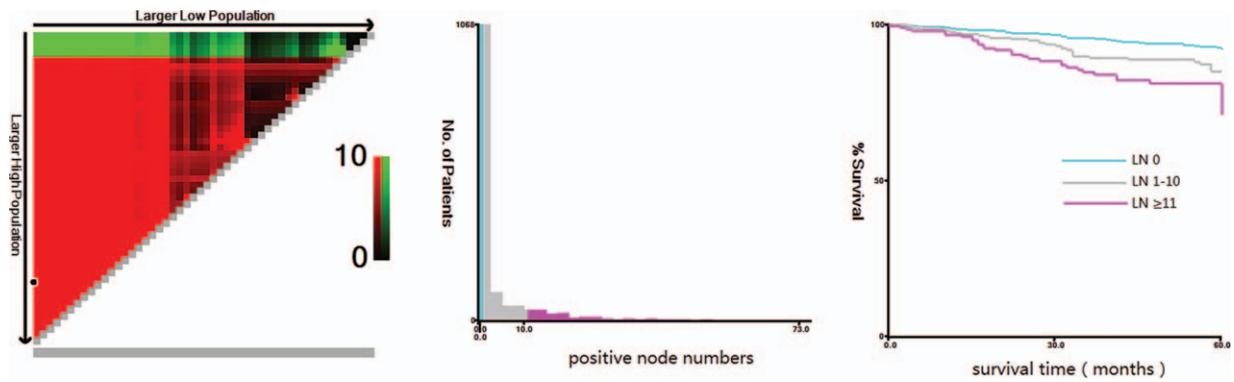
## 4. Discussion

The impact of LN metastases on survival of MTC remains uncertain. There were many researches regarded LN metastases as an indispensable prognostic parameter for analysis in both univariate and multivariate model. Most previous researches defined LN status using different criteria, such as AJCC N categories,<sup>[3,4,12]</sup> ipsilateral or contralateral,<sup>[13]</sup> metastatic LN ratio,<sup>[14,15]</sup> and LN metastases present or not.<sup>[2,16]</sup> Whereas based on above criteria, status of nodal metastases served as a significant prognostic factor of OS in univariate analysis as opposed to be independent in multivariate analysis, even in large population analysis.<sup>[17]</sup> Given the failure in multivariate analysis, some authors opposed LN status to be a survival factor.<sup>[2,3]</sup> Only a few studies have explored the counts of positive LN as prognostic indicator by now.<sup>[8,10,18]</sup> Esfandiari et al found the number of LN metastases notably influenced OS in multivariate model.<sup>[8]</sup> From our research, we also demonstrated the predictive effect of LN number categories in survival analysis, emphasizing the importance of LN quantification.

For N staging, the AJCC TNM classification uses metastatic LN locations instead of incremental N categories for LN evaluation. Machens et al designed a study which divided patients according to LN counts (0, 1–10, 11–20, and >20 involved nodes), and confirmed the quantity of LN metastases clearly contributed to prognostic prediction.<sup>[10]</sup> Similar result was achieved in Esfandiari's study with classification of LN counts (0, 1–5, 6–10, 11–15, and >16 involved nodes) in a large population-based research.<sup>[8]</sup> Our finding was in agreement with the prognostic status of number-based LN classification.

In aforementioned researches, investigators used distinct criteria for LN categorization and the best threshold for distinction between low-risk and high-risk is not established. Thus, different LN numbers cut-point applied making it difficult to compare between studies. Our study introduced X-tile program to identify the optimal cut-point for LN classification (0, 1–10, ≥11) in 1466 MTC patients, which made our research more reliable. It is noteworthy that positive LN ≥11 is an adverse predictor of OS and DSS in our research.

The AUC value showed LN number categories and N staging are both high power markers for prognostic prediction. As it known to all, N staging is an important prognostic instrument. It is important to recognize that N staging is suggested to be combined with quantity of LN metastases for better risk stratification.



**Figure 1.** X-tile analysis of survival data from the SEER registry. X-tile analysis was done on patient data from the SEER registry, equally divided into training and validation sets. X-tile plots of training sets are shown in the left panels, with plots of matched validation sets shown in the smaller inset. The plot shows the  $\chi^2$  log-rank values produced when dividing the cohort with two cut-points, producing high, middle, and low subsets. The optimal cut-point highlighted by the black circle in the left panels is shown on a histogram of the entire cohort (middle panels) and a Kaplan–Meier plot (right panels). P values were determined by using the cut-point defined in the training set and applying it to the validation set. Figures show positive node numbers divided at the optimal cut-point (1 and 11,  $\chi^2 = 25.10$ ,  $P < .001$ ). SEER = Surveillance, Epidemiology, and End Results.

**Table 2**  
Univariate and multivariate Cox proportional hazard analysis for survival-related factors of overall survival.

	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Age at diagnosis (years)						
Median	1.064	1.051–1.077	<.001	1.067	1.054–1.081	<.001
<45	1					
≥45	8.189	3.827–17.521	<.001			
Gender						
Male	1			1		
Female	0.588	0.420–0.822	.002	0.858	0.603–1.221	.395
Race			.143			.404
White	1			1		
Black	0.530	0.247–1.135	.102	0.673	0.313–1.449	.311
other	0.609	0.268–1.382	.235	0.668	0.290–1.540	.344
Tumor size (cm)			<.001			.002
≤2	1			1		
>2 and ≤4	1.666	1.116–2.487	.013	1.919	1.272–2.896	.002
>4	2.892	1.917–4.362	<.001	1.939	1.247–3.014	.003
Extent of tumor			<.001			.811
Intrathyroidal	1			1		
Minimal extrathyroidal	1.812	1.119–2.932	.016	1.210	0.693–2.113	.502
Moderately advanced extrathyroidal	3.407	1.945–5.969	<.001	1.343	0.689–2.618	.386
Very advanced extrathyroidal	3.590	1.574–8.190	.002	1.265	0.511–3.131	.611
Lymph node group			<.001			.040
0	1			1		
1–10	1.761	1.177–2.635	.006	1.525	0.969–2.400	.068
≥11	2.659	1.758–4.022	<.001	1.943	1.144–3.303	.014
Type of surgery			.771			
Local excision	1					
Lobectomy or lobectomy with isthmusectomy	–	–	.929			
Total/subtotal thyroidectomy	–	–	.927			
Unknown			.920			
Radiation			<.001			.073
Yes	1			1		
No	0.398	0.273–0.579	<.001	0.616	0.396–0.959	.032
Unknown	0.175	0.024–1.278	.086	0.301	0.041–2.237	.241

CI = confidence intervals, HR = hazard ratio.

**Table 3**  
**Univariate and multivariate Cox proportional hazard analysis for survival-related factors of disease-specific survival.**

	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Age at diagnosis (years)						
Median	1.036	1.017–1.056	<.001	1.040	1.018–1.062	<.001
<45	1					
≥45	6.631	2.060–21.346	.002			
Gender						
Male	1			1		
Female	0.438	0.247–0.777	.005	0.803	0.436–1.479	.482
Race			.767			
White	1					
Black	0.885	0.317–2.469	.816			
other	0.601	0.145–2.485	.482			
Tumor size (cm)			<.001			.005
≤2	1			1		
>2 and ≤4	3.990	1.805–8.820	.001	3.505	1.560–7.873	.002
>4	7.960	3.624–17.483	<.001	3.360	1.462–7.724	.004
Extent of tumor			<.001			.122
Intrathyroidal	1			1		
Minimal extrathyroidal	5.388	2.697–10.762	<.001	2.137	0.957–4.773	.064
Moderately advanced extrathyroidal	10.134	4.637–22.146	<.001	2.416	0.964–6.055	.060
very advanced extrathyroidal	13.879	5.232–36.819	<.001	3.014	0.995–9.131	.051
Lymph node group			<.001			.022
0	1			1		
1–10	6.267	2.933–13.394	<.001	3.245	1.392–7.566	.006
≥11	9.240	4.265–20.018	<.001	3.019	1.176–7.749	.022
Type of surgery			.972			
Local excision	1					
Lobectomy or lobectomy with isthmusectomy	–	–	.959			
Total/subtotal thyroidectomy	–	–	.957			
Unknown			1			
Radiation			<.001			.092
Yes	1			1		
No	0.182	0.103–0.321	<.001	0.471	0.240–0.925	.029
Unknown	–	–	.961	–	–	.975

CI=confidence intervals, HR=hazard ratio.

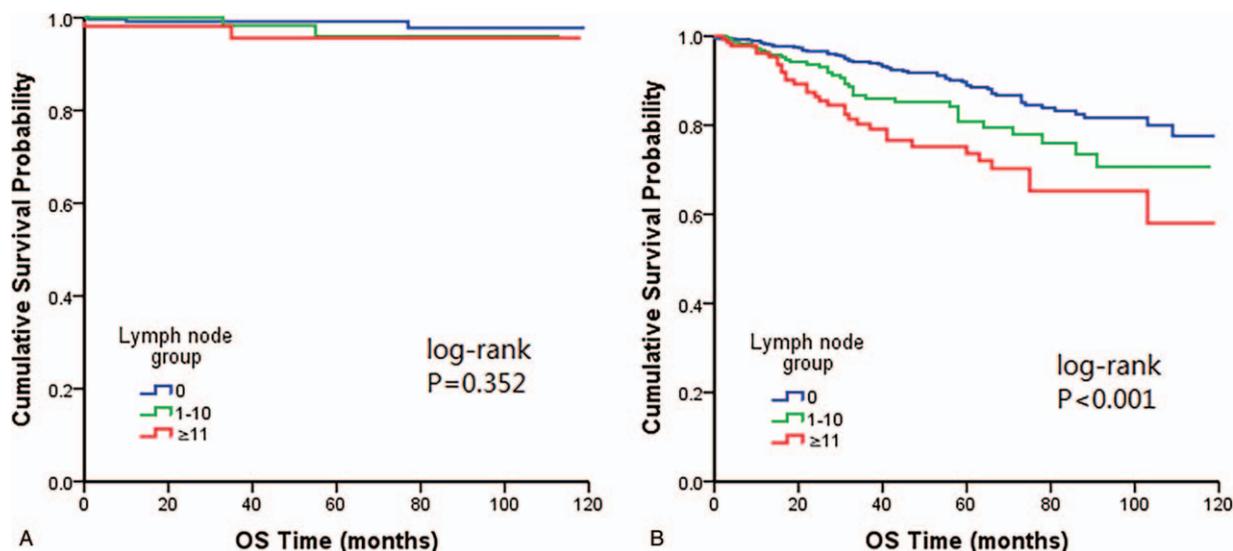


Figure 2. Kaplan-Meier plots showing overall survival stratified by age categories (A) age <45 years (B) age ≥45 years.

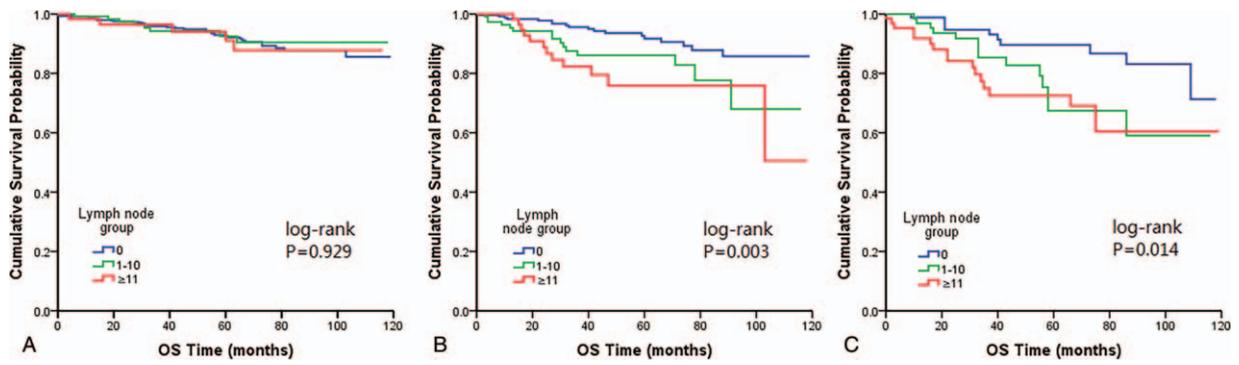


Figure 3. Kaplan–Meier plots showing overall survival stratified by tumor size categories (A) tumor size  $\leq 2$  cm (B) tumor size 2–4 cm (C) tumor size  $> 4$  cm.

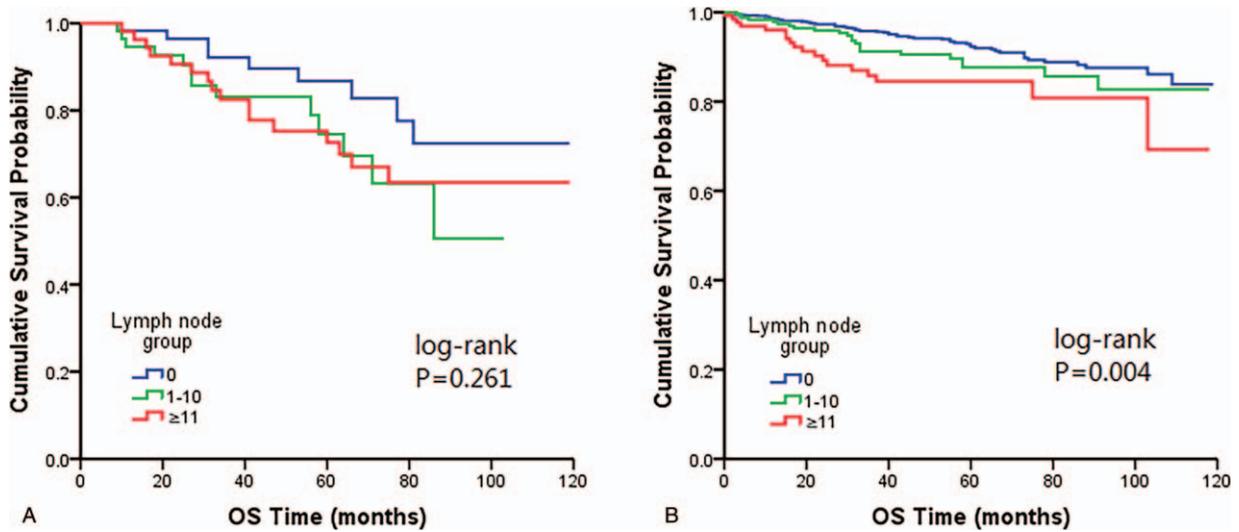


Figure 4. Kaplan–Meier plots showing overall survival stratified by radiation categories (A) with radiation (B) without radiation.

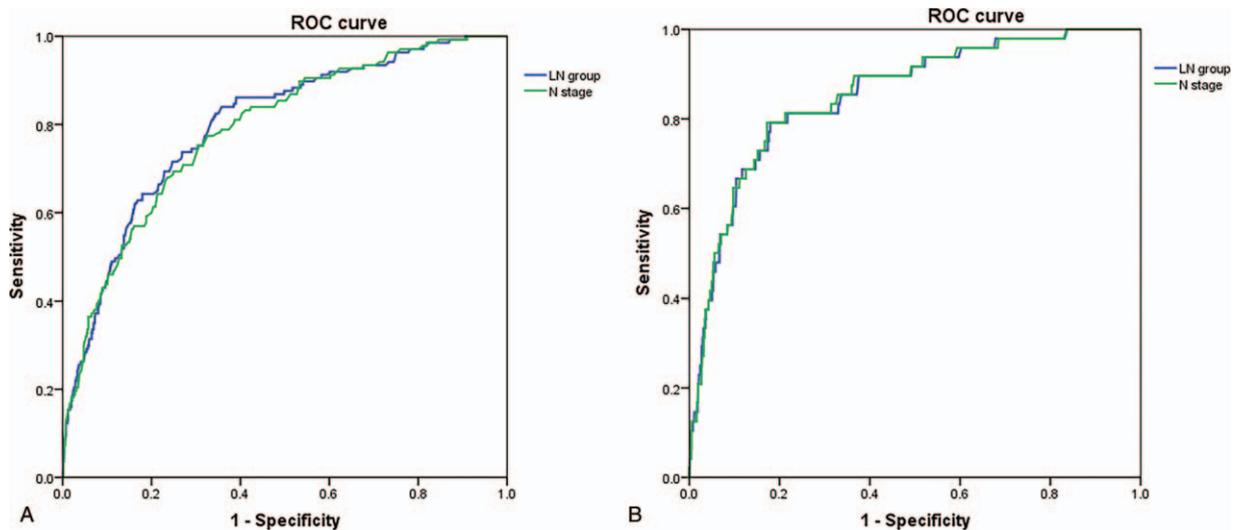


Figure 5. Predictive values of LN group and N stage systems. Both LN group and N stage had the same predictive power for OS (A) and DSS (B). DSS = disease-specific survival, LN = lymph node, OS = overall survival.

Our results indicated that declining values of LN were obviously implying improved OS in the subgroup of patient  $\geq 45$  years. Modigliani et al found that disease detection at early stage would cause survival improvement after the long-term observation of family screening population.<sup>[13]</sup> We hence recommend regular measurement of CT for elders as a screening marker, especially for those who have family history of MTC.

Numbers of LN remain an independent OS predictor after stratified tumor size in our research. Miccoli et al assumed that lymphatic metastasis developed following extrathyroidal capsule spreading.<sup>[19]</sup> Yet Esfandiari et al considered frequencies of lymphatic spread appeared to be associated with tumor size.<sup>[8]</sup> The greater tumor is the higher possibility of lymphatic involvement. Although with different tumor size, LN numbers still have strong association with disease outcome.

The radiotherapy is not a prognostic indicator for MTC patient in previous researches.<sup>[2,12]</sup> However, patients with metastasis were included in above researches. Our study focused on patients with local disease, and those dispensed with radiation had significantly better prognosis in our study indicating patients receiving radiotherapy usually with more advanced disease. Furthermore, the impact of LN number categories on OS was well established in subgroup excluding radiation confounding.

Biochemical normalization is widely regarded as a strong indicator of disease recurrence and survival, which reflects tumor persistence and occult hematogenous metastasis.<sup>[20]</sup> Approximately 97.7% MTC patients achieved 10 years survival with biochemical normalization of preoperative CT.<sup>[7]</sup> On the other hand, rising metastatic LN numbers significantly related to hypercalcitoninemia, resulting elevated rates of distant metastases,<sup>[7,10,18,20]</sup> regardless of involved LN site. Although some patients lead a normal life without biochemical normalization,<sup>[21]</sup> absence of involved LN is still a determinant of prolonged survival.<sup>[13,22]</sup> Strong evidence support  $\geq 10$  positive LNs preclude normalization of serum CT after surgical treatment<sup>[18,20]</sup> and our study further verified  $\geq 11$  is a threshold for high risk. Given the significant effect of LN numbers on postoperative CT level, this parameter should be evaluated in treatment decisions for optimum assessment.

In addition, age at diagnosis and stage of disease appeared to be the most important factors in multivariate analysis published so far.<sup>[2,13,18]</sup> Scopsi et al,<sup>[3]</sup> Gulben et al,<sup>[23]</sup> and Brierley et al<sup>[16]</sup> were found thyroid capsule status were a remarkable predictor of survival in patients with MTC. Our study demonstrated that age and tumor size also contributed to OS and disease specific survival.

However, our study using data from cancer registries also had limitations. As MTC specific biomarker, CT and carcinoembryonic antigen levels are not recorded in SEER database, which are known to be determinants of OS. An additional limitation is that details on genetic result, especially the expression of proto-oncogene *RET* are unknown. This may influence our results. Moreover, the SEER database does not contain information regarding recurrence data.

## 5. Conclusion

In conclusion, quantitative metastatic LNs showed prognostic power in survival analysis. Age and tumor size were also the most important prognostic factors for MTC. It is noteworthy that LN number group and N stage both serve as a powerful predictor in OS and DSS and the two LN systems can be evaluated together in MTC treatment decisions for optimum assessment.

## Author contributions

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