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Original Article

Preoperative prediction of lymph node metastasis in patients with papillary thyroid carcinoma by an artificial intelligence algorithm

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Abstract: Background: It is necessary to identify patients at risk of developing lymph node metastasis prior to papillary thyroid carcinoma (PTC) surgery. This can be challenging due to limiting factors, and an artificial intelligence algorithm may be a viable option. Objective: In this study, we aimed to evaluate whether combining an artificial intelligence algorithm (support vector machine and probabilistic neural network) and clinico-pathologic data can preoperatively predict lymph node metastasis of papillary thyroid carcinoma (PTC). Methods: We retrospectively examined 251 PTCs with lymph node metastasis and 194 PTCs without lymph node metastasis. The artificial intelligence algorithm included the support vector machine (SVM) and the probabilistic neural network (PNN). Results: The ACR TI-RADS (Thyroid Imaging, Reporting and Data System), number of tumours, no well-defined margin, lymph node status and rim calcification on ultrasonography (US), age, sex, tumour size, and presence of Hashimoto's thyroiditis were significantly more frequent among PTCs with central lymph node metastasis than those without metastasis ($P<0.05$). The PNN classifier revealed an F1 score of 0.88 on the central lymph node metastasis test set. The SVM classifier revealed an F1 score of 0.93 on the lateral lymph node metastasis test set. Our study demonstrates that combining artificial intelligence algorithms and clinico-pathologic data can effectively predict the lymph node metastasis of papillary thyroid carcinoma prior to surgery.

Keywords: Artificial intelligence algorithm, papillary thyroid carcinoma, lymph node metastasis

Introduction

The incidence of thyroid cancer has grown rapidly over the last decade, making it the most common endocrine malignancy [1, 2]. Along with advances in fine-needle aspiration biopsy (FNAB) and ultrasonography (US), early diagnosis and surgery of thyroid cancer have increased [3-5]. Papillary thyroid carcinoma (PTC) is the most common sub-type of thyroid carcinoma, accounting for 85% [6]. Although the prognosis for PTC is excellent, up to 10% of PTC patients suffer regional or distant metastatic recurrence after surgical treatment [7]. Lymph node metastasis is a very important predictor of local recurrence and distant metastasis of PTC. According to prior studies, patients with PTC generally have been found to have the following predictors for lymph node metastasis, which fall into three main categories: demographic, ultrasound, and pathological characteristics. The most commonly reported factors include age, sex, tumour size and location, multifocality, bilaterality, the presence of Hashimoto's thyroiditis, the presence of BRAF (V600E) mutations, and lymph node abnormalities found on ultrasound [8-10]. Therefore, the development of a predictive model for PTC recurrence, such as an artificial intelligence algorithm, has the possibility to improve the clinical management of patients by aiding in risk stratification.

Artificial intelligence algorithms have been around for decades and, more recently, have been applied to medical research [11-13]. Artificial intelligence algorithms consist of SVM, PNN, artificial neural networks (ANNs), and various other intelligence algorithms [14-18]. Liu et al. found that, compared to pathologists, artificial intelligence algorithms were able to achieve higher tumour-level sensitivity [19]. Wang et al. discovered that combining artificial intelligence algorithms and CT images was able to predict EGFR-mutation status in lung adenocarcinoma patients [20]. Researchers demonstrated that, compared to dermatologists, deep neural networks were more accurate in identifying skin cancer [21]. All of these studies imply that artificial intelligence algorithms have proven to be applicable in medical testing and diagnostics.

In our study, we retrospectively examined 251 PTCs with lymph node metastasis and 194 PTCs without lymph node metastasis. We found that combining artificial intelligence algorithms and clinico-pathologic data was able to effectively predict lymph node metastasis of PTCs prior to surgery.

Materials and methods

Patient selection and data collection

This study included 445 patients with PTC who underwent radical thyroid cancer surgery at the First Affiliated Hospital of Wenzhou Medical University between January 2018 and June 2020 and who underwent preventive central lymph node dissection; of these, 128 patients underwent further lateral lymph node dissection. All pathological diagnoses were made by two experienced pathologists. None of the patients had a history of neck surgery or neck irradiation. This study retrospectively analysed electronic pathology and clinical data and collected clinico-pathologic data. The research protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University (approval no. 2018-40).

Ultrasound examination and image evaluation

The ultrasound examinations were carried out with the help of Acuson Sequoia and 128XP sonographic scanners (Siemens Medical Solutions, Mountain View, CA, USA) using 8-13 MHz linear probes. Selection criteria for investigating the risk of central lymph node metastasis are indicated in **Table 1**, and selection criteria for analysing the risk of lateral lymph node metastasis are shown in **Table 2**. Largest tumour diameter size was measured using B-mode ultrasound. Multifocal PTMC was defined as the presence of more than one lesion in a given paraffin section; the lesion with the largest diameter or the most suspicious nodule was analysed. The margin was categorized as well defined or not well defined. B-mode ultrasound was used to determine the state of the lymph node, skin, and medullary junction and whether to explore enlarged lymph nodes. Based on preoperative ultrasound images, tumour location was classified into four domains, i.e., upper, middle, lower, and isthmus.

Model development

We retrospectively used support vector machine (SVM) and probabilistic neural network (PNN) algorithms for the development of statistical models to predict central lymph node metastasis and lateral lymph node metastasis based on clinico-pathologic factors and B-mode ultrasound features. We used the MATLAB 2014a modelling platform to establish the SVM model using the RBF kernel function, and the PNN model using the newpnn function. Based on the Kennard-Stone algorithm (KS), central lymph node metastasis is divided into 350 training sets and 95 test sets, and the lateral lymph node metastasis is divided into 90 training sets and 38 test sets. Also, during the development of the SVM model, a grid search method was used to debug the model. When the highest verification accuracy rate is reached, the obtained c and g are the best parameters. In the grid search method, the global search is performed at intervals of 0.5, and the ranges of c and g are both 2^{-10} to 2^{10}. The RBF kernel function is $K(x_i,x_j) = \exp(-g\|x_i-x_j\|)^2$. The kernel function parameter is g, which controls the range of the input space. The above optimization problem is transformed into:

$$\begin{cases} \min \frac{1}{2}\sum_{i-1}^{n}\sum_{j-1}^{n} y_i y_j a_i a_j \exp(-g\|x_i - x_j\|)^2 - \sum_{i-1}^{n} a_j \\ s.t \sum_{i-1}^{n} y_i a_i = 0, 0 \le a_i \le c \end{cases}$$

The SVM prediction problem depends on two important parameters, c and g. The parameter c, which is common to all SVM kernels, can compete with the simplicity of the decision-making surface and can be a valuable conversion to the misclassification of training sam-

Table 1. Baseline characteristics of the 445 patients with TPC with and without metastatic central lymph nodes

Characteristics	The status of metastatic central lymph nodes		P
	Positive (n=251)	Negative (n=194)	
Age (y)	44.28±12.67	48.03±11.28	0.001
Sex			<0.0001
Female	167	166	
Male	84	28	
Tumour size (mm)	12.93±8.28	8.86±5.16	<0.0001
Hashimoto's thyroiditis			0.024
Yes	46	53	
No	205	141	
No. of tumour			0.002
Unilateral unifocal	146	144	
Unilateral multifocal	25	10	
Bilateral multifocal	80	40	
Tumour location			0.548
Lower	61	52	
Upper/middle/isthmus	190	142	
Margin			0.001
Well defined	151	147	
Not well defined	100	47	
Calcification			<0.0001
Present	211	123	
Absent	40	71	
Lymph node status			<0.0001
Clear junction of LN, skin and marrow	16	10	
Unclear junction of LN, skin and marrow	82	19	
Absent	153	165	
TI-RADS			<0.0001
III	7	7	
IVa	76	75	
IVb	59	72	
IVc	66	22	
V	21	7	
VI	22	11	

ples. A smaller c makes the decision surface smoother, while a larger c tends to correctly classify all training samples. The variable g defines how much impact a single training sample can have. A larger g will affect other samples more. We used the newpnn function that comes with the MATLAB 2014a modelling platform to build the PNN model.

Newpnn function net = newpnn (P.T. spread)

P: R*Q matrix, including Q input vectors of length R.

T: S*Q matrix, including Q target vectors.

Spread: scalar, representing the spreading speed of the probabilistic neural network; the default value is 0.1. At the same time, we used the F1 score and kappa coefficient to evaluate the predictive performance of the classifier. Our patients were divided into two groups. A positive value indicated positive lymph node metastasis, and a negative value indicated negative lymph node metastasis.

Statistical analysis and combined model

PTCs with and without lymph nodes metastasis were compared based on patient demographic

Table 2. Multivariate logistic regression analysis associated with central lymph node metastases of PTC

Clinico-pathologic characteristics	OR	95% CI	P
Age	0.979	0.960-0.997	0.026
Sex			
Male	3.24	1.872-5.606	<0.001
Tumour size	1.088	1.043-1.136	<0.001
Hashimoto's thyroiditis			
Yes	0.847	0.498-1.439	0.539
No. of tumour			
Unilateral unifocal			0.002
Unilateral multifocal	2.359	1.019-5.461	0.045
Bilateral multifocal	2.345	1.398-3.934	0.001
Margin[a]			
Not well defined	1.657	1.018-2.696	0.042
Calcification[a]			
Present	1.886	1.116-3.187	0.018
Lymph node status[a]			
Absent			0.007
Clear junction of LN, skin and marrow	0.954	0.378-2.409	0.920
Unclear junction of LN, skin and marrow	2.73	1.440-5.174	0.002
TI-RADS[a]			
III			0.162
IVa	2.38	0.618-9.168	0.207
IVb	1.427	0.367-5.555	0.608
IVc	3.063	0.741-12.668	0.122
V	2.481	0.462-13.323	0.289
VI	2.943	0.632-13.695	0.169

a = Thyroid nodules observed under Ultrasound.

information. The application of an independent two-sample t-test was built to carry out the evaluation of records in a normal distribution. Categorical variables were analysed using the chi-square test, while continuous variables were analysed using Student's t-test. Variables with P<0.05 in the univariate analysis were advanced to a multivariate analysis by means of forward stepwise selection. The results are presented as odds ratio (OR) and 95% CI as well as *P*-value. All *P*-values were two-sided. Furthermore, the *P*-value <0.05 was considered statistically significant. Statistical analysis was carried out using SPSS software version 22.0 (SPSS, Chicago, IL, USA).

We retrospectively used support vector machine (SVM) and probabilistic neural network (PNN) algorithms for the development of statistical models to predict central lymph node metastasis and lateral lymph node metastasis based on clinico-pathologic factors and B-mode ultrasound features. We used the MATLAB 2014a modelling platform to establish the SVM model using the RBF kernel function and the PNN model using the newpnn function. Also, during the development of the SVM model, a grid search method was used to debug the model. Our patients were divided into two groups. A positive value indicated the presence of lymph node metastasis and a negative value indicated the absence of lymph node metastasis.

Results

Relationship of central lymph node metastasis of PTC with clinico-pathologic and US features

In our study, we enrolled 445 PTCs, including 251 PTCs with central lymph node metastasis and 194 PTCs without central lymph node metastasis. To understand the central lymph node metastasis of PTCs, we investigated the relationship of central lymph node metastasis with clinico-pathologic factors and ultrasound features (**Table 1**). The results indicated that PTCs with central lymph node metastasis occurred at a younger age (P=0.001); with a larger tumour size (P<0.001); in the presence of calcification (P<0.001); with no well-defined margin (P=0.001); with unclear junction of lymph node, skin and marrow (P<0.001); at higher levels of TI-RADS (P≤0.001); and with a higher number of thyroid cancer nodules (P=0.002) than PTCs without central lymph node metastasis. Men (P<0.001) and PTCs with concurrent Hashimoto's thyroiditis (P=0.024) had a greater chance of central lymph node metastasis. We used multivariate logistic regression to determine whether these elements were independently associated with central lymph node metastasis (**Table 2**). Our analyses suggest that men (P<0.001); younger age (P=0.026); larger tumour size (P<0.001); no well-defined margin (P=0.001); an unclear junction of lymph node, skin and marrow (P=0.007); and the

Table 3. Baseline characteristics of the 128 patients with TPC with and without metastatic lateral lymph nodes

Characteristics	The status of metastatic lateral lymph nodes		P
	Positive (n=87)	Negative (n=41)	
Age	44.08±14.34	45.95±11.77	0.468
Sex			0.108
Female	58	33	
Male	29	8	
Tumour size	16.24±10.59	12.46±7.99	0.045
Hashimoto's thyroiditis			0.004
Yes	14	16	
No	73	25	
No. of tumour			0.378
Unilateral unifocal	55	31	
Unilateral multifocal	6	2	
Bilateral multifocal	26	8	
Central lymph nodes metastasis			<0.001
Yes	77	14	
No	10	27	
Tumour location			0.132
Upper	23	4	
Middle	44	22	
Lower	16	12	
Isthmus	4	3	
Margin			0.02
Well defined	47	31	
Not well defined	40	10	
Calcification			0.757
Present	76	6	
Absent	11	11	
Lymph node status			0.001
Clear junction of skin and marrow	5	8	
Unclear junction of skin and marrow	69	19	
Absence	13	14	
TI-RADS			0.201
III	1	1	
IVa	6	7	
IVb	22	12	
IVc	39	12	
V	14	4	
VI	5	5	

presence of calcification (P=0.018) were independently predictive of central lymph node metastasis.

Relationship of central lymph node metastasis of PTC with clinico-pathologic and US features

A total of 128 PTCs underwent both central and lateral lymph node dissection. To better comprehend lateral lymph node metastasis of PTCs, we further explored the relationship between lateral lymph node metastasis and clinico-pathologic factors and US features (**Table 3**). Our results reveal that PTCs associated with Hashimoto's thyroiditis (P=0.004) may negatively predict lateral lymph node metastasis, whereas larger tumour size (P=0.045), no well-defined margin (P=0.02), and

Table 4. Multivariate logistic regression analysis associated with lateral lymph node metastases of PTC

Clinico-pathologic characteristics	OR	95% CI	P
Age	1.016	0.977-1.056	0.43
Sex			
Male	2.396	0.672-8.541	0.178
Tumour size	1.029	0.968-1.093	0.359
Hashimoto's thyroiditis			
Yes	0.327	0.104-1.032	0.057
Central lymph nodes metastasis			
Yes	14.956	4.673-47.861	<0.001
Margin[a]			
Not well defined	2.157	0.161-1.339	0.155
Lymph node status[a]			
Absence			0.034
Clear junction of skin and marrow	0.091	0.011-0.731	0.024
Unclear junction of skin and marrow	0.849	0.234-3.078	0.804

a = Thyroid nodules observed under Ultrasound.

Table 5. Diagnostic performance of the predictive factors for central lymph node metastasis of PTC using PNN

Predictors		
Training performance	Accuracy	1
	Sensitivity	1
	Specificity	1
Test performance	Accuracy	0.884211
	Sensitivity	0.803921
	Specificity	0.977273
	F1 score	0.8842
	Kappa	0.8439

Table 6. The predictive value of the PNN model and independent predictors

Independent predictors	Sensitivity (%)	Specificity (%)
Sex	33.5	85.6
Tumour location	24.3	73.2
No. of tumour	41.8	74.2
Margin	39.8	75.8
Calcification	84.1	36.6
Lymph node status	39	85.1
PNN model	80.4	97.7

unclear junction of lymph node, skin and marrow (P<0.001) have a higher probability of lateral lymph node metastasis. In addition, men with central lymph node metastasis have increased odds of having lateral lymph node metastasis (P<0.001). Multivariate logistic regression was used to obtain a deeper understanding (**Table 4**) and revealed that unclear junction of lymph node, skin and marrow (P=0.034) and the presence of central lymph node metastasis (P<0.001) were independently predictive of lateral lymph node metastasis.

The predictive model

We constructed a model to predict central lymph node metastasis using a PNN algorithm. We used the Kennard-Stone (KS) algorithm, among others, to divide 445 patients into a training set of 350 cases and a test set of 95 cases. In the test set, 51 cases were pathologically diagnosed as lymph node positive, and 44 cases were pathologically diagnosed as lymph node negative. The prediction results are shown in **Table 5**. When spread is 0.5, accuracy is 0.88, sensitivity is 0.80, and specificity is 0.98. The PNN classifier showed a high F1 score and kappa on the test folds (F1 score =0.88, kappa =0.84). The sensitivity and specificity of the PNN model were found to be 80.4% and 97.7%, respectively (**Table 6**). The model had a satisfactory predictive value when compared to other single predictors.

The SVM algorithm was used to predict lateral lymph node metastasis of PTCs. Using the KS algorithm, 128 patients were divided into the training set (90 patients) and the test set (38 patients). Among the test set, 27 patients were pathologically diagnosed as lymph node positive, and 11 patients were pathologically diagnosed as lymph node negative. The prediction results are shown in **Table 7**. Accuracy was 0.95, sensitivity was 0.96, specificity was 0.91, the best c was 0.75786, and the best g was 0.14359. The performance of the SVM classifier showed the F1 score to be 0.93 and the kappa coefficient to be 0.94. The sensitivity and specificity for the SVM model were found to be 100% and 81.8%, respectively (**Table 8**). The model had a satisfactory predictive value when compared to other single predictors.

Discussion

With the advancement of preoperative sonography and ultrasound-guided FNAB, the diag-

Table 7. Diagnostic performance of the predictive factors for lateral lymph node metastasis of PTC using SVM

Predictors		
Training performance	Accuracy	0.84444
	Sensitivity	0.96667
	Specificity	0.6
Test performance	Accuracy	0.947368
	Sensitivity	1
	Specificity	0.8181
	F1 score	0.9321
	Kappa	0.9435

Table 8. The predictive value for the SVM model and independent predictors

Independent predictors	Sensitivity (%)	Specificity (%)
Hashimoto's thyroiditis	83.9	39
Central lymph nodes metastasis	88.5	65.9
SVM model	100	81.8

nosis and treatment of PTC have developed rapidly in recent years [22-24]. Although most of the PTCs had a slow clinical course together with a good prognosis, the incidence of lymph node metastasis was identified as an important poor prognostic indicator [25, 26]. Although lymph node dissection for PTC may be one way to decrease the probability of recurrence and metastasis, an aggressive treatment approach for PTC may lead to negative results, such as injury to the laryngeal nerve leading to damage to the voice [27, 28]. Hay et al. reported that aggressive treatment has nothing to do with prolonged survival or reduced recurrence in PTC [26]. This is the reason that some PTC patients can choose to be monitored rather than aggressively treated. Although PTC is a disease with an excellent outcome, patients presenting with metastatic disease do have poor outcomes [29]. In clinical practice, the decision for surgery mainly depends on the individual doctor or the patient. To better treat patients, we urgently need a clinical approach that can predict whether lymph nodes have metastasized prior to surgery.

Numerous articles have elucidated multiple and varied factors related to lymph node metastasis [30-33]. Medas et al. found that the incidence of lymph node metastasis in PTMC is considerable and that tumour size appears to be the most significant predictive factor for lymph node metastasis [10]. Kim et al. reported that, as the size of thyroid nodules increase, so does the likelihood of lymph node metastasis [34]. In addition, Wang et al. have found that no well-defined margin was a significant ultrasound feature of aggressive PTC [35]. Tian et al. found that age, sex, ultrasound-reported LN status and ultrasound signature were the strongest predictors of CLNM in PTC patients, which has aided in the development of a predictive nomogram [36]. In our research, men, younger age, larger tumour size, the presence of calcifications, no well-defined margin, an unclear junction of the lymph node, skin and marrow, higher levels of TI-RADS, greater numbers of thyroid cancer nodules, and PTCs associated with Hashimoto's thyroiditis were significantly linked to central lymph node metastasis. Multivariate logistic regression revealed that men, younger age, larger tumour size, no well-defined margin, an unclear junction of the lymph node, skin and marrow, and the presence of calcification were independently predictive of central lymph node metastasis. Furthermore, PTCs associated with Hashimoto's thyroiditis ($P=0.004$) may be an inhibitor of lateral lymph node metastasis, whereas larger tumour size ($P=0.045$), no well-defined margin ($P=0.02$), and an unclear junction of the lymph node, skin and marrow ($P<0.001$) have a higher probability of lateral lymph node metastasis. Multivariate logistic regression showed that an unclear junction of the lymph node, skin and marrow and the presence of central lymph node metastasis were independently predictive of lateral lymph node metastasis.

The diagnosis of lymph node metastasis showed low sensitivity by preoperative sonography. We combined clinico-pathologic features and ultrasonographic findings to enhance the diagnostic accuracy of lymph node metastasis by PNN and SVM algorithms. In our study, we used one set of features for the PNN classifier (on average 10 features across different folds) from 455 samples (251 PTCs with central lymph node metastasis and 194 PTCs without metastasis). By contrast, we used a different set of features for the SVM classifier from 128 samples (87 PTCs with lateral lymph node metastasis and 41 PTCs without lateral lymph node metastasis). The PNN classifier showed a high F1 score and kappa coefficient on the test folds (F1 score =0.88, kappa =0.84), while the performance of SVM classifiers showed an F1 score of 0.93 and kappa of 0.94.

Despite these findings, there remain limitations to our study. First, in those patients with multifocal nodules, we investigated the most suspicious or the largest lesions only in those instances where data about other nodules were not available. Second, to generate more convincing results, the quantity of the validated set and test set should be expanded.

Conclusion

In summary, our study demonstrated that combining an artificial intelligence algorithm and clinico-pathologic data can effectively predict lymph node metastasis of papillary thyroid carcinoma prior to surgery.

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Written, informed consent was obtained from each individual participant.

Disclosure of conflict of interest

None.

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