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

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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. 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. 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. Others, however, advocated performing thyroidectomy appears to provide a survival benefit in those patients. 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). The cause of this phenomenon may due to the histologic subtype of PTC cells in elderly individuals are usually more aggressive...
than that of young PTC patients (more proportion of columnar cells, diffused sclerosing, or even tall cell variant). \cite{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. \cite{11,12} Studies have shown that approximately 30%–70% of PTMC patients have cervical lymph node metastasis at diagnosis. \cite{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. \cite{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 elderly PTMC patients who have received surgical treatment between 2010 and 2018 in 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 the multivariate Cox regression models. Binary logistic regression model was used to select independent risk factors in CLNM prediction. 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. \cite{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 isthmeectomy) 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 \( P < .01 \)), tumor extension (\( P < .01 \)), 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).
### Table 1
Prognostic variables for overall survival and cancer-specific survival in elderly PTMC patients.

|                      | All patients (n = 5165) | Overall survival | Cancer-specific survival |
|----------------------|--------------------------|------------------|-------------------------|
|                      | N                        | Univariate analysis | Multivariate analysis | Univariate analysis | Multivariate analysis |
| Age at diagnosis, y  |                          |                  |                         |                  |                         |
| 70–74                | 2676                     | 51.8             | 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                | 597                      | 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               |
| 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.

|                      | Overall survival |          |          |          | Cancer-specific survival |          |          |
|----------------------|------------------|----------|----------|----------|--------------------------|----------|----------|
|                      | Patients (n = 3968) |          |          |          |                          |          |          |
|                      | N                | Percentage (%) | 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 |
| 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 |
| 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 |
| Race                 |                  |          |          |          |                          |          |          |
| White                | 3477             | 87.6     | Reference | Reference |                          | Reference | Reference |
| Black                | 239              | 6.0      | 1.26 (0.95–1.66) | .11 | 1.29 (0.97–1.71) | .08 | 0.44 (0.06–1.18) | .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 | 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 | 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 | 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 | Reference |
| No                   | 3244             | 81.8     | 0.98 (0.82–1.17) | .84 | — | — | Reference |
| Tumor size           |                  |          |          |          |                          |          |          |
| ≥7                   | 1345             | 33.9     | Reference | Reference |                          | Reference | Reference |
| <7                   | 2623             | 66.1     | 0.93 (0.80–1.08) | .34 | — | — | Reference |
| LN retrieved         |                  |          |          |          |                          |          |          |
| Yes                  | 1162             | 29.3     | Reference | Reference |                          | Reference | Reference |
| No                   | 2806             | 70.7     | 0.96 (0.81–1.12) | .59 | — | — | 2.45 (1.33–4.5) | <.01* |
| Extent of tumor      |                  |          |          |          |                          |          |          |
| Localized            | 3712             | 93.5     | Reference | Reference |                          | Reference | Reference |
| Further extension    | 256              | 6.5      | 1.05 (0.79–1.41) | .72 | — | — | 5.51 (2.76–11.01) | <.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) | <.01* | 6.18 (2.77–15.45) | <.01* |
| M stage              |                  |          |          |          |                          |          |          |
| MO                   | 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* |

Cl = 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).

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

Table 3

Risk factors associated with cervical lymph node metastasis.

| 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  |   |
| Further extension           | 1.83 (1.07–2.96) | .02* |
| Capsular extension          | 5.78 (4.15–8.00) | <.01* |

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

* P < .05 (2-tailed).
years.\cite{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.

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.\cite{3,19} Some advocated that PTMC should be managed with less aggressive treatment.\cite{20–22} According to our study, elderly PTMC patients who were initially treated with surgical approach had better OS and CSS compared with nonsurgical 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 comorbidity, 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.\cite{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.\cite{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%.\cite{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.\cite{26} Zhang et al.\cite{27} showed that prophylactic CLND did not increase

![Figure 2](image_url)

**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.

![Figure 3](image_url)

**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.
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 extra-thyroidal 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 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.

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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References

[1] McLeod DS, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. Lancet (London, England) 2013;381:1046–57.
[2] Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. JAMA 2006;295:2164–7.
[3] Ito Y, Miyauchi A, Kihara M, et al. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid 2014;24:27–34.
[4] Ito Y, Miyauchi A, Inoue H, et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World Journal of Surgery 2010;34:28–35. doi:10.1007/s00268-009-0303-0.
[5] Oda H, Miyauchi A, Ito Y, et al. Incidences of unfavorable events in the management of low-risk papillary microcarcinoma of the thyroid by active surveillance versus immediate surgery. Thyroid 2016;26:150–5.
[6] Ito Y, Miyauchi A, Kihara M, et al. Relationship between prognosis of papillary thyroid carcinoma patient and age: a retrospective single-institution study. Endocrine J 2012;59:399–405.
[7] Anderson KL, Jr, Youngwirth LM, Scheri RP, et al. T1a versus T1b differentiated thyroid cancers: do we need to make the distinction? Thyroid 2016;26:1046–52.
[8] Wang LY, Nixon JJ, Palmer FL, et al. Comparable outcomes for patients with pT1a and pT1b differentiated thyroid cancer: Is there a need for change in the AJCC classification system? Surgery 2014;156:1484–9. discussion 1489–1490. doi:10.1016/j.surg.2014.08.037.
[9] Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050–7. discussion 1057-1058.
[10] Kazaure HS, Roman SA, Sosa JA. Aggressive variants of papillary thyroid cancer: incidence, characteristics and predictors of survival among 43,738 patients. Ann Surg Oncol 2012;19:1874–80.
[11] Lundgren CI, Hall P, Dickman PW, et al. Clinically significant prognostic factors for differentiated thyroid carcinoma: a population-based, nested case-control study. Cancer 2006;106:524–31.
[12] Gemsenjäger E, Perren A, Seifert B, et al. Lymph node surgery in papillary thyroid carcinoma. J Am Coll Surg 2003;197:182–90.
[13] Bernet V. Approach to the patient with incidental papillary microcarcinoma. J Clin Endocrinol Metab 2010;95:3586–92. doi:10.1210/jc.2010-0698.
[14] Ahn JE, Lee JH, Yi JS, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World J Surg 2008;32:1552–8.
[15] Hveng HS, Orloff LA. Efficacy of preoperative neck ultrasound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope 2011;121:487–91.
[16] Kramer AA, Zimmerman JE. Assessing the calibration of mortality benchmarks in critical care: The Hosmer-Lemeshow test revisited. Crit Care Med 2007;35:2052–6.
[17] Amphlett B, Lawson Z, Abdulrahman GO Jr, et al. Recent trends in the incidence, geographical distribution, and survival from thyroid cancer in Wales, 1985-2010. Thyroid 2013;23:1470–8.
[18] Banerjee M, Muenz DG, Chang JT, et al. Tree-based model for thyroid cancer prognostication. J Clin Endocrinol Metab 2014;99:3737–45.
[19] Megwali UC. Observation versus thyroidectomy for papillary thyroid microcarcinoma. J Laryngol Otol 2017;131:173–6.
[20] Liu Z, Huang T. Papillary thyroid microcarcinoma: an over-treated malignancy? World J Surg 2016;40:764–5.
[21] Lin HW, Bhattacharyya N. Survival impact of treatment options for papillary microcarcinoma of the thyroid. Laryngoscope 2009;119:1983–7.
[22] Wang X, Lei J, Wei T, et al. Clinicopathological characteristics and recurrence risk of papillary thyroid microcarcinoma in the elderly. Cancer management and research 2019;11:2371–7.
[23] Wang K, Xu J, Li S, et al. Population-based study evaluating and predicting the probability of death resulting from thyroid cancer among patients with papillary thyroid microcarcinoma. Cancer Med 2019;8:6977–85.

[24] Vini L, Hyer SL, Marshall J, et al. Long-term results in elderly patients with differentiated thyroid carcinoma. Cancer 2003;97:2736–42.

[25] Qu N, Zhang L, Ji QH, et al. Risk factors for central compartment lymph node metastasis in papillary thyroid microcarcinoma: a meta-analysis. World J Surg 2015;39:2459–70. doi:10.1007/s00268-015-3108-3.

[26] Thompson AM, Turner RM, Hayen A, et al. A preoperative nomogram for the prediction of ipsilateral central compartment lymph node metastases in papillary thyroid cancer. Thyroid 2014;24:675–82.

[27] Zhang L, Liu Z, Liu Y, et al. The clinical prognosis of patients with cN0 papillary thyroid microcarcinoma by central neck dissection. World J Surg Oncol 2015;13:138.

[28] Boufraqech M, Klabo-Gwiedzinska J, Kebebew E. MicroRNAs in the thyroid. Best Pract Res Clin Endocrinol Metab 2016;30:603–19.