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Research article

Development and validation of a nomogram to predict cancer-specific survival in middle-aged patients with papillary thyroid cancer: A SEER database study

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ABSTRACT

Background: Thyroid cancer (TC) accounts for more than 90% of endocrine tumours and is a typical head and neck tumour in adults. The aim of this study was to develop a predictive tool to predict cancer-specific survival (CSS) in middle-aged patients with papillary thyroid carcinoma (PTC).

Methods: The patients from 2004 to 2015 were randomly divided into a training cohort (n = 25,342) and a internal validation cohort (n = 10,725). The patients from 2016 to 2018 were treated as an external validation cohort (n = 11353). COX proportional hazard model was used to screen meaningful independent risk factors. These factors were constructed into a nomogram to predict CSS in middle-aged patients with PTC. The performance and accuracy of the nomogram were then evaluated using the concordance index (C-index), calibration curve and the area under the curve (AUC). The clinical value of nomogram was evaluated by decision curve analysis (DCA).

Results: Age, gender, marriage, tumour grade, T stage, N stage, M stage, surgery, chemotherapy, and tumour size were independent prognostic factors. The C-indexes of the training, internal validation, and external validation cohorts were 0.906, 0.887, and 0.962, respectively. The AUC and calibration curves show good accuracy. DCA shows that the clinical value of the nomogram is higher than that of Tumour, Node and Metastasis (TNM) staging.

Conclusion: We developed a new prediction tool to predict CSS in middle-aged patients with PTC. The model has good performance after internal and external validation, which can be friendly to help doctors and patients predict CSS.

Abbreviations: TC, thyroid cancer; CSS, cancer-specific survival; PTC, papillary thyroid carcinoma; AUC, area under the curve; DCA, decision curve analysis.

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1. Introduction

Thyroid cancer (TC) accounts for more than 90% of endocrine tumours and is a common head and neck tumour that occurs in adults [1]. Over the past three decades, the global incidence of thyroid cancer has tripled and is still increasing at a rate of 3.6% per year, and the mortality rate is also steadily increasing at a rate of 1.1% per year [2]. According to histological type, it is divided into papillary thyroid cancer (PTC), anaplastic thyroid cancer, follicular thyroid cancer (FTC) and medullary thyroid cancer [3]. PTC and FTC are classified as well-differentiated thyroid cancer (DTC) because of their high degree of differentiation and good prognosis. DTC accounts for about 95% of TC, while PTC accounts for 85%–90% of DTC [4]. TC has been the fastest-growing malignancy in the United States in the past few decades, and the growth of PTC determines the overall trend of TC morbidity and mortality [5]. Although the significant increase in the number of diagnoses of TC is related to the advancement of imaging equipment, such as colour Doppler ultrasonography, it is also related to the overdiagnosis of indolent and small cancers [6]. However, studies have also shown a potentially real increase in the incidence of TC, given the increased incidence of advanced disease and increased incidence-based mortality [7,8].

The prognosis of PTC is generally good, with a 10-year survival rate of 80%–95% [9]. However, middle-aged PTC is prone to local lymphatic metastasis and distant metastasis. Among them, it is associated with poor prognosis [10]. A study has shown that patients with distant metastatic PTC have a 10-year survival rate of 25%–70% [11]. In addition, the poor prognosis of PTC is also related to some variant subtypes. First, some variants of PTC, such as diffuse sclerosis, columnar cell and insular cell differentiation, usually exhibit varying degrees of invasive behaviour [12]. Second, another group of variants of PTC, such as trabecular, oncocytic, solid, microfollicular, and clear cell, all have a more malignant phenotype than conventional PTC, predicting a worse prognosis [13,14]. Because the prognosis of PTC varies greatly, while the prognosis of most patients is good, the outcomes of distant metastasis, recurrence and even death cannot be ignored [15]. The expected remaining life of middle-aged patients is between 30 and 40 years or even longer. In recent years, quality of life and the psychological burden has become the biggest problems middle-aged PTC patients face [16]. Therefore, it is important to accurately predict the survival of middle-aged PTC patients, including cancer-specific survival (CSS).

Traditionally, Tumour, Node and Metastasis (TNM) staging is the main standard for judging the prognosis of cancer patients. However, TNM staging lacks sufficient biological characteristics of malignant tumours [17]. At present, nomogram has gradually replaced the traditional TNM staging, which contains many non-anatomical factors to achieve more accurate prognostic prediction [18]. Today, many prediction models have been established and applied to TC, but mainly for poor prognostic histological types such as ATC and MTC. The study population is also dominated by middle-aged and children [19–21]. However, for the middle-aged group with the highest incidence of PTC and long life expectancy, there is still no effective and reliable nomogram to predict prognosis.

In this study, we collected patients information in the Surveillance, Epidemiology, and End Results (SEER) database and developed a prediction tool to predict CSS in PTC patients. It can effectively reduce the anxiety of patients and provide help for clinicians to formulate individualized treatment plans while making up for relevant research gaps.

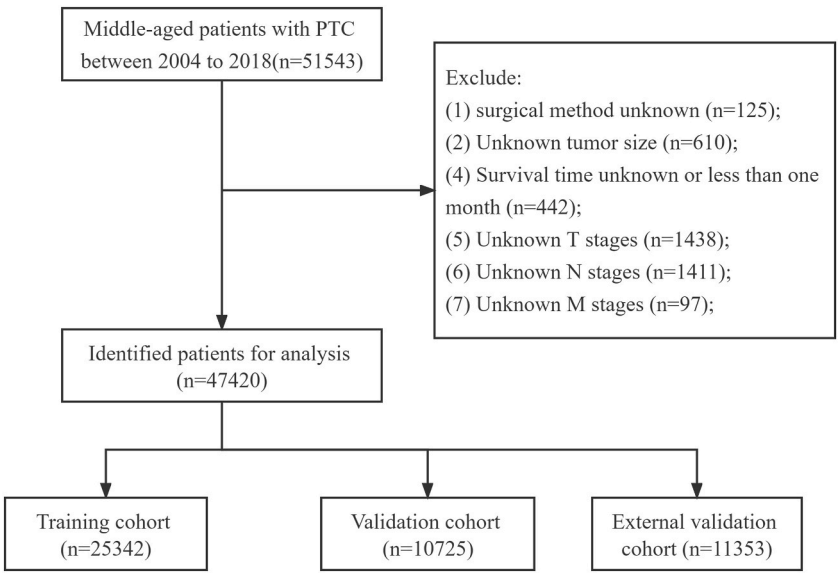

Fig. 1. Inclusion and exclusion of patient flow chart.

2. Methods

2.1. Data source and data extraction

Using the SEER database, we conducted a population-based retrospective cohort study. All data in this study were collected from the SEER database, and all case data were extracted using the SEER*Stat (version 8.3.5) tool released on March 6, 2018. Extracted information such as age, gender, race, marriage, year of diagnosis, tumour grade, TNM stage, tumour size, surgery, chemotherapy, radiotherapy, and survival time.

Inclusion criteria: (1) 40–64 years old; (2) Histological classification: papillary thyroid cancer. Exclusion criteria: (1) Unknown surgical method; (2) Unknown tumour size; (3) Unknown survival time or less than one month; (4) Unknown T stage; (5) Unknown N stage; (6) Unknown M stage. The patient inclusion and exclusion flow chart is shown in Fig. 1.

All included patients were between 40 and 64 years old. The race had black, white and other. marriage was divided into unmarried and married. Tumour grades include I-IV (Well differentiated, moderately differentiated, poorly differentiated, undifferentiated), unknown. T stage provides T1, T2, T3, and T4. M stage includes M0 and M1. Surgery was divided into Lobectomy, Subtotal or near-total thyroidectomy, and Total thyroidectomy.

Table 1
Clinicopathological characteristics of middle-aged patients with PTC.

	All	Training cohort	validation cohort	p
	N = 36067	N = 25342	N = 10725	
Age	51.7 (7.14)	51.7 (7.12)	51.8 (7.20)	0.418
Race				0.109
White	29358 (81.4%)	20675 (81.6%)	8683 (81.0%)	
Black	2046 (5.67%)	1396 (5.51%)	650 (6.06%)	
Other	4663 (12.9%)	3271 (12.9%)	1392 (13.0%)	
Sex				0.564
Male	8713 (24.2%)	6144 (24.2%)	2569 (24.0%)	
Female	27354 (75.8%)	19198 (75.8%)	8156 (76.0%)	
Marital				0.939
No	11173 (31.0%)	7847 (31.0%)	3326 (31.0%)	
Married	24894 (69.0%)	17495 (69.0%)	7399 (69.0%)	
Year of diagnosis				0.002
2004–2009	14761 (40.9%)	10505 (41.5%)	4256 (39.7%)	
2010–2015	21306 (59.1%)	14837 (58.5%)	6469 (60.3%)	
Grade				0.731
I	6321 (17.5%)	4445 (17.5%)	1876 (17.5%)	
II	1179 (3.27%)	830 (3.28%)	349 (3.25%)	
III	214 (0.59%)	152 (0.60%)	62 (0.58%)	
IV	68 (0.19%)	53 (0.21%)	15 (0.14%)	
Unknown	28285 (78.4%)	19862 (78.4%)	8423 (78.5%)	
T				0.278
T1	23662 (65.6%)	16582 (65.4%)	7080 (66.0%)	
T2	4391 (12.2%)	3126 (12.3%)	1265 (11.8%)	
T3	6799 (18.9%)	4761 (18.8%)	2038 (19.0%)	
T4	1215 (3.37%)	873 (3.44%)	342 (3.19%)	
N				0.513
N0	27504 (76.3%)	19290 (76.1%)	8214 (76.6%)	
N1a	5360 (14.9%)	3775 (14.9%)	1585 (14.8%)	
N1b	3203 (8.88%)	2277 (8.99%)	926 (8.63%)	
M				0.079
M0	35792 (99.2%)	25135 (99.2%)	10657 (99.4%)	
M1	275 (0.76%)	207 (0.82%)	68 (0.63%)	
Tumour size	15.6 (15.4)	15.6 (15.4)	15.6 (15.4)	0.731
Surgery				0.988
No	539 (1.49%)	379 (1.50%)	160 (1.49%)	
Lobectomy	3954 (11.0%)	2773 (10.9%)	1181 (11.0%)	
Subtotal or near total thyroidectomy	1329 (3.68%)	929 (3.67%)	400 (3.73%)	
Total thyroidectomy	30245 (83.9%)	21261 (83.9%)	8984 (83.8%)	
Chemotherapy				0.459
No/Unknown	35931 (99.6%)	25242 (99.6%)	10689 (99.7%)	
Yes	136 (0.38%)	100 (0.39%)	36 (0.34%)	
Radiation				1.000
No/Unknown	18074 (50.1%)	12699 (50.1%)	5375 (50.1%)	
Yes	17993 (49.9%)	12643 (49.9%)	5350 (49.9%)	
Survival months	92.1 (41.8)	92.4 (42.0)	91.6 (41.5)	0.114

2.2. Development and validation of the nomogram

Patients were randomly divided into a training and a validation cohorts at a ratio of 7 : 3. COX regression analysis was used to screen meaningful independent prognostic factors. A nomogram was constructed to predict 3-, 5-, and 10-year CSS in middle-aged patients with PTC. The concordance index (C-index), calibration curve and AUC were then used to evaluate the discrimination and accuracy of the nomogram. The calibration curve compares the survival outcome predicted by the nomogram with the actual observed survival outcome. The calibration curve along the 45-degree line shows a very good agreement between the prediction value and the actual observation value.

2.3. Clinical utility

The clinical value of nomogram was evaluated by decision curve analysis (DCA). Based on the score of each patient, the patients were divided into a high-risk group and a low-risk group, K-M curve was used to describe the survival curve of the two groups, and the log-rank test was used to compare the CSS difference between the two groups. Finally, the log-rank test was used to compare the effect of different surgical methods on CSS in patients.

Table 2
Univariate and multivariate analyses of CSS in training cohort.

	Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P
Age	1.11	1.09–1.13	<0.001	1.085	1.067–1.102	<0.001
Race						
White	reference					
Black	0.93	0.57–1.52	0.772			
Other	0.97	0.7–1.34	0.844			
Sex						
Male	reference			reference		
Female	0.28	0.23–0.35	<0.001	0.575	0.457–0.724	<0.001
Marriage						
No	reference			reference		
Married	0.73	0.59–0.91	0.005	0.664	0.53–0.831	<0.001
Year of diagnosis						
2004–2010	reference					
2010–2018	0.89	0.7–1.13	0.333			
Grade						
I	reference			reference		
II	1.48	0.76–2.88	0.251	1.011	0.516–1.98	0.974
III	22.04	13.6–35.73	<0.001	3.944	2.331–6.672	<0.001
IV	99	60.72–161.43	<0.001	5.922	3.26–10.759	<0.001
Unknown	1.19	0.85–1.67	0.303	0.999	0.71–1.403	0.993
T						
T1	reference			reference		
T2	3.16	2.11–4.72	<0.001	2.524	1.674–3.803	<0.001
T3	5.85	4.28–8.01	<0.001	3.529	2.52–4.943	<0.001
T4	42.68	31.64–57.56	<0.001	8.73	5.971–12.762	<0.001
N						
N0	reference			reference		
N1a	3.15	2.36–4.22	<0.001	2.149	1.576–2.931	<0.001
N1b	10.95	8.6–13.93	<0.001	3.514	2.616–4.722	<0.001
M						
M0	reference			reference		
M1	41.46	31.66–54.3	<0.001	4.454	3.193–6.212	<0.001
Tumour size	1.01	1.01–1.01	<0.001	1.007	1.005–1.008	<0.001
Surgery						
No	reference			reference		
Lobectomy	0.13	0.08–0.22	<0.001	0.607	0.357–1.032	0.065
Subtotal or near total thyroidectomy	0.13	0.07–0.25	<0.001	0.346	0.175–0.685	0.002
Total thyroidectomy	0.13	0.09–0.2	<0.001	0.279	0.18–0.43	<0.001
Chemotherapy						
No/Unknown	reference			reference		
Yes	38.28	26.85–54.58	<0.001	1.698	1.042–2.767	0.033
Radiation						
No/Unknown	reference					
Yes	2.26	1.79–2.86	<0.001			

2.4. Statistical analysis

The SPSS statistical software was used for all statistical analysis, survival curves were drawn by the Kaplan-Meier method, and a Log-rank test was performed. Univariate and multivariate COX regression analysis was used to screen meaningful independent prognostic factors. R software (R 4.1.0) was used to calculate the C-index, draw calibration curve, AUC, and DCA. $P < 0.05$ indicated that the difference was statistically significant.

3. Result

3.1. Clinical features

A total of 47420 middle-aged patients with PTC were included. The patients from 2004 to 2015 were randomly divided into training and internal validation cohorts. The patients from 2016 to 2018 were treated as an external validation cohort. In terms of race, 29,358 (81.4%) were white, accounting for the largest proportion; regarding gender, 27354 patients (75.8%) were female; 11173 patients (31.0%) were unmarried, and 24894 patients (69.0%) were married. The year of diagnosis was divided into two groups, 14161 patients (40.9%) in the 2004–2009 group and 21306 patients (59.1%) from 2010 to 2015. The tumour grades of patients were I, II, III, IV and unknown, and the respective numbers and proportions were 6321 (17.5%), 1179 (3.27%), 214 (0.59%), 68 (0.19%), and 28285 (78.4%). Five hundred thirty-nine patients without surgery (1.49%), 3954 (11.0%) patients with lobectomy, 1329 (3.68%) patients with subtotal or near-total thyroidectomy, and 30245 (83.9%) patients with total thyroidectomy. There was no significant difference in clinical characteristics between the training and the internal validation cohorts (Table 1).

3.2. COX regression analysis

Age, gender, marriage, tumour grade, TNM stage, surgery, radiotherapy, chemotherapy, and tumour size were significantly associated with CSS in middle-aged patients with PTC ($P < 0.05$). Multivariate COX regression analysis showed that age, gender, marriage, tumour grade, T stage, N stage, M stage, surgery, chemotherapy and tumour size were independent prognostic factors affecting CSS ($P < 0.05$) (Table 2).

3.3. Construction and validation of the nomogram

Through COX regression analysis, age, gender, marriage, tumour grade, TNM stage, surgery, chemotherapy, and tumour size were

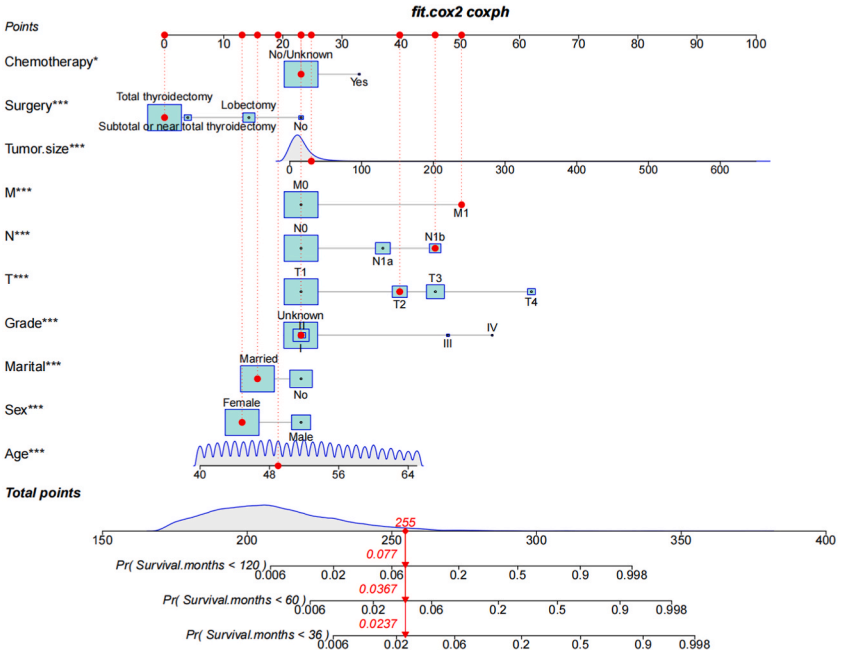

Fig. 2. The nomogram of CSS in middle-aged patients with PTC at 3-, 5-, and 10-year. Red dots show the clinicopathological parameters of a patient (Age: 50; sex: female; marriage: married; grade: II; T stage: T2; N stage: N1b; M stage: M1; tumour size: 21 cm; surgical method: total thyroidectomy; chemotherapy: No). The first line shows the scores corresponding to each parameter, and the sum of the scores of all parameters is the total score (255) of the patient. The 3-, 5-, and 10-year mortality rates corresponding to the 255 scores were 2.37%, 3.67%, and 7.7%, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

identified as independent prognostic factors for CSS in middle-aged PTC patients. These ten variables were used to develop a prediction model that could predict and affect the CSS of middle-aged PTC (Fig. 2). The nomogram was then validated, and the C-index was 0.906 (0.897–0.915) for the training cohort, 0.887 (0.874–0.9) for the internal validation cohort, and 0.962 (0.951–0.973) for the external validation cohort. The calibration curve showed good agreement between the predicted value and the actual survival rate (Fig. 3(A and B)), which indicated that the nomogram we developed could more accurately predict CSS in middle-aged patients with PTC. The AUC and C-index results were consistent, showing that the nomogram had good discrimination (Fig. 4(A and B)).

With the help of our developed nomogram, the survival probability of middle-aged patients with PTC can be individually predicted. An example to illustrate the use of nomogram: as shown in Fig. 2, the red dots represent the clinicopathological parameters of a certain patient. All parameters correspond to a score, and the scores of all parameters add up to 255 points. The patient's risk score was 225, and the corresponding 3-, 5-, and 10-year mortality rates were 2.37%, 3.67%, and 7.7%, respectively.

3.4. Clinical utility

The DCA results show that the model has a good net benefit compared with the TNM staging model (Fig. 5(A and B)), which confirms that the prediction tool can predict the survival prognosis of middle-aged PTC patients. In the external validation cohort, DCA suggests that the prediction tool has potential clinical value (Fig. 6(A and B)). At the same time, patients were divided into a low-risk group (total score $\leq$27.2) and a high-risk group (total score $>$27.2) based on their scores in the nomogram. The K-M curve shows significant CSS differences among risk groups (Fig. 7(A and B)). In the low-risk group, there was no significant difference in the effect of the surgical method on CSS. However, in the high-risk group, the CSS of patients undergoing surgery was higher than that of patients without surgery. (Fig. 8(A and B)).

4. Discussion

Here, we developed a new prediction tool to predict CSS in middle-aged PTC patients. Our study found that age, gender, marriage, TNM stage, tumour size, grade, surgery, and chemotherapy were independent risk factors. Age is a key factor in the death of PTC patients. The risk of cancer gene mutations increases with age. The high prevalence of malignant tumours in elderly patients is associated with changes in DNA methylation, and this mutation is usually considered to be the first step in cancer development [22]. Escudier et al. [23] found that age is a factor affecting the survival of patients and is more important than pathological grade and distant metastasis. After analyzing DTC patients of different ages in Europe, Velsen et al. found that under the same TNM staging, different ages have very different accuracies [24]. Rossi et al. investigated the population and found that with increasing age, the subclinical variation rate of PTC also increased [25]. Ho AS et al. also came to the same conclusion after analyzing the TC patients and believed that the increase in age and tumour size led to a gradual increase in the mortality of non-surgical TC patients [26]. Studies have shown that thyroid cancer's overall survival (OS) begins to decline steadily from age 40 [27]. A German population-based study found a significant decrease in all-cause mortality in patients $>$60 years of age when DTC patients were compared with the general population [28]. In this study, we also found that age was an important factor in predicting patient prognosis in PTC patients aged 40–64 years, and the risk of cancer-specific death gradually increased with age.

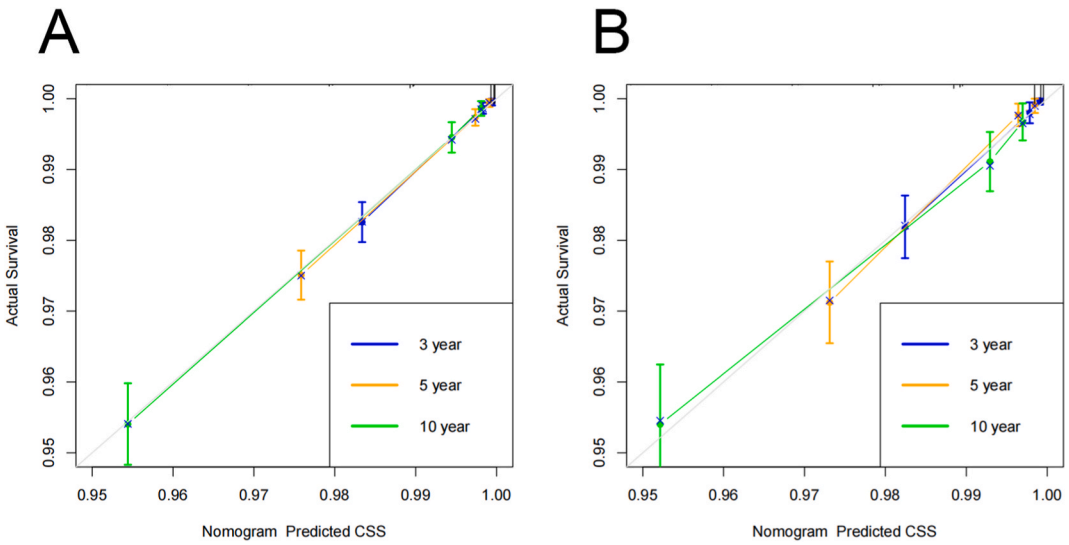

Fig. 3. Calibration curve for predicting patient survival. in the training cohort (A) and in the internal validation cohort. The X-axis represents the predicted value of the nomogram, and the Y-axis represents the actual value of the patient. The alignment of the calibration curve with the diagonal height suggests high prediction accuracy of the nomogram.

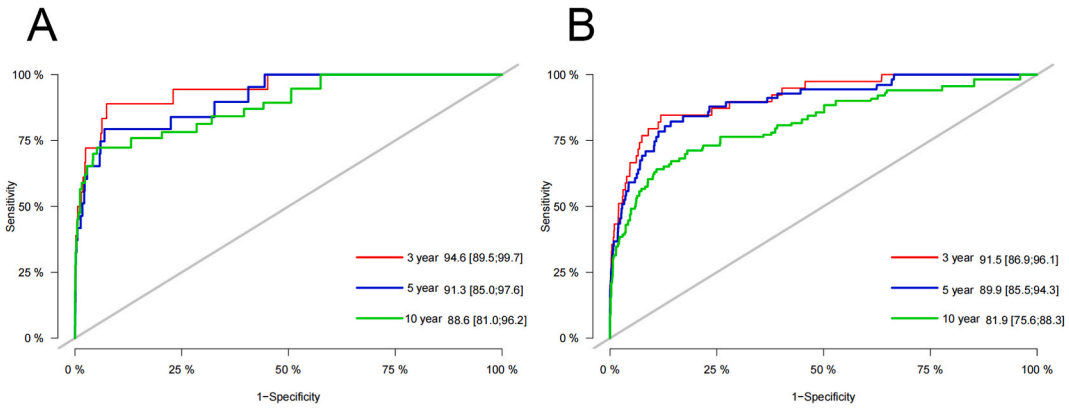

Fig. 4. The AUC value of the nomogram in the training cohort (A) and the internal validation cohort (B).

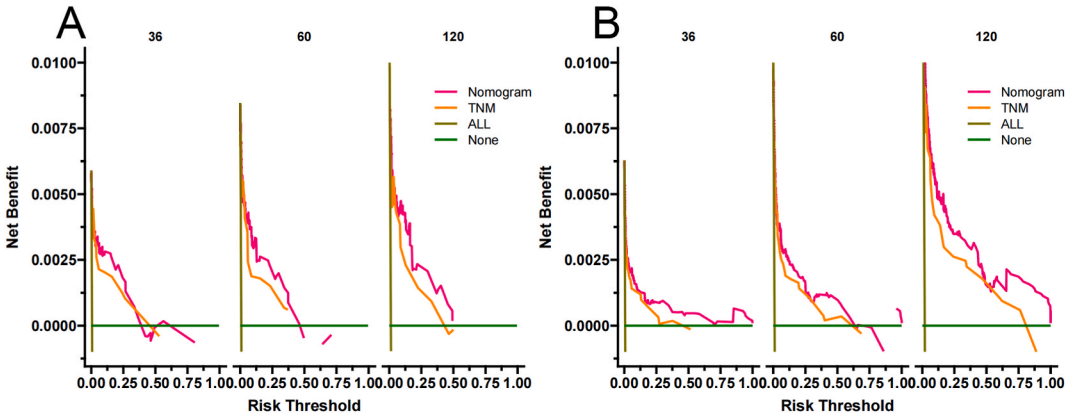

Fig. 5. The DCA of the prediction model in the training cohort (A) and the validation cohort (B).The x-axis represents the threshold of the model, and the y-axis represents the net benefit of the prediction model. The green line and the dark green line represent two extreme values, namely no patient death and all patient deaths. When the threshold is between 0% and 80%, the net benefit of the prediction model exceeds two extreme values. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

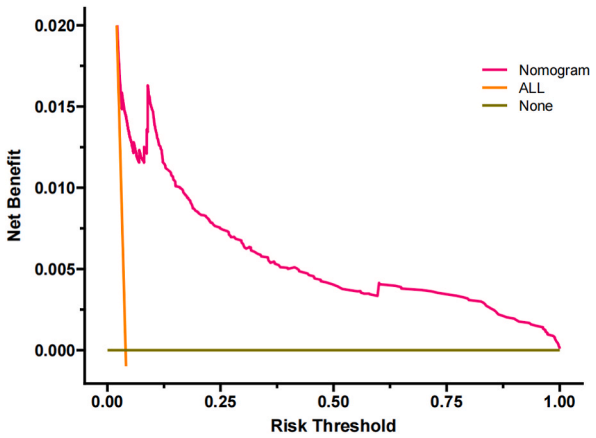

Fig. 6. DCA of the prediction model in the external validation cohort.

It is well known that tumour size has always been an important factor in the prognosis of TC. Through data analysis, Nguyen et al. concluded that increasing the size of the tumour threshold to 2.5 cm did not affect survival and recommended increasing the size of the thyroid biopsy [29]. Mao et al. applied a systematic review and meta-analysis to show that a tumour diameter greater than 1.0 cm is an

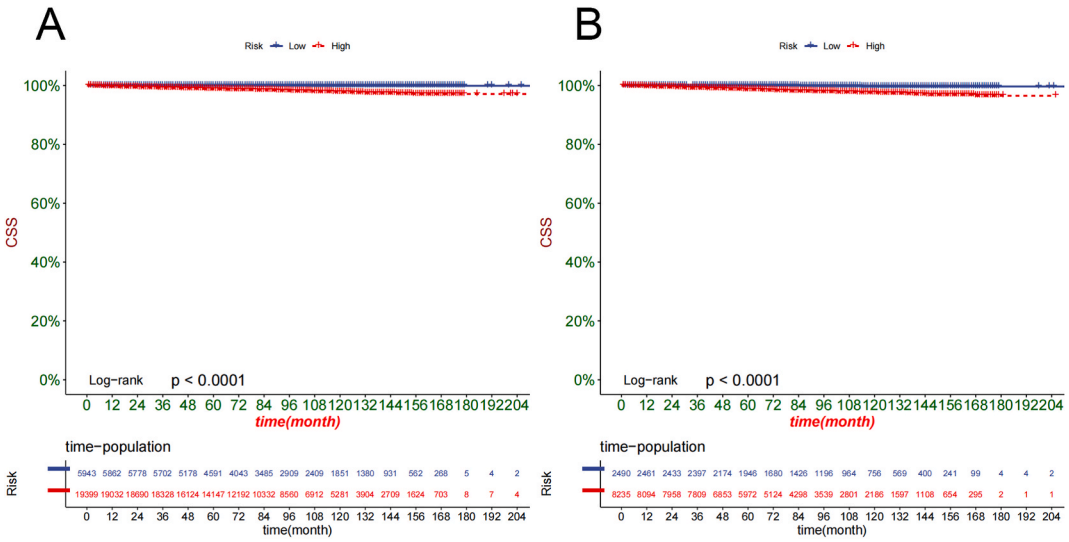

Fig. 7. The K-M curves of PTC patients in the training cohort (A) and the validation cohort (B) according to the risk grouping.

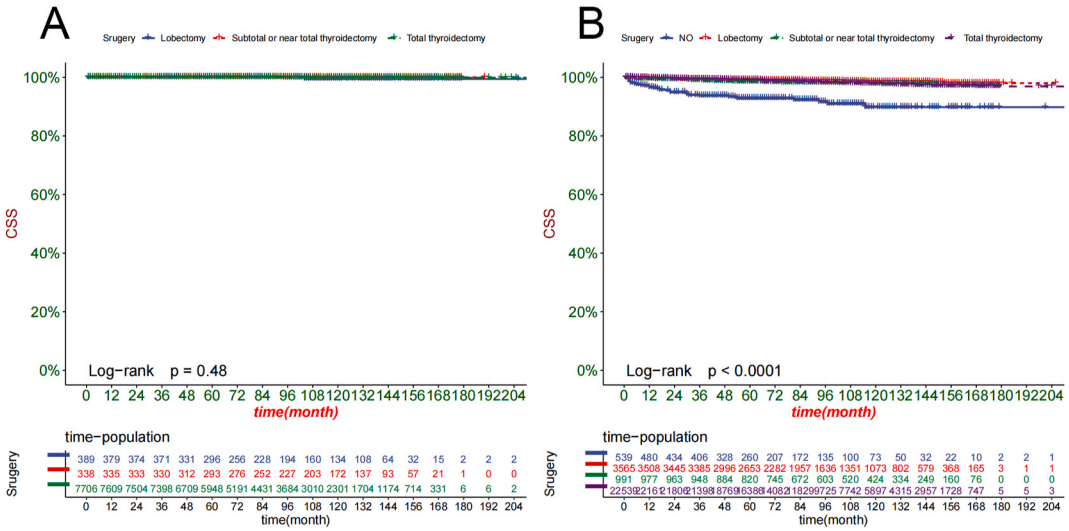

Fig. 8. K-M curves of patients in the low-risk group (A) and the high-risk group (B) underwent different surgical methods.

independent risk factor for increased lymph node metastasis and mortality in PTC [30]. Londero et al. conducted a nationwide prospective cohort study in Denmark and found that tumour size was a dual predictor of PTC mortality and recurrence, with an important role [31]. Adam et al. also demonstrated that patient age and tumour volume significantly correlated with mortality in PTC patients. More importantly, there was no clear cut-off point to distinguish differences in survival [32]. Our study showed that the tumour size of middle-aged PTC patients was mainly distributed within 10 mm, which is the definition of thyroid microcarcinoma. This is a controversial issue, and in the 2009 American Thyroid Association (ATA) guidelines, it is recommended that nodules smaller than 1 cm detected by ultrasonography should be confirmed by biopsy [33]. In the 2015 ATA guideline update, this threshold was raised, and it was recommended not to routinely perform needle biopsies in patients with thyroid nodules without obvious positive signs [34]. This update to this guideline avoids the overtreatment of many patients with early-stage PTC without increasing mortality. In this study, we found that the risk of death in patients increased with tumour size. For small tumours, especially those less than 1 cm, whether the treatment will affect the survival of patients remains to be further studied.

Gender differences play a decisive role in the endocrine system, and middle age is one of the periods when the secretion of endocrine hormones is most prosperous. Estrogen in women is thought to have an inhibitory effect on the development of TC. Studies have shown that thyroid cancer cells contain many estrogen receptors, possibly because estrogen can promote the release of thyroid-stimulating hormone (TSH) from the pituitary [35]. On the contrary, the secretion of androgens and testosterone in middle-aged men is strong. Thiruvengadam et al. used testosterone to intervene in female mice and showed that testosterone has a promoting effect on the

occurrence and development of thyroid cancer [36]. However, whether gender differences have a decisive impact on the prognosis of TC remains controversial. A Chinese study showed that among DTC subtypes with better prognosis, the incidence in women was three times higher than in men. However, in ATC and MTC with poor prognoses, the incidence is almost identical in males and females [37]. Several studies have found that in PTC, men's OS and CSS are significantly lower than women's, and gender is an important factor affecting the prognosis of PTC. Also, the tumour recurrence rate in men is 2.44 times higher than in women [38–40]. In contrast, Nilubol et al. collected information on TC patients from the SEER database from 1988 to 2007 for analysis and confirmed that gender is not an prognostic factor for TC [41]. Coincidentally, the study by Grogan et al. also reported similar results, arguing that there is no significant correlation between gender and the prognosis of patients with PTC [42]. This study found that gender was an independent risk factor for CSS in middle-aged PTC patients. It may be because middle-aged women have relatively high levels of estrogen, which stimulates the secretion of TSH in the body. Previous studies have confirmed that TSH can inhibit the occurrence and development of thyroid cancer [35], resulting in a protective effect on the thyroid. In addition, female patients accounted for a large proportion (75.8%) in this study, which may affect the results. Whether gender will affect the cancer-specific survival of middle-aged patients with PTC still needs to be confirmed by prospective controlled studies.

Interestingly, in our previous study, married patients had a significantly better prognosis among less malignant tumours [43,44]. We found in this study that marriage also has a certain predictive role in the prognosis of middle-aged PTC patients. Still, the difference is not as obvious as other tumours, such as renal cell carcinoma. The reason may be that environmental factors have a greater impact on thyroid cancer. For example, the incidence of TC in iodine-deficient countries and regions will increase significantly [1,2,4]. At the same time, Frich et al. found that the incidence of thyroid cancer in women was significantly higher when the spouses were agricultural, forestry and fishermen [45]. Brownlie et al. also confirmed that the assimilation of living habits increases the risk of thyroid disease shared by both spouses [46].

In this study, we found that the following parameters were independent risk factors affecting the CSS of patients: age, gender, tumour size, marriage, TNM stage, tumour grade, surgical method, and chemotherapy. As shown in Fig. 2, the patient received a score for each parameter, and the sum of the scores for all parameters corresponded to the patient's 3-, 5-, and 10-year mortality rates. This nomogram was verified by calibration curve, AUC and C-index, and proved to have good accuracy and discrimination. DCA display nomogram has higher clinical value than traditional TNM staging system. It shows that the nomogram we constructed can accurately and efficiently predict the survival of patients.

The current study has some limitations. First, we were limited by the SEER database, incomplete data collection (no important clinical information such as smoking, alcohol consumption, family history, weight and height, and data on medical comorbidities), and inconsistent tumour classification. In addition, this study was retrospective, and there may be unavoidable selection bias. However, we included key factors such as gender, age, marriage, and surgery, and the results would not be significantly biased. Finally, our model must be prospectively validated in a multicenter study to confirm its accuracy.

5. Conclusion

Our study found that age, gender, tumour size, marriage, TNM stage, tumour grade, surgical method, and chemotherapy were independent risk factors for CSS in middle-aged PTC patients. We developed a new prediction tool to predict CSS in middle-aged patients with PTC. After internal and external validation, the model has good performance, which can provide doctors with clinical decision-making help and provide consultation for patients.

Declaration

Authors' contributions

Conceived and designed the experiments: JT, HYT and CHZH; Performed the experiments: CHZH, JT, LL, YCX, and HYT; Analyzed and interpreted the data: JT, CHZH, KZ, CCW and BY; Contributed reagents, materials, analysis tools or data: CHZH, ZY and BY; Wrote the paper: JT and CHZH.

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Availability of data and materials

The SEER data analyzed in this study is available at https://seer.Cancer.gov/.

Ethics approval and consent to participate

The data of this study is obtained from the SEER database. The patients' data is public and anonymous, so this study does not require ethical approval and informed consent.

Consent for publication

None.

Competing interests

The authors declare that they have no competing interests.

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References

[1] U. Megwalu, P.K. Moon, Thyroid cancer incidence and mortality trends in the United States: 2000 - 2018, Thyroid (2022 Feb 8), https://doi.org/10.1089/thy.2021.0662. Epub ahead of print. PMID: 35132899.
[2] H. Lim, S.S. Devesa, J.A. Sosa, D. Check, C.M. Kitahara, Trends in thyroid cancer incidence and mortality in the United States, 1974-2013, JAMA 317 (13) (2017 Apr 4) 1338–1348, https://doi.org/10.1001/jama.2017.2719. PMID: 28362912; PMCID: PMC8216772.
[3] Z.W. Baloch, S.L. Asa, J.A. Barletta, et al., Overview of the 2022 WHO classification of thyroid neoplasms, Endocr. Pathol. 33 (1) (2022) 27–63, https://doi.org/10.1007/s12022-022-09707-3.
[4] L.G. Morris, A.G. Sikora, T.D. Tosteson, L. Davies, The increasing incidence of thyroid cancer: the influence of access to care, Thyroid 23 (7) (2013 Jul) 885–891, https://doi.org/10.1089/thy.2013.0045. Epub 2013 Apr 18. PMID: 23517343; PMCID: PMC3704124.
[5] S. Filetti, C. Durante, D. Hartl, S. Leboulleux, L.D. Locati, K. Newbold, M.G. Papotti, A. Berruti, ESMO Guidelines Committee, Electronic address: clinicalguidelines@esmo.org. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 30 (12) (2019 Dec 1) 1856–1883, https://doi.org/10.1093/annonc/mdz400. PMID: 31549998.
[6] L. Davies, H.G. Welch, Current thyroid cancer trends in the United States, JAMA Otolaryng. Head Neck Surg. 140 (4) (2014 Apr) 317–322, https://doi.org/10.1001/jamaoto.2014.1. PMID: 24557566.
[7] Z.J. Qian, M.C. Jin, K.D. Meister, U.C. Megwalu, Pediatric thyroid cancer incidence and mortality trends in the United States, 1973-2013, JAMA Otolaryng. Head Neck Surg. 145 (7) (2019 Jul 1) 617–623, https://doi.org/10.1001/jamaoto.2019.0898. PMID: 31120475; PMCID: PMC6547136.
[8] L.G. Morris, R.M. Tuttle, L. Davies, Changing trends in the incidence of thyroid cancer in the United States, JAMA Otolaryng. Head Neck Surg. 142 (7) (2016 Jul 1) 709–711, https://doi.org/10.1001/jamaoto.2016.0230. PMID: 27078686; PMCID: PMC4956490.
[9] J. Maciel, D. Cavaco, C. Silvestre, J. Simões Pereira, H. Vilar, V. Leite, Clinical outcomes of a cohort of 271 patients with lung metastases from differentiated thyroid carcinoma, Clin. Endocrinol. (2022 Feb 22), https://doi.org/10.1111/cen.14700. Epub ahead of print. PMID: 35192239.
[10] P. Lin, F. Liang, J. Ruan, P. Han, J. Liao, R. Chen, B. Luo, N. Ouyang, X. Huang, A preoperative nomogram for the prediction of high-volume central lymph node metastasis in papillary thyroid carcinoma, Front. Endocrinol. 12 (2021 Dec 22), 753678, https://doi.org/10.3389/fendo.2021.753678. PMID: 35002954; PMCID: PMC8729159.
[11] J. Jonklaas, N.J. Sarlis, D. Litofsky, K.B. Ain, S.T. Bigos, J.D. Brierley, D.S. Cooper, B.R. Haugen, P.W. Ladenson, J. Magner, J. Robbins, D.S. Ross, M. Skarulis, H. R. Maxon, S.I. Sherman, Outcomes of patients with differentiated thyroid carcinoma following initial therapy, Thyroid 16 (12) (2006 Dec) 1229–1242, https://doi.org/10.1089/thy.2006.16.1229. PMID: 17199433.
[12] H. Zhao, T. Huang, H. Li, Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer, Surgery 166 (1) (2019 Jul) 55–60, https://doi.org/10.1016/j.surg.2019.01.025. Epub 2019 Mar 12. PMID: 30876667.
[13] S. Roman, J.A. Sosa, Aggressive variants of papillary thyroid cancer, Curr. Opin. Oncol. 25 (1) (2013 Jan) 33–38, https://doi.org/10.1097/CCO.0b013e32835b7c6b. PMID: 23197194.
[14] R. Miftari, V. Topçiu, A. Nura, V. Haxhibeqiri, Management of the patient with aggressive and resistant papillary thyroid carcinoma, Med. Arch. 70 (4) (2016 Jul 27) 314–317, https://doi.org/10.5455/medarh.2016.70.314-317. PMID: 27703298; PMCID: PMC5034967.
[15] W. Dong, K. Horiuchi, H. Tokumitsu, A. Sakamoto, E. Noguchi, Y. Ueda, T. Okamoto, Time-varying pattern of mortality and recurrence from papillary thyroid cancer: lessons from a long-term follow-up, Thyroid 29 (6) (2019 Jun) 802–808, https://doi.org/10.1089/thy.2018.0128. Epub 2019 May 1. PMID: 30931815.
[16] C.A. Harms, L. Cohen, J.A. Pooley, S.K. Chambers, D.A. Galvão, R.U. Newton, Quality of life and psychological distress in cancer survivors: the role of psychosocial resources for resilience, Psycho Oncol. 28 (2) (2019 Feb) 271–277, https://doi.org/10.1002/pon.4934. Epub 2018 Dec 4. PMID: 30380589.
[17] Y.H. Park, S.J. Lee, E.Y. Cho, Y. La Choi, J.E. Lee, S.J. Nam, J.H. Yang, J.H. Shin, E.Y. Ko, B.K. Han, J.S. Ahn, Y.H. Im, Clinical relevance of TNM staging system according to breast cancer subtypes, 2011, Ann. Oncol. 30 (12) (2019 Dec 1), https://doi.org/10.1093/annonc/mdz223. Erratum for: Ann Oncol. 2011 Jul;22 (7):1554-1560. PMID: 31408085.
[18] G.N. Hortobagyi, S.B. Edge, A. Giuliano, New and important changes in the TNM staging system for breast cancer, Am. Soc. Clin. Oncol. Educ. Book 38 (2018 May 23) 457–467, https://doi.org/10.1200/EDBK_201313. PMID: 30231399.
[19] A.S. Ho, L. Wang, F.L. Palmer, C. Yu, A. Toset, S. Patel, M.W. Kattan, R.M. Tuttle, I. Ganly, Postoperative nomogram for predicting cancer-specific mortality in medullary thyroid cancer, Ann. Surg Oncol. 22 (8) (2015 Aug) 2700–2706, https://doi.org/10.1245/s10434-014-4208-2. Epub 2014 Nov 4. PMID: 25366585; PMCID: PMC4986610.
[20] L. Yang, W. Shen, N. Sakamoto, Population-based study evaluating and predicting the probability of death resulting from thyroid cancer and other causes among patients with thyroid cancer, J. Clin. Oncol. 31 (4) (2013 Feb 1) 468–474, https://doi.org/10.1200/JCO.2012.42.4457. Epub 2012 Dec 26. PMID: 23270002.
[21] J. Ye, J.W. Feng, W.X. Wu, J. Hu, L.Z. Hong, A.C. Qin, W.H. Shi, Y. Jiang, Papillary thyroid microcarcinoma: a nomogram based on clinical and ultrasound features to improve the prediction of lymph node metastases in the central compartment, Front. Endocrinol. 12 (2022 Jan 12), 770824, https://doi.org/10.3389/fendo.2021.770824. PMID: 35095755; PMCID: PMC8790095.
[22] Q. Lin, W. Wagner, Epigenetic aging signatures are coherently modified in cancer, PLoS Genet. 11 (6) (2015 Jun 25), e1005334, https://doi.org/10.1371/journal.pgen.1005334. PMID: 26110659; PMCID: PMC4482318.
[23] B. Escudier, C. Porta, M. Schmidinger, N. Rioux-Leclercq, A. Bex, V. Khoo, V. Grünwald, S. Gillessen, A. Horwich, ESMO Guidelines Committee, Electronic address: clinicalguidelines@esmo.org. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 30 (5) (2019 May 1) 706–720, https://doi.org/10.1093/annonc/mdz056. PMID: 30788497.

[24] E.F.S. van Velsen, W.E. Visser, M.T. Stegenga, U. Mäder, C. Reiners, F.J. van Kemenade, T.M. van Ginhoven, F.A. Verburg, R.P. Peeters, Finding the optimal age cutoff for the UICC/AJCC TNM staging system in patients with papillary or follicular thyroid cancer, Thyroid 31 (7) (2021 Jul) 1041–1049, https://doi.org/10.1089/thy.2020.0615. Epub 2021 Mar 4. PMID: 33487121.

[25] E.D. Rossi, S. Mehrotra, A.I. Kilic, I.E. Toslak, J. Lim-Dunham, M. Martini, G. Fadda, C.P. Lombardi, L.M. Larocca, G.A. Barkan, Noninvasive follicular thyroid neoplasm with papillary-like nuclear features in the pediatric age group, Cancer Cytopathol 126 (1) (2018 Jan) 27–35, https://doi.org/10.1002/cncy.21933. Epub 2017 Oct 12. PMID: 29024469; PMCID: PMC6186393.

[26] A.S. Ho, M. Luu, C. Zalt, L.G.T. Morris, I. Chen, M. Melany, N. Ali, C. Patio, Y. Chen, J. Mallen St-Clair, G.D. Braunstein, W.L. Sacks, Z.S. Zumsteg, Mortality risk of nonoperative papillary thyroid carcinoma: a corollary for active surveillance, Thyroid 29 (10) (2019 Oct) 1409–1417, https://doi.org/10.1089/thy.2019.0060. Epub 2019 Sep 24. PMID: 31407637; PMCID: PMC7476400.

[27] L. Qi, W. Zhang, X. Ren, R. Xu, C. Liu, C. Tu, Z. Li, Incidence and predictors of synchronous bone metastasis in newly diagnosed differentiated thyroid cancer: a real-world population-based study, Front Surg 9 (2022 Jan 24), 778303, https://doi.org/10.3389/fsurg.2022.778303. PMID: 35141273; PMCID: PMC8819693.

[28] F.A. Verburg, U. Mäder, K. Tanase, E.D. Thies, S. Diessl, A.K. Buck, M. Luster, C. Reiners, Life expectancy is reduced in differentiated thyroid cancer patients ≥ 45 years old with extensive local tumor invasion, lateral lymph node, or distant metastases at diagnosis and normal in all other DTC patients, J. Clin. Endocrinol. Metab. 98 (1) (2013 Jan) 172–180, https://doi.org/10.1210/jc.2012-2458. Epub 2012 Nov 12. PMID: 23150687.

[29] X.V. Nguyen, K. Roy Choudhury, F.N. Tessler, J.K. Hoang, Effect of tumor size on risk of metastatic disease and survival for thyroid cancer: implications for biopsy guidelines, Thyroid 28 (3) (2018 Mar) 295–300, https://doi.org/10.1089/thy.2017.0526. Epub 2018 Feb 22. PMID: 29373949.

[30] J. Mao, Q. Zhang, H. Zhang, K. Zheng, R. Wang, G. Wang, Risk factors for lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis, Front. Endocrinol. 11 (2020 May 15) 265, https://doi.org/10.3389/fendo.2020.00265. PMID: 32477264; PMCID: PMC7242632.

[31] S.C. Londero, A. Krogdahl, L. Bastholt, J. Overgaard, H.B. Pedersen, C.H. Hahn, J. Bentzen, S. Schytte, P. Christiansen, O. Gerke, C. Godballe, Danish Thyroid Cancer Group-DATHYRCA (part of the DAHANCA organization). Papillary thyroid carcinoma in Denmark, 1996-2008: outcome and evaluation of established prognostic scoring systems in a prospective national cohort, Thyroid 25 (1) (2015 Jan) 78–84, https://doi.org/10.1089/thy.2014.0294. PMID: 25368981.

[32] M.A. Adam, S. Thomas, T. Hyslop, R.P. Scheri, S.A. Roman, J.A. Sosa, Exploring the relationship between patient age and cancer-specific survival in papillary thyroid cancer: rethinking current staging systems, J. Clin. Oncol. 34 (36) (2016 Dec 20) 4415–4420, https://doi.org/10.1200/JCO.2016.68.9372. Epub 2016 Oct 28. PMID: 27998233; PMCID: PMC6366247.

[33] American Thyroid Association (ATA), Guidelines taskforce on thyroid nodules and differentiated thyroid cancer, cooper DS, doherty GM, haugen BR, kloos RT, lee SL, mandel SJ, mazzaferri EL, McIver B, pacini F, schlumberger M, sherman SI, steward DL, tuttle RM. Revised American thyroid association management guidelines for patients with thyroid nodules and differentiated thyroid cancer, Thyroid 19 (11) (2009 Nov) 1167–1214, https://doi.org/10.1089/thy.2009.0110. Erratum in: Thyroid. 2010 Aug;20(8):942. Hauger, Bryan R [corrected to Haugen, Bryan R]. Erratum in: Thyroid. 2010 Jun;20(6):674-1214. PMID: 19860577.

[34] B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S. I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer, Thyroid 26 (1) (2015) 1–133, https://doi.org/10.1089/thy.2015.0020, 2016 PMID: 26462967; PMCID: PMC4739132.

[35] K.S. Banu, P. Govindarajulu, M.M. Aruldhas, Testosterone and estradiol have specific differential modulatory effect on the proliferation of human thyroid papillary and follicular carcinoma cell lines independent of TSH action, Endocr. Pathol. 12 (3) (2001 Fall) 315–327, https://doi.org/10.1385/ep:12:3:315. PMID: 11740053.

[36] A. Thiruvengadam, P. Govindarajulu, M.M. Aruldhas, Modulatory effect of estradiol and testosterone on the development of N-nitrosodiisopropanolamine induced thyroid tumors in female rats, Endocr. Res. 29 (1) (2003 Feb) 43–51, https://doi.org/10.1081/erc-120018675. PMID: 12665317.

[37] L. Du, Z. Zhao, R. Zheng, H. Li, S. Zhang, R. Li, W. Wei, J. He, Epidemiology of thyroid cancer: incidence and mortality in China, 2015, Front. Oncol. 10 (2020 Nov 10) 1702, https://doi.org/10.3389/fonc.2020.01702. PMID: 33240801; PMCID: PMC7683719.

[38] P. Li, Y. Ding, M. Liu, W. Wang, X. Li, Sex disparities in thyroid cancer: a SEER population study, Gland Surg. 10 (12) (2021 Dec) 3200–3210, https://doi.org/10.21037/gs-21-545. PMID: 35070880; PMCID: PMC8749097.

[39] S. Kruijff, J.F. Petersen, P. Chen, A.M. Aniss, R.J. Clifton-Bligh, S.B. Sidhu, L.W. Delbridge, A.J. Gill, D. Learoyd, M.S. Sywak, Patterns of structural recurrence in papillary thyroid cancer, World J. Surg. 38 (3) (2014 Mar) 653–659, https://doi.org/10.1007/s00268-013-2286-0. PMID: 24149717.

[40] F. Bian, C. Li, D. Han, F. Xu, J. Lyu, Competing-risks model for predicting the postoperative prognosis of patients with papillary thyroid adenocarcinoma based on the surveillance, Epidemiology, and End results (SEER) database, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 26 (2020 Jul 25), e924045, https://doi.org/10.12659/MSM.924045. PMID: 32710734; PMCID: PMC7401823.

[41] N. Nilubol, L. Zhang, E. Kebebew, Multivariate analysis of the relationship between male sex, disease-specific survival, and features of tumor aggressiveness in thyroid cancer of follicular cell origin, Thyroid 23 (6) (2013 Jun) 695–702, https://doi.org/10.1089/thy.2012.0269. Epub 2013 May 28. PMID: 23194434; PMCID: PMC3675841.

[42] R.H. Grogan, S.P. Kaplan, H. Cao, R.E. Weiss, L.J. Degroot, C.A. Simon, O.M. Embia, P. Angelos, E.L. Kaplan, R.B. Schechter, A study of recurrence and death from papillary thyroid cancer with 27 years of median follow-up, ; discussion 1446-7, Surgery 154 (6) (2013 Dec) 1436–1446, https://doi.org/10.1016/j.surg.2013.07.008. Epub 2013 Sep 26. PMID: 24075674.

[43] J. Wang, C. Zhanghuang, X. Tan, T. Mi, J. Liu, L. Jin, M. Li, Z. Zhang, D. He, Development and validation of a nomogram to predict distant metastasis in elderly patients with renal cell carcinoma, Front. Public Health 9 (2022 Jan 28), 831940, https://doi.org/10.3389/fpubh.2021.831940. PMID: 35155365; PMCID: PMC8831843.

[44] J. Wang, C. Zhanghuang, X. Tan, T. Mi, J. Liu, L. Jin, M. Li, Z. Zhang, D. He, A nomogram for predicting cancer-specific survival of osteosarcoma and ewing's sarcoma in children: a SEER database analysis, Front. Public Health 10 (2022 Feb 1), 837506, https://doi.org/10.3389/fpubh.2022.837506. PMID: 35178367; PMCID: PMC8843936.

[45] L. Frich, L.A. Akslen, E. Glattre, Increased risk of thyroid cancer among Norwegian women married to fishery workers–a retrospective cohort study, Br. J. Cancer 76 (3) (1997) 385–389, https://doi.org/10.1038/bjc.1997.395. PMID: 9252208; PMCID: PMC2224058.

[46] B.E. Brownlie, J.M. Hedley, J.M. Bremner, Conjugal thyroid disease–six couples with thyrotoxicosis, one couple with hypothyroidism, and one couple with thyroid cancer, N. Z.Med. J. 91 (657) (1980 Apr 9) 246–248. PMID: 6930586.