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Treatment strategies and predicting lymph node metastasis in elderly patients with papillary thyroid microcarcinoma

Wenhan Li, MD, PhD[a,b], Yao Tang, MD[c], Jianhui Li, MD, PhD[a,b], Wei Han, MD[a,b], Danfang Wang, MD[a,d], Yongheng Wang, MD[a,b,*]

Abstract

This study aims to explore the prognostic variables for elderly papillary thyroid microcarcinoma (PTMC) patients as well as create a nomogram that could predict the occurrence of cervical lymph node metastasis (CLNM) on the basis of a large population database with high quality.

A total of 5165 PTMC patients from Surveillance, Epidemiology, and End Results database database were enrolled in the study. In the meantime, we retrospectively collected 205 PTMC patients who underwent thyroidectomy in our medical center as an external control to test the accuracy of the model. The independent predictors of survival were identified by multivariate Cox regression analysis. Risk factors were selected as nomogram parameters to develop a model to predict CLNM. The C-index and calibration plots were used to evaluate CLNM model discrimination. The predictive nomogram was further validated in the external validation set.

76.8% of the enrolled patients underwent thyroidectomy. Overall survival and cancer-specific survival were significantly better in patients who underwent surgery than in those who did not ($P < .001$). Sex, tumor size, and extent of tumor were included in a multivariable logistic regression model to predict lymph node metastasis. The nomogram had good discrimination with a C-index of 0.71. The calibration curves showed perfect agreement between nomogram predictions and actual observations.

Elderly PTMC patients who received a surgical approach without radiotherapy showed survival advantage than those with other treatment strategies. Moreover, a nomogram model was established to predict the risk of CLNM, which will help clinicians in making treatment decisions.

Abbreviations: AJCC = American joint committee on cancer, CLND = cervical lymph node dissection, CLNM = cervical lymph node metastasis, CSS = cancer-specific survival, CT = computed tomography, OR = odds ratio, OS = overall survival, PTC = papillary thyroid cancer, PTMC = papillary thyroid microcarcinoma, SEER = Surveillance, Epidemiology, and End Results Database.

Keywords: lymph node metastasis, papillary thyroid microcarcinoma, SEER database

1. Introduction

The incidence of thyroid cancer is increasing due in part to an increased and aging population, and the implementation of regular cancer screenings.[1] Papillary thyroid microcarcinoma (PTMC), which refers to papillary thyroid cancer (PTC) with no >1 cm in maximal diameter, contributes to 50% of the rise in PTC incidence.[2] As the most common endocrine malignancy, PTC usually exhibits an indolent character with a favorable prognosis. However, progressive disease could still be observed in clinical practice which would significantly threaten patient's life expectancy. Some researchers thought that incidental PTMC should not be treated with aggressive therapy, especially for elderly patients with relatively lower life expectancy.[3–5] Others, however, advocated performing thyroidectomy appears to provide a survival benefit in those patients.[6–8] Therefore, we need to weigh the risks and benefits in the prevalence of strategies used to treat elderly PTMC.

Age has been recognized as the most important prognostic factor for PTC. Patients being diagnosed at older ages (55 years and up) will be stratified into a higher stage in tumor prognostic scoring system (TNM, AMES, and MACIS staging system).[9] The cause of this phenomenon may due to the histologic subtype of PTC cells in elderly individuals are usually more aggressive

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WL and YT have contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Surgical Oncology, Shaanxi Provincial People's Hospital, [b] Department of Surgical Oncology,The Third Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, [c] Department of General Surgery, Xi'an No.3 hospital, [d] Department of Surgical Oncology, The Affiliated Hospital of Xi'an Medical University, Xi'an Medical University, Xi'an, Shaanxi, China.

[*] Correspondence: Yongheng Wang, Department of Surgical Oncology, Shaanxi Provincial People's Hospital, No. 256 Yanta West Road, Xi'an, Shaanxi 710068, China (e-mail: wyh990009@163.com).

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than that of young PTC patients (more proportion of columnar cells, diffused sclerosing, or even tall cell variant).[10] For those elderly PTMC patients, the effectiveness of prophylactic cervical lymph node dissection (CLND) continues to be debated for the lack of randomized controlled data[11,12] Studies have shown that approximately 30%–70% of PTMC patients have cervical lymph node metastasis at diagnosis.[13] Current methods for detecting level VI lymph nodes metastasis, such as computed tomography (CT) and ultrasound, are helpful but often not sensitive to detect micrometastasis early in evaluation.[14,15] As such, we tried to create a validated nomogram tool that could quantify the likelihood of cervical lymph node metastasis (CLNM) in elderly PTMC patients. It may help clinicians to make surgical strategies in institutions where routine prophylactic approach is not adopted.

In this study, we first retrospectively collected data of elderly PTMC patients from Surveillance, Epidemiology, and End Results (SEER) database. Eligible clinicopathological characteristics were extracted and we identified some prognostic related factors as well as CLNM related risk factors in elderly PTMC patients. Finally, by analyzing all relevant risk factors, we built a nomogram to predict CLNM in elderly PTMC patients.

2. Materials and methods

2.1. Patient selection

The records of patient with PTMC from 2004 to 2015 were retrieved from SEER database using the SEER*Stat software (version 8.3.5). In the meantime, clinicopathological information of 205 elderly PTMC patients who have received surgical treatment between 2010 and 2018in Shaanxi provincial people's hospital was also included as external validation. Cases were considered eligible for this analysis if they met all the following criteria: patients with pathologically diagnosed PTMC; patients who were older than 70 years; all the following variables are available: age, sex, race, marital status, surgery, radiotherapy, tumor size, lymph node involvement, metastasis, and survival status. We signed a SEER data-use agreement for the proper use of its research data files. The database is open to the public and does not require ethical approval.

2.2. Statistical analyses

All statistical analyses were performed with SPSS 13.0 and R software version 3.6.1 (http://www.rproject.org) for windows. Survival analysis was performed using the Kaplan-Meier method. Differences between groups were assessed by using the log-rank test. Univariate and multivariate Cox proportional hazard models were performed to identify variables that are correlated with overall survival (OS) and cancer-specific survival (CSS). Only variables that were statistically significant in the univariate Cox regression models were analyzed in multivariate Cox regression models. Binary logistic regression model was used to select independent risk factors in CLNM predication. Sex, tumor size, and extent of tumor were included in the nomogram model as categorical variables. The discriminative abilities of the nomogram were measured by the concordance index (C-index). Calibration curves were plotted to validate the accuracy and reliability of the nomogram by the Hosmer–Lemeshow test.[16] Two-sided P values <.05 were considered statistically significant.

3. Results

A total of 5165 patients who met the inclusion criteria were identified from SEER database. The study population consisted of 3781 female and 1384 male patients. 76.8% of the included patients received operation. The median follow-up time was 64 months (range, 0–354 months). Overall, the 5-year OS rate and CSS rate for all patients were 82.9% and 98.6%, respectively. Figure 1 showed the Kaplan–Meier curves for the OS and the CSS in patients with PTMC according to different clinical characteristics. The OS and CSS were significantly shorter as age increases ($P<.01$). Similar results were observed in cases with patients who underwent surgery lived longer than those who did not (all $P<.01$). In the meantime, the OS was significantly different in patients with different ages, races, sex, and marital status (all $P<.01$). Interestingly, the CSS of the patients who received radiotherapy was significantly shorter than those who did not ($P<.01$), although the OS was insignificant ($P=.914$).

Univariate analysis of prognostic factors showed that age at diagnosis, race, sex, marital status, and treatment strategy (including surgery and radiotherapy) were significantly correlated with OS (all $P<.01$) (Table 1). We further confirmed the above independent predictors for OS by using a multivariate Cox regression analysis. Meanwhile, age at diagnosis and treatment strategies were significantly associated with CSS in elderly PTMC patients in both univariate and multivariate analyses (all $P<.01$).

We next explored the independent prognostic factors in the set of patients who underwent a surgical procedure (including total/subtotal thyroidectomy, local excision or lobectomy and/or isthmectomy) in a univariate Cox-regression model. Results showed that age at diagnosis ($P<.01$), race ($P<.01$), sex ($P<.01$), marital status ($P<.01$), surgery type ($P=.046$), lymph node involvement ($P<.01$), and distant metastasis ($P<.01$) were significantly affected OS (Table 2). In multivariate analysis that adjusted for the prognostic covariates, we confirmed the above factors were independent risk factors for OS expect distant metastasis ($P=.13$). We next analyzed the potential predictors of CSS in PTMC patients who received operation (Table 2). Age at diagnosis (70–74 vs 80–84, $P=.02$), treatment strategies (including radiotherapy and lymph nodes dissection) (all $p<0.01$), tumor extension ($p<0.01$), lymph node involvement ($P<.01$), and distant metastasis ($P<.01$) were preliminarily identified as possible prognostic factors. Moreover, by using the multivariate analysis model, we confirmed the above factors (besides the conduction of lymph nodes dissection [$P=.97$]) were independent risk factors for CSS.

We next investigated the risk factors for CLNM. As shown in Table 3, in multivariable binary logistic regression model, patient sex (odds ratio [OR]: 0.35, 95% confidence interval [CI]: 0.27–0.45, $P<.01$), tumor size (OR: 0.71, 95% CI: 0.55–0.92, $P<.01$), and tumor extension (Capsular extension: OR: 1.83, 95% CI: 1.07–2.96, $P=.02$; further extension: OR: 5.78, 95% CI: 4.15–8.00, $P<.01$) were all associated with the presence of lymph node metastases. These independent risk factors were therefore included in a nomogram model to predict the possibility of CLNM in elderly PTMC patients (Fig. 2). We found that tumor extension status made the largest contribution, followed by sex and tumor size. Then we used a statistical method to verify the prediction accuracy. First, we conducted a calibration plot for predicting CLNM. The curve demonstrated that predicted CLNM risk was closely associated with actual CLNM risk, with which it was always within a 10% margin of error (Fig. 3A).

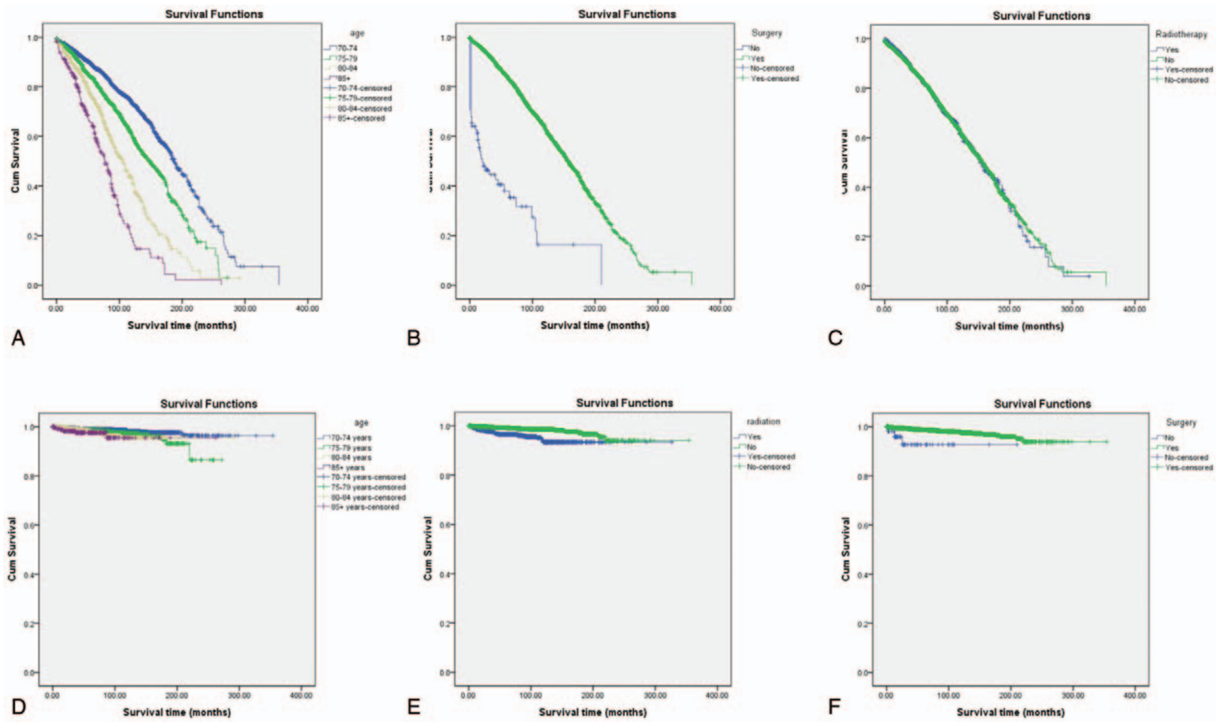

Figure 1. Stratification analysis of various clinicopathological factors by Kaplan–Meier curves for the patients with papillary thyroid microcarcinoma in the Surveillance, Epidemiology, and End Results Database. Kaplan–Meier curves of overall survival (OS) and cancer-specific survival (CSS) in different subgroups stratified by (A, D) age (OS: $P<.01$; CSS: $P<.01$), (B, E) radiotherapy (OS: $P=.914$; CSS: $P<.01$) and (C, F) surgery (OS: $P<.01$; CSS: $P<.01$). Notes: The difference between different groups is evaluated for significance based on the log-rank test.

Table 1

Prognostic variables for overall survival and cancer-specific survival in elderly PTMC patients.

	All patients (n=5165)		Overall survival				Cancer-specific survival			
			Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	N	Percentage (%)	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis, y										
70–74	2676	51.8	Reference		Reference		Reference		Reference	
75–79	1548	30.0	1.57 (1.39–1.77)	<.01*	1.53 (1.35–1.72)	<.01*	1.74 (1.06–2.87)	.03*	1.76 (1.07–2.90)	.03
80–84	695	13.5	2.62 (2.29–3.01)	<.01*	2.49 (2.17–2.87)	<.01*	2.27 (1.24–4.14)	.01*	2.56 (1.40–4.70)	<.01*
85+	246	4.8	4.28 (3.55–5.18)	<.01*	3.77 (3.11–4.59)	<.01*	2.95 (1.23–7.09)	.02*	2.78 (1.14–6.78)	.02
Race										
White	4458	86.3	Reference		Reference		Reference		—	
Black	310	6	1.34 (1.10–1.64)	<.01*	1.42 (1.16–1.74)	<.01*	0.66 (0.21–2.11)	.49	—	—
Other	397	7.7	0.75 (0.61–0.93)	<.01*	0.75 (0.61 -0.93)	<.01*	1.04 (0.48–2.27)	.91	—	—
Sex										
Male	1386	26.8	Reference		Reference		Reference		—	
Female	3779	73.2	0.67 (0.60–0.74)	<.01*	0.60 (0.58–0.67)	<.01*	0.81 (0.50–1.29)	.37	—	—
Marital status										
Married	2967	57.4	Reference		Reference		Reference		—	
Other	2198	42.6	1.28 (1.16–1.42)	<.01*	1.30 (1.16–1.45)	<.01*	1.01 (0.65–1.55)	.98	—	—
Surgery										
Yes	5087	98.5	Reference		Reference		Reference		Reference	
No	78	1.5	6.20 (4.68–8.24)	<.01*	4.54 (3.40–6.06)	<.01*	5.72 (1.80–18.16)	<.01*	6.45 (1.96–21.15)	<.01*
Radiotherapy										
Yes	952	18.4	Reference		—		Reference		Reference	
No	4213	81.6	0.99 (0.88–1.12)	.92	—	—	0.29 (0.10–0.45)	<.01*	0.26 (0.17–0.41)	<.01*

P (univariate and multivariate analysis) indicates that the *P* value was analyzed via Cox proportional hazards regression models. CI = confidence interval, HR = hazard ratio, PTMC=papillary thyroid microcarcinoma.

* $P<.05$ (2-tailed).

Table 2

Prognostic variables for overall survival and cancer-specific survival in elderly PTMC patients who underwent surgery.

	Patients (n=3968)		Overall survival				Cancer-specific survival			
			Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	N	Percentage (%)	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at diagnosis, y										
70–74	2094	52.8	Reference		Reference		Reference		Reference	
75–79	1175	29.6	1.57 (1.32–1.87)	<.01*	1.51 (1.27–1.80)	<.01*	1.72 (0.83–3.57)	.14	1.80 (0.86–3.75)	.12
80–84	518	13.1	2.76 (2.28–3.34)	<.01*	2.59 (2.14–3.15)	<.01*	2.59 (1.13–5.91)	.02*	2.70 (1.17–6.20)	.02*
85+	181	4.6	4.73 (3.68–6.10)	<.01*	4.22 (3.25–5.46)	<.01*	2.99 (0.87–10.38)	.08	2.67 (0.72–9.95)	.14
Race										
White	3477	87.6	Reference		Reference		Reference		—	
Black	239	6.0	1.26 (0.95–1.66)	.11	1.29 (0.97–1.71)	.08	0.44 (0.06–3.18)	.41	—	—
Other	292	7.4	0.61 (0.43–0.87)	<.01*	0.65 (0.46–0.93)	.02*	1.36 (0.48–3.81)	.56	—	—
Sex										
Male	1029	25.9	Reference		Reference		Reference		—	
Female	2939	74.0	0.69 (0.59–0.80)	<.01*	0.62 (0.53–0.73)	<.01*	0.73 (0.38–1.40)	.34	—	—
Marital status										
Married	2306	58.1	Reference		Reference		Reference		—	
Other	1662	41.9	1.48 (1.28–1.70)	<.01*	1.47 (1.26–1.71)	<.01*	1.39 (0.76–2.57)	.29	—	—
Surgery										
TT or STT	2834	71.4	Reference		Reference		Reference		—	
LE or LT and/or IT	1134	28.6	1.17 (1.00–1.36)	.04*	1.22 (1.04–1.43)	.01*	0.51 (0.22–1.15)	.10	—	—
Radiotherapy										
Yes	724	18.2	Reference		—		Reference		Reference	
No	3244	81.8	0.98 (0.82–1.17)	.84	—	—	0.23 (0.13–0.43)	<.01*	0.45 (0.22–0.92)	.03*
Tumor size										
≥7	1345	33.9	Reference		—		Reference		—	
<7	2623	66.1	0.93 (0.80–1.08)	.34	—	—	0.86 (0.46–1.62)	.64	—	—
LN retrieved										
Yes	1162	29.3	Reference		—		Reference		Reference	
No	2806	70.7	0.96 (0.81–1.12)	.59	—	—	2.45 (1.33–4.5)	<.01*	0.99 (0.43–2.25)	.97
Extent of tumor										
Localized	3712	93.5	Reference		—		Reference		Reference	
Further extension	256	6.5	1.05 (0.79–1.41)	.72	—	—	5.51 (2.76–11.01)	<.01*	2.62 (1.22–5.61)	.01*
LN involvement										
No involvement	3671	92.5	Reference		Reference		Reference		Reference	
Lymph node involvement	297	7.5	1.63 (1.15–2.27)	<.01*	1.65 (1.18–2.32)		6.18 (2.77–15.45)	<.01*	5.35 (1.24–9.80)	<.01*
M stage										
M0	3948	99.5	Reference		Reference		Reference		Reference	
M1	20	0.5	2.69 (1.34–5.40)	<.01*	1.75 (0.85–3.60)	.13	19.11 (5.90–61.97)	<.01*	7.56 (2.11–27.06)	<.01*

CI=confidence interval, HR=hazard ratio, IT=indicates isthmectomy, LE=local excision, LN=lymph nodes, LT=lobectomy, PTMC=papillary thyroid microcarcinoma, STT=subtotal thyroidectomy, TT=total thyroidectomy. *P* (univariate and multivariate analysis) indicates that the *P* value was analyzed via Cox proportional hazards regression models.

* $P=.05$ (2-tailed).

Table 3

Risk factors associated with cervical lymph node metastasis.

	Multivariate analysis	
Risk factor	OR (95% CI)	*P*
Sex		
Male	Reference	
Female	0.35 (0.27–0.45)	<.01*
Tumor size		
≥7	Reference	
<7	0.71 (0.55–0.92)	<.01*
Extent of tumor		
Localized	Reference	
Capsular extension	1.83 (1.07–2.96)	.02*
Further extension	5.78 (4.15–8.00)	<.01*

95% CI=95% confidence interval; LN=lymph node; OR=odds ratio.

* $P<.05$ (2-tailed).

Moreover, Harrell's C index was used to determine the predictive accuracy of our system. The C index is 0.711, which is higher than the value of 0.7 expected for a system with accurate risk prediction. Last but not least, 205 elderly PTMC patients from our department, including 44 males and 161 females with 21.5% overall rate of nodal metastases, were retrospectively collected as an external validation set to test our model accuracy. As shown in Figure 3B, the calibration curve indicated that the discrimination accuracy of the model is good.

4. Discussion

Unlike other tumors, age, to some extent, is the most important factor for PTC patient's clinicopathologic stage. According to American Joint Committee on Cancer (AJCC), 55 years' old has been set as one of the cutoff values for tumor stage. However, some researchers suggested age cut-off ranging from 40 to 70

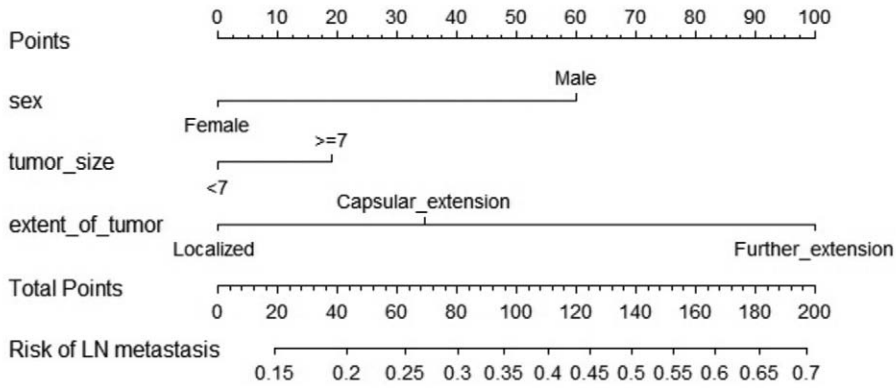

Figure 2. Nomogram for predicting cervical lymph node metastases in patients with elderly papillary thyroid microcarcinoma. Notes: All the points assigned on the top point scale for each factor are summed together to generate a total point score. The total point score is projected on the bottom scales to determine the probability of cancer metastasis in an individual.

years.[17,18] Given the relatively low life expectancy of elderly patients and excellent prognosis of PTMC, personalization of treatment strategy is of growing importance. In this study, we chose to use the age limit of 70 years as our major inclusion criteria. After extracting and screening data of PTMC patients from SEER database, 5165 individuals were accepted into our study. CSS was used as the major parameter for evaluating treatment strategies and other prognostic indexes.

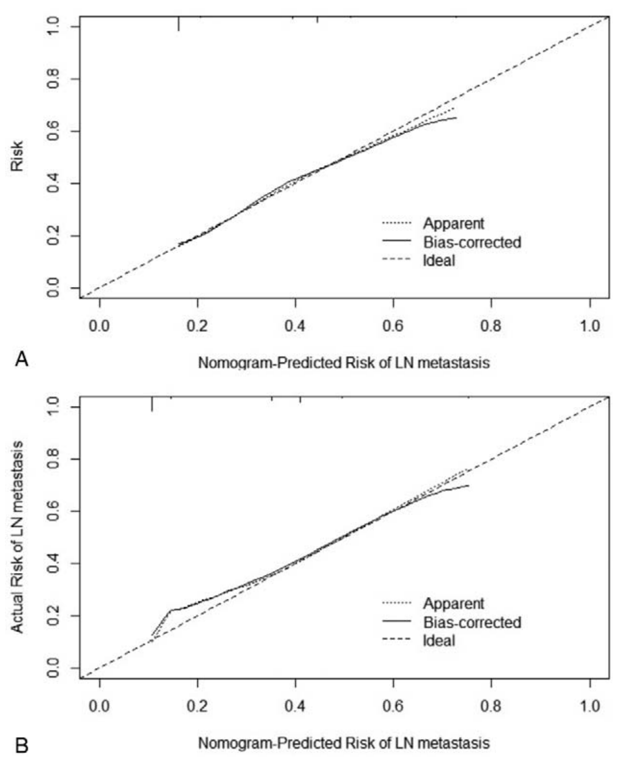

Figure 3. Calibration curves for predicting cervical lymph node metastases in the training set (A) and in the validation set (B) are shown. The predicted cervical lymph node metastasis (CLNM) risk (solid line) in both training set and validation set were closely associated with actual CLNM risk (dotted line), with which it was always within a 10% margin of error. Notes: The nomogram-predicted frequency of metastasis is plotted on the *x*-axis, and the actual observed frequency of metastasis is plotted on the *y*-axis.

Over the past few decades, the benefits of operation in elderly PTMC patients were controversial. Some authors suggested that PTMC can be safely treated with active surveillance, especially in elderly patients.[3,19] Some advocated that PTMC should be managed with less aggressive treatment.[20–22] According to our study, elderly PTMC patients who were initially treated with surgical approach had better OS and CSS compared with non-surgical patients. Meanwhile, total thyroidectomy does not offer any CSS advantage over localized surgery ($P=.1$), whereas their OS difference was significant ($P<.01$). Since SEER database does not provide co-morbidity information, the fitness of the patient for surgery, the available surgical expertise, and the patient's wishes should be taken into consideration when clinicians making surgical strategies. We should notice that for elderly patients with preexisting comorbiditie, reoperation may increase the probability of complications; therefore, total thyroidectomy should be considered initially.

Our study also identified some independent prognostic factors that were correlated with CSS in patients who received operation (including age, tumor extension, perioperative radiotherapy, lymph node involvement, and distant metastasis). Tumor size, race, sex, and marital status, however, were statistically insignificant. Our results were basically consistent with a previous study conducted by Wang et al.[23] They analyzed PTMC patients without age limitation based on SEER database. Sex was also associated with CSS in their study, indicating that PTMC patients older than 70 years may have special clinicopathologic features compared with the others. It is noteworthy that radiotherapy may have reverse effect on patient's survival. Vini et al [24] demonstrated that radioactive iodine ablation may not be effective in elderly patients for the capacity of tumor cells of iodine uptake is reduced. Our data confirmed their hypothesis; thereby the application of radiotherapy should be taken careful consideration among elderly PTMC patients.

On the basis of the survival analysis mentioned above, we decided to further explore risk factors that may associate with CLNM. It has been reported that the rate of CLNM varying from 30% to 70%.[22,25] In our cases, CLNM was detected in 34.3% of PTMC patients. Although CLND could significantly reduce the rate of local recurrence, the survival benefit continues to be debated for the lack of high-quality prospective evidence.[26] Zhang et al[27] showed that prophylactic CLND did not increase long-term postoperative complications in high-volume surgical units (defined as >30 thyroidectomies per year). Nevertheless, some experts considered that prophylactic CLND might increase the risk of permanent hypoparathyroidism and recurrent laryngeal nerve injury in low-volume centers if the procedure became an acceptable standard of care.

Since prophylactic management of lymph node is not routinely adopted in some therapeutic center and the drawbacks of preoperative imaging examination, we developed a nomogram tool to predict the risk of CLNM in clinical N0 PTMC patients. By using logistic regression analysis, we included sex, tumor size, and tumor extension into our model. We found that extrathyroidal spread was the strongest risk factor of CLNM. Unlike the other 2 factors (sex and tumor size), locoregional tumor invasion is hard to detect preoperatively in PTMC cases for the poor diagnostic sensitivity of ultrasound. We only chose clinicopathological parameters as risk factors that are readily available in daily clinical practice. Fundamental factors, such as tumor biomarkers,[28] immunohistochemical staining patterns of fine-needle aspiration samples may be involved in future practice when they are widely applied.

The accuracy of our nomogram prediction scheme was validated based on C-index and calibration curves in both a training cohort (internally) and a validation cohort (externally). Our model demonstrated good discrimination with a favorable C-index (0.711). The calibration curve in both the training and verification cohorts are close to 45-degree line, indicating acceptable agreement between predicted and actual probability of CLNM.

Certain limitations should be noticed when we interpret the results. First, the SEER database has some inherent limitations (For instance, coding errors, lack of information on perioperative examination outcomes, and disease recurrence). Second, exclusion of cases without complete information brings about selection bias inevitably. Finally, genetic information was not included in our nomogram model, which may elevate prediction accuracy.

5. Conclusions

According to our study, elderly PTMC patients who received a surgical approach without radiotherapy showed survival advantage than those with other treatment strategies. Additionally, we developed a nomogram model that could be used to predict patient risk on CLNM. By analyzing the external cohort validation, we concluded that our nomogram performs well with high accuracy and reliability. It may provide clinicians with reference information on surgical decision making in the management of PTMC.

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Author contributions

Conceptualization: Wenhan Li, Yongheng Wang.
Data curation: Yongheng Wang.
Formal analysis: Yao Tang, Danfang Wang, Yongheng Wang.
Methodology: Jianhui Li, Danfang Wang.
Project administration: Wenhan Li.
Software: Jianhui Li.
Supervision: Jianhui Li, Yongheng Wang.
Validation: Wei Han.
Writing – original draft: Wenhan Li, Yongheng Wang.
Writing – review & editing: Wenhan Li, Yao Tang, Jianhui Li, Wei Han, Yongheng Wang.

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