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Predictive risk-scoring model for lateral lymph node metastasis in papillary thyroid carcinoma

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This study aims to evaluate candidate risk factors for lateral lymph node metastasis (LLNM) and develop a predictive model to identify high-risk groups among patients with papillary thyroid carcinoma (PTC). Additionally, we identified risk factors for recurrence to inform postoperative therapeutic decisions and follow-up for physicians and patients. A total of 4107 patients (4884 lesions) who underwent lymph node dissection at our hospital from 2005 to 2014 were evaluated. LLNM risk was stratified, and a risk-scoring model was developed based on identified independent risk factors for LLNM. Cox's proportional hazards regression model was used to investigate the risk factors for recurrence. Lateral Lymph Node (LLN) metastasis was observed in 10.49% (431/4107) of patients. Multivariate analysis identified the following independent risk predictors for LLN metastasis: Age ≤ 35 years ($P = 0.002$), tumor size > 1.0 cm ($P = 0.000$), lobe dissemination (+) ($P = 0.000$), and CLNM (+) ($P = 0.000$). A 12-point risk-scoring model was constructed to predict stratified LLNM in PTC patients, with an area under the receiver operating characteristic curve (AUROC) of 0.794 (95% CI: 0.774–0.814) ($P < 0.01$). The Cox regression model indicated that tumor size > 1.0 cm, lobe dissemination (+), multifocality, Central Lymph Node Metastasis (CLNM), and LLNM were significant risk factors associated with poor outcomes. Based on the risk scoring model, additional investigations and comprehensive considerations are recommended for patients with a total score greater than 5, and prophylactic cervical lymph node dissection is performed if necessary. Additionally, more aggressive treatment and more frequent follow-ups should be considered for patients with tumor size > 1.0 cm, lobe dissemination (+), multifocality, CLNM, and LLNM.

Keywords Papillary thyroid carcinoma, Lateral lymph node metastasis, Risk-scoring model, Central lymph node metastasis, Prognostic factors, Disease-free survival

Over the past three decades, the incidence of thyroid cancer has increased rapidly in various populations worldwide[1]. In southeastern China, particularly in Zhejiang Province, the incidence of thyroid cancer has shown a significant upward trend, which is markedly higher than the national average, especially concerning the proportion of papillary thyroid cancer[2,3]. Papillary thyroid carcinoma (PTC) is the most common form of thyroid cancer, accounting for approximately 80% of all thyroid cancers globally. In the Chinese population, the incidence of PTC may be as high as 95.1%[4]. Despite the excellent prognosis of patients with PTC, with a 5-year disease-specific survival rate of over 98%[5], 40–60% of patients with PTC experience cervical lymph node metastases, which may indicate future recurrence, further development, or distant metastases[6].

The central compartment is the most commonly involved area, and the American Thyroid Association (ATA) Guidelines suggest that prophylactic central lymph node (CLN) dissection can be considered, especially for patients with advanced primary tumors (T3 or T4). However, prophylactic lateral lymph node (LLN) dissection

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is not recommended by the ATA[7]. There are no uniform professional guidelines for LLN dissection, and the necessity of prophylactic LLN remains controversial. Some scholars argue that prophylactic lateral neck dissection for thyroid cancer may increase complications without proven benefits in survival[8]. Conversely, others believe that positive pathological lymph node metastasis is an independent risk factor for recurrence, leading to higher mortality, and that incomplete surgical resection is a significant reason for increased mortality in patients with stage I PTC[9,10]. Although less frequent, metastases to lymph nodes in the lateral compartment (levels I-V) may be associated with a worse prognosis[11]. Patients who did not assess lymph nodes during surgery had the highest risk of death, followed by the N1b, N1a, and N0 groups. Compared with N0 patients, N1 patients are more likely to develop lung metastasis[12]. Additionally, some scholars have found that lateral lymph node metastasis (LLNM) is related to the number of central lymph node metastases (CLNMs). For patients with 1–2 CLNMs, younger age, calcification, nodular goiter, tumor size > 10 mm, and upper tumor location all indicate higher probabilities of occult and LLNM[13]. However, "skip metastasis", where the patient has lateral cervical lymph node metastasis without central neck disease, is also possible, with reported incidences ranging from 6.8–37.5%[14]. Therefore, identifying high-risk groups among PTC patients is becoming increasingly crucial.

Currently, due to the limitations of clinical examinations, it is challenging to detect subclinical lymph node metastasis in PTC patients, which may lead to incomplete clinical treatment and significantly threaten patient health. Thus, discovering appropriate clinical and pathological predictors of lymph node metastasis is imperative to guide treatment decisions. While numerous potential risk factors have been reported, the results vary, necessitating further investigation[15].

The aim of this study was to retrospectively analyze the clinical and pathological data of PTC patients diagnosed between 2005 and 2014 to evaluate candidate risk factors for LLN metastasis and develop a model based on these factors to predict high-risk groups of LLNM among PTC patients. Additionally, we gathered data on prognosis to identify risk factors for recurrence, thereby guiding postoperative therapeutic decisions and follow-up for physicians and patients.

Materials and methods

Patient selection

This retrospective study was approved by the medical ethics review committee in Zhejiang Provincial People's Hospital (Approval No. [Zhe Ren Yi Lun Shen 2024 Other [259]). A total of 4107 patients (4884 lesions) who were first treated in Zhejiang Provincial People's Hospital between January 2005 and December 2014 were evaluated retrospectively. All patients were diagnosed with PTC based on pathology. Patients with any of the following criteria were excluded: (i) previous thyroid resection at another institution; (ii) other types of thyroid malignancy; (iii) tumor in the thyroid isthmus; (iv) history of neck surgery for other diseases or radiation exposure; (v) distant metastasis.

Preoperative examination and criteria for tumor location

All patients underwent ultrasonography (US) examination preoperatively to determine the tumor and lymph node status. The majority of patients also received CT scans to evaluate both the tumor and lymph nodes. Tumor number was assessed based on preoperative US examination and CT scans, and lesions were categorized into either the Solitary group (one nodule) or the Multifocality group (more than one nodule). The location of the primary tumor in the thyroid gland was classified as upper pole, middle pole, or lower pole according to the levels of the isthmus. The upper level of the isthmus was defined as the boundary of the upper and middle poles, while the lower level was defined as the boundary of the middle and lower poles. Tumor location was determined by the center of the tumor when it crossed a boundary. Tumors with multiple nodules in one lobe, those occupying the entire lobe, or those covering two boundaries were excluded from the tumor location groups.

Surgical strategy

Total thyroidectomy and bilateral CLN dissection were performed in patients with bilateral PTC. Patients with unilateral PTC underwent either unilateral lobectomy plus isthmusectomy or total thyroidectomy and ipsilateral CLN dissection, depending on the primary tumor's condition. Total thyroidectomy was considered for unilateral PTC patients meeting one or more of the following conditions: (i) tumor size > 4 cm; (ii) multifocality in one lobe; (iii) extrathyroidal invasion, according to the guidelines of the Chinese Thyroid Association. All patients underwent ipsilateral prophylactic CLN dissection, including pretracheal, paratracheal, precricoid, and perithyroidal nodes, including lymph nodes along the recurrent laryngeal nerves. Ipsilateral LLN dissection was performed based on preoperative US imaging, fine needle aspiration biopsy, or intraoperative frozen section results. Patients underwent ipsilateral LLN dissection if they met one or more of the following conditions: (i) suspected LLN metastasis in preoperative US examination; (ii) confirmed positive LLN by fine needle aspiration biopsy; (iii) confirmed positive LLN by intraoperative frozen section. Comprehensive neck dissection, including levels IIa, III, IV, and Vb, was performed as needed, while levels I, IIb, and Va were only dissected when lymph nodes were proven positive in those compartments. Patients who met none of the above conditions and were assessed as lateral lymph node negative by at least two ultrasound experts did not undergo LLN dissection. As it is difficult and inappropriate to conduct a prospective study on LLN metastasis, and to minimize selection bias in analysis, patients with radiologically negative LLN will be classified as LLN-negative, with ultrasound (US) results serving as the primary evidence, while CT findings will also be comprehensively assessed.

Grouping

There were 777 patients with bilateral lesions and 3330 patients with unilateral lesions. All bilateral lesions were regarded as independent lesions, resulting in a total of 4884 lesions included in the study. The patients who underwent lymph node dissection were grouped according to gender, age, tumor size, tumor number, lobe

dissemination, presence of psammoma bodies, bilaterality, capsule invasion, and tumor location (Table 1). Tumor size was determined by the maximum diameter of the tumor. Tumor number and location were determined by preoperative ultrasonography. Data on capsule invasion, lobe dissemination, psammoma bodies, and CLNM for the predictive risk-scoring model were based on intraoperative frozen-section examination results and confirmed by paraffin-section post-operation.

Postoperative treatment and follow-up

TSH suppression therapy was conventionally performed in PTC patients postoperatively. Postoperative RAI ablation therapy was performed in patients with total thyroidectomy and one or more of the following conditions: (i) T3 or T4; (ii) positive LLN metastasis; (iii) distant metastasis. Patients underwent a conventional US examination every 3 months to detect local recurrence and a CT examination of the chest every year to detect lung metastasis. Recurrence in the remnant thyroid gland or regional lymph nodes was diagnosed by US and confirmed by fine needle aspiration or histological examination post-operation. Distant metastasis was diagnosed by CT and RAI scintigraphy after the completion of total thyroidectomy.

	Central lymph node metastasis in PTC patients				Lateral lymph node metastasis in PTC patients			
	–	+	Positive rate	*P* value	–	+	Positive rate	*P* value
Gender				0.000				
Male	463	446	49.06%		793	116	12.76%	0.011
Female	2085	1113	34.80%		2883	315	9.85%	
Age (years)				0.000				0.000
≤ 25	50	110	68.75%	0.000*	128	32	20.00%	0.000*
25–35	322	339	51.29%		559	102	15.43%	
35–45	785	472	37.55%		1136	121	9.63%	
45–55	880	425	32.57%		1189	116	8.89%	
55–65	415	165	28.45%		541	39	6.72%	
> 65	96	48	33.33%		123	21	14.58%	
Tumor size (cm)				0.000				0.000
≤ 0.5	1570	322	17.02%	0.000**	1840	52	2.75%	0.000**
0.5–1.0	1094	634	36.69%		1602	126	7.29%	
1.0–1.5	316	306	49.20%		531	91	14.63%	
1.5–2.0	113	168	59.79%		211	70	24.91%	
> 2.0	132	229	63.43%		237	124	34.35%	
Lobe dissemination				0.000				0.000
–	3124	1448	31.67%		4218	354	7.74%	
+	101	211	67.63%		203	109	34.94%	
Psammoma body				0.000				0.003
–	3198	1593	33.25%		4345	446	9.31%	
+	27	66	70.97%		76	17	18.28%	
Tumor number								
Solitary	2597	1229	32.12%	0.000	2526	153	5.71%	0.000
Multifocality	628	430	40.64%		1895	310	14.06%	
Bilateral				0.598				0.064
–	2207	1123	33.72%		3032	298	8.95%	
+	1018	536	34.49%		1389	165	10.62%	
Capsule invasion				0.000				0.002
–	1988	691	25.79%		3489	337	8.81%	
+	1237	968	43.90%		932	126	11.91%	
Tumor location				0.946				0.000
Upper pole	437	206	32.04%		545	98	15.24%	
Middle pole	1331	648	32.74%		1847	132	6.67%	
Lower pole	558	269	32.53%		758	69	8.34%	
CLN metastasis								0.000
–					3114	111	3.44%	
+					1307	352	21.22%	

Table 1. Correlation between clinical factors and central lymph node metastasis (CLNM) and lateral lymph node metastasis (LLNM). *Age ≤ 35 years versus age > 35 years. **Φ ≤ 1.0 cm versus Φ > 1.0 cm.

Statistics analysis

The Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL, USA) was used for statistical analysis. Univariate analysis was performed using the chi-square criterion, while multivariate analysis was conducted using logistic regression analysis. A Cox regression model was used to determine prognostic factors. A difference was considered statistically significant when $p < 0.05$.

Results

Baseline characteristics

Among the patients who underwent LLN dissection, 78.32% (430/549) and 77.78% (462/594) of lesions were confirmed with histologically positive lateral lymph node metastasis (LLNM). To minimize selection bias in the analysis, we considered the patients who did not undergo LLN dissection as LLN negative in this study. Among all patients, 37.96% (1559/4107) and 33.96% (1659/4884) of lesions were confirmed with histologically positive central lymph node metastasis (CLNM), and 10.49% (431/4107) and 9.48% (463/4884) of lesions with histologically positive LLNM. Furthermore, among the patients with positive CLN, about 21.22% (352/1659) of lesions were confirmed with histologically positive LLNM. The study included a total of 909 males and 3198 females, with a male/female ratio of 1:3.52. The age of the patients ranged from 12 to 82 years, with a median age of 45.21 years. The diameter of the tumors ranged from 0.1 cm to 8.0 cm, with a median diameter of 0.92 cm. The median follow-up time was 44.0 months (ranging from 18.0 to 140.0 months) (Table 1).

Risk factors for CLLM and LLNM

In the univariate analysis, gender, age, tumor size, lobe dissemination, presence of psammoma bodies, tumor number, and capsule invasion were significantly associated with CLN metastasis ($P < 0.05$). No significant correlation was found between bilaterality, tumor location, and CLN metastasis ($P > 0.05$) (Table 1). Similarly, there were statistically significant differences in the rates of LLN metastasis between the groups based on gender, age, tumor size, lobe dissemination, presence of psammoma bodies, tumor number, capsule invasion, tumor location, and central lymph node metastasis ($P < 0.05$). No significant correlation was found between bilaterality and LLN metastasis ($P > 0.05$) (Table 1). In the multivariate analysis, age ≤ 35 years ($P = 0.002$, odds ratio 0.696), tumor size > 1.0 cm ($P = 0.000$, odds ratio 2.916), lobe dissemination (+) ($P = 0.000$, odds ratio 3.411), and CLNM (+) ($P = 0.000$, odds ratio 4.676) were independent risk predictors of LLN metastasis (Table 2).

The rate of CLNM and LLNM increased notably with decreasing age within a certain range, and there were significant differences in the rate of LLNM between groups aged ≤ 25 years and 25 < age ≤ 35 years, as well as between 25 < age ≤ 35 years and 35 < age ≤ 45 years ($P < 0.01$). Additionally, the rate of LLNM was found to fluctuate significantly between the groups aged 25 < age ≤ 35 years and 35 < age ≤ 45 years (15.43% vs. 9.63%), becoming relatively stable when age ≥ 35 years. This suggests that age 35 years could be used as a cut-off point to predict LLNM. Thus, we regrouped the patients and found the LLNM rate was significantly higher in the group aged ≤ 35 years compared to those > 35 years ($P < 0.01$) (Table 1).

Patients were divided into five groups based on the maximum diameter of the tumor. Significant differences in the rates of CLNM and LLNM were found between different groups, with the LLNM rate increasing markedly with tumor size. The LLNM rate in the group with $\Phi < 1.0$ cm was significantly lower than in the other groups. Moreover, a nearly linear correlation was found between the LLNM rate and tumor size across the five groups ($y = 0.0808x + 0.0746$; $R^2 = 0.9803$). To identify a cut-off point for predicting LLNM, an ROC analysis was conducted, and the area under the curve was 0.765 ($P < 0.01$), indicating that $\Phi = 1.0$ cm could be considered a threshold to predict LLNM according to the curve (Fig. 1A).

Development of risk-scoring model to predict LLNM

The final method of displaying the relationships among age, tumor size, lobe dissemination, capsule invasion, CLNM, and the probability of LLNM involves constructing a scoring model. The score for each risk factor was weighted according to the beta coefficient obtained from the logistic regression model. For simplicity, all beta coefficients were divided by the smallest one (0.366 in this study) and then rounded to the nearest whole

	B	S.E.	Sig.	Exp(B)	95.0% CI Exp (B)	
					down	up
Gender (male vs. female)	0.116	0.118	0.324	1.124	0.891	1.416
Age (≤ 35 years vs. > 35 years)	−0.362	0.120	0.002	0.696	0.551	0.880
Tumor size (Φ > 1.0 cm vs. Φ ≤ 1.0 cm)	1.070	0.163	0.000	2.916	2.121	4.011
Lobe dissemination(positive vs. negative)	1.227	0.142	0.000	3.411	2.582	4.507
Psammoma body (positive vs. negative)	−0.041	0.294	0.888	0.960	0.539	1.708
Capsule invasion (positive vs. negative)	0.384	0.115	0.001	1.468	1.173	1.838
Bilateral (positive vs. negative)	0.223	0.114	0.116	1.250	0.999	1.563
Tumor number (multifocality vs. solitary)	0.190	0.123	0.123	1.209	0.950	1.538
CLNM (positive vs. negative)	1.542	0.121	0.000	4.676	3.691	5.922
Constant	−4.129	0.193	0.000	0.016		

Table 2. Multivariate logistic regression for LLNM.

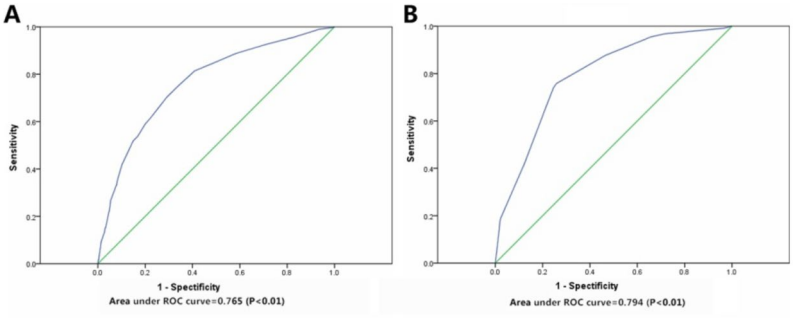

Fig. 1. (**A**) ROC curve illustrating the ability of tumor size to predict the likelihood of metastasis to lateral lymph nodes. (**B**) ROC curve illustrating the ability of the risk-scoring model to predict the likelihood of metastasis to lateral lymph nodes.

	OR (95% CI)	Sig.	Beta coefficient	Point
Age				
> 35 years				0
≤ 35 years	0.696 (0.551, 0.88)	0.002	0.366	1
Tumor size				
Φ ≤ 1.0 cm				0
Φ > 1.0 cm	2.916 (2.121, 4.011)	0.000	1.109	3
Lobe dissemination				
Negative				0
Positive	3.411 (2.582, 4.507)	0.000	1.343	3
Capsule invasion				
Negative				0
Positive	1.468 (1.173, 1.838)	0.001	0.223	1
CLNM				
Negative				0
Positive	4.676 (3.691, 5.922)	0.000	1.433	4

Table 3. Development of a 12-point risk-scoring model to predict LLNM in PTC patients.

number. The total score for each patient represented the sum of scores for each risk factor, resulting in a 12-point risk-scoring model to predict stratified LLNM in PTC patients (Table 3). Using this model, the rate of positive LLNM ranged from 0.98 to 50.00%, depending on the total scores of the PTC patients (Table 4).

To evaluate the predictive performance of the scoring model and determine an appropriate cut-off point, we used the receiver operating characteristic curve (ROC curve) and evaluated it by the area under the ROC curve (AUROC). The AUROC of the model for predicting LLNM was 0.794 (95% CI: 0.774–0.814) ($P < 0.01$) (Fig. 1B), indicating good discriminative power. A total score of 5 was selected as the appropriate cut-off point. Patients with total scores ranging from 0 to 5 were classified into the low-risk group for LLNM, while patients with scores above 5 were classified into the high-risk group. The sensitivity of the model was 75.80%, and the specificity was 74.20%.

Predictors of DFS in patients with PTC

A total of 4107 patients were followed up, with an average follow-up time of 48.39 months (standard deviation: ± 24.15 months) and a median follow-up time of 44 months (range: 18–140 months). Recurrence was found in 100 patients (2.43%), and 25 patients (0.61%) died, of which only 9 (0.22%) deaths were due to PTC. Therefore, we evaluated disease-free survival (DFS) instead of overall survival due to the small number of deaths. The Cox regression model showed that tumor size > 1.0 cm ($P = 0.016$, hazard ratio 2.189), lobe dissemination (+) ($P = 0.005$, hazard ratio 2.051), multifocality ($P = 0.000$, hazard ratio 2.916), CLNM ($P = 0.002$, hazard ratio 2.314), and LLNM ($P = 0.000$, hazard ratio 2.749) were risk predictors of recurrence (Table 5).

As shown above, tumor size > 1.0 cm, lobe dissemination (+), multifocality, CLNM, and LLNM were significant risk factors associated with poor outcomes. Consequently, we regrouped the patients into five groups based on the number of these risk factors. There were 889 patients with 0 factors, 1347 patients with 1 factor, 1014 patients with 2 factors, 656 patients with 3 factors, 172 patients with 4 factors, and 29 patients with 5 factors. Significant differences in disease-free survival (DFS) rates were observed between the five groups. The DFS rate was highest in the 0-factor (99.6% at 131 months) and 1-factor (99.3% at 131 months) groups, lowest in the 5-factor group (62.1% at 131 months), and intermediate in the 2-factor (94.7% at 131 months), 3-factor

Risk score	Negative	Positive	Total	Positive rate
0	159	4	163	2.45%
1	1111	11	1122	0.98%
2	251	6	257	2.33%
3	112	5	117	4.27%
4	732	31	763	4.06%
5	914	55	969	5.68%
6	54	8	62	12.90%
7	142	38	180	21.11%
8	404	111	515	21.55%
9	444	107	551	19.42%
10	13	7	20	35.00%
11	36	36	72	50.00%
12	49	44	93	47.31%

Table 4. Risk scores and percentage of positive lateral lymph node metastasis in PTC patients.

	B	SE	Sig.	Exp(B)	95.0% CI Exp(B)	
					Down	Up
Gender (male vs. female)	0.239	0.22	0.277	1.271	0.825	1.956
Age (≤ 35 years vs. > 35 years)	0.19	0.207	0.359	1.209	0.806	1.812
Tumor size (Φ > 1.0 cm vs. Φ ≤ 1.0 cm)	0.783	0.327	0.016	2.189	1.154	4.152
Lobe dissemination (positive vs. negative)	0.718	0.255	0.005	2.051	1.245	3.379
Psammoma body (positive vs. negative)	0.729	0.427	0.088	2.073	0.897	4.79
Capsule invasion (positive vs. negative)	− 0.154	0.217	0.478	0.857	0.56	1.312
Bilateral (positive vs. negative)	− 0.24	0.254	0.346	0.787	0.478	1.295
Tumor number (Multifocality vs. Solitary)	1.07	0.222	0.000	2.916	1.887	4.507
CLN metastasis (positive vs. negative)	0.839	0.273	0.002	2.314	1.356	3.949
LLN metastasis (positive vs. negative)	1.011	0.225	0.000	2.749	1.77	4.269

Table 5. Cox's proportional hazards regression model for recurrence.

(95.5% at 131 months), and 4-factor (89.0% at 131 months) groups (Fig. 2). Patients with a greater number of risk factors were generally more vulnerable to recurrence.

Discussion

The necessity of LLN dissection for therapeutic purposes in PTC patients is undisputed, while the need for prophylactic LLN dissection remains a topic of ongoing debate. According to recommendations 27a and 28 of the ATA Thyroid Cancer Guidelines, lateral neck dissection should be performed solely as a therapeutic intervention for known disease, and prophylactic LLN dissection is not recommended due to the significant risks and lack of impact on survival[7]. Yan et al.[16] evaluated four studies, including 483 participants, and concluded that lymph node dissection had no advantage in preventing PTC recurrence. Moreover, lymph node dissection may even increase the incidence of surgical complications. Conversely, Huang et al.[17] argue that prophylactic CLN and LLN dissection could modify PTC staging and simplify postoperative management for clinicians. They suggest that DLNs in PTC patients should be dissected and sent for consultation during surgery. If the result is positive, thorough CLN dissection and further evaluation of LLN should be conducted. Metastases to lymph nodes in the lateral compartment (levels I-V) have been associated with a worse prognosis[6]. Consequently, an increasing number of scholars propose performing prophylactic ipsilateral LLN dissection on high-risk patients. The challenge now is identifying patients at high risk of LLN metastasis.

Imaging modalities such as ultrasound, iodine scans, computed tomography (CT), hybrid imaging modalities, technetium-99 m methoxyisobutylisonitrile scintigraphy (MIBI scan), and magnetic resonance imaging (MRI) can each play a crucial role in assessing the lateral neck. According to recommendations 21 and 22 of the ATA Thyroid Cancer Guidelines, ultrasound examination is considered the primary screening and surveillance imaging for detecting lateral neck metastasis due to its low cost, wide availability, bedside utility, and real-time imaging capabilities[7]. However, clinical examinations, including ultrasound, have limitations. Ultrasound can detect suspicious cervical lymph node enlargement in only 20–31% of patients. Additionally, the sensitivity of ultrasound in diagnosing central lymph node metastasis is low (10.5–61%), while central lymph nodes are most likely to harbor metastasis. The diagnostic accuracy of LNM via ultrasound is significantly affected by operator variability[18], potentially leading to incomplete clinical treatment and severe health threats for patients.

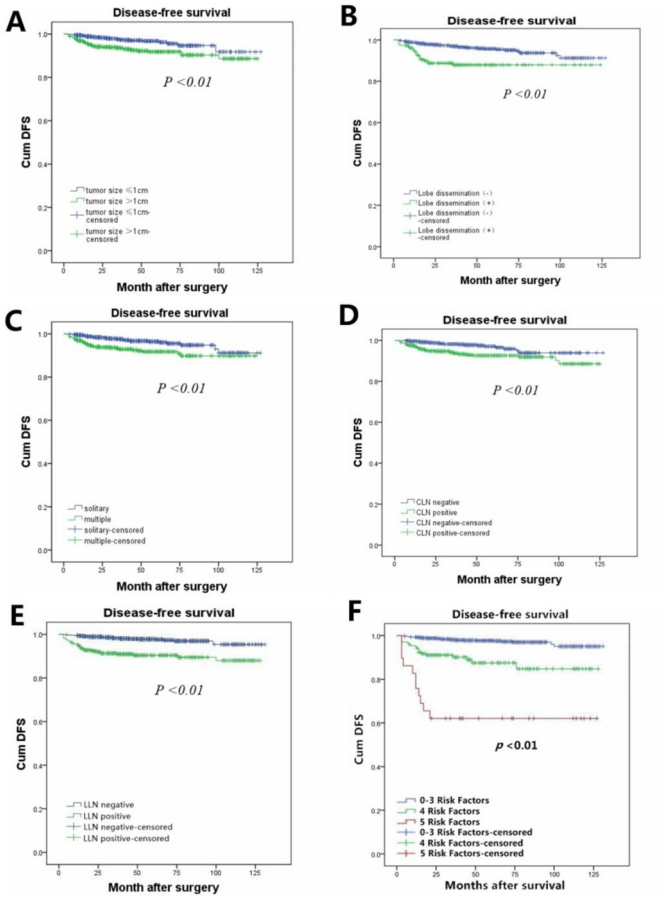

Fig. 2. (**A**) Comparison of DFS rates between patients with tumor size > 1.0 cm and tumor size ≤ 1.0 cm ($P < 0.01$). (**B**) Comparison of DFS rates between patients with lobe dissemination (+) and lobe dissemination (−) ($P < 0.01$). (**C**) Comparison of DFS rates between patients with solitary tumors and multifocality ($P < 0.01$). (**D**) Comparison of DFS rates between patients with CLN negative and CLN positive ($P < 0.01$). (**E**) Comparison of DFS rates between patients with LLN negative and LLN positive ($P < 0.01$). (**F**) DFS rates in the 5-factor group and 4-factor group were significantly lower than in other groups ($P < 0.01$).

Therefore, discovering appropriate clinical and pathological predictors of lymph node metastasis to guide treatment decisions has become increasingly crucial.

Currently, there are no uniform evaluation criteria for cervical lymph node metastasis. Several studies have reported various possible risk factors, but the results are inconsistent, warranting further investigation. Therefore, in our study, we analyzed the correlation between gender, age, tumor size, tumor number, capsule invasion, tumor location, lobe dissemination, presence of psammoma bodies, and CLN and LLN metastasis based on existing thyroid carcinoma staging or prognosis rating systems, including EORTC (European Organization for Research and Treatment of Cancer), MACIS (Metastases, Age, Completeness of resection, Invasion, Size), and TNM (Tumor, Node, Metastasis) systems[19].

In recent decades, the lymphatic drainage pattern of the thyroid has been extensively investigated, and lymph node metastasis was found primarily in the central compartment before spreading to the ipsilateral lateral compartment. Some studies[20] reported that the status of central lymph nodes is valuable in predicting lateral node metastasis. The number of positive CLNs and the CLN ratio in PTC were also used to determine the presence of LLN metastasis and inform postoperative follow-up. In our study, the rate of LLN metastasis in the CLN metastasis positive group was significantly higher than in the CLN metastasis negative group (21.22% vs. 3.44%, $p < 0.01$), consistent with previous studies. In multivariate analysis, CLN metastasis was an independent risk factor for LLN metastasis ($P = 0.000$, odds ratio 4.676) and indicated a poor prognosis ($P = 0.002$, odds ratio 2.314).

It is widely accepted that women are more susceptible to PTC. Miranda-Filho[1] believed that there was a significant correlation between the incidence of PTC and estrogen levels in women. Fan et al.[21] found that estrogen receptor α could promote the growth of PTC by enhancing an important prosurvival catabolic process, autophagy, in PTC cells. Zhu et al.[22] found that estrogen can accelerate the growth, migration, invasion, and glycolysis of PTC cells by enhancing DNMT3B-mediated FAM111B methylation. Our study included 909 males and 3198 females, with a male-to-female ratio of 1:3.52, consistent with previous studies. Moreover, our results showed that the LLN metastasis rate in males (12.76%) was significantly higher than in females (9.85%) ($P < 0.01$),

while in multivariate analysis, no significant difference was found in the rate of LLN metastasis between males and females.

Age has long been a prognostic predictor in PTC patients, but its role in LLNM remains controversial[23]. Some studies[24] suggest no significant difference in lymph node metastasis rates between patients older than 45 years and those younger than 45 years, while others[25] identify age > 70 as a key factor influencing metastasis. Conversely, several studies[26] report a significantly higher rate of lymph node metastasis in younger patients (≤ 45 years) compared to older patients (> 45 years) with papillary microcarcinoma of the thyroid (65.8% vs. 34.2%, $P = 0.001$). Our findings support the latter. Potential reasons for the increased susceptibility of younger patients to LLNM include tumor biological characteristics (e.g., rapid proliferation), genetic mutations (e.g., BRAF V600E), and immune system activity. This remains an area of active research, with further studies needed to clarify the underlying mechanisms. In our study, patients were grouped by age (per 10-year intervals). We found that the LLNM rate was significantly higher in patients ≤ 35 years old compared to those > 35 years (19.51% vs. 9.91%, $P < 0.01$), with the rate stabilizing after age 35. This suggests that patients under 35 are more vulnerable to LLNM, and age 35 could serve as a cutoff point for predicting LLNM. However, no significant correlation was found between age and recurrence ($P > 0.05$).Some studies suggested that patients with tumor size > 3 cm are more susceptible to lymph node recurrence[27]. Wang et al.[28] found that tumor size was significantly associated with lateral lymph node metastasis. In our study, LLN metastasis increased with tumor size ($P < 0.01$). A nearly linear correlation ($y = 0.0808x + 0.0746$; $R^2 = 0.9803$) was found between LLNM rate and tumor size, and $\Phi = 1.0$ cm was presented as a cut-off point for predicting LLNM by ROC curve (Fig. 1). Furthermore, our study found that tumor size exceeding 1.0 cm presented a higher risk of recurrence ($P = 0.016$, odds ratio 2.189) (Fig. 2). Capsule invasion has always been considered a symbol of tumor progression, with patients exhibiting higher mortality and recurrence rates[29].

Wu et al.[30] suggested that extrathyroidal extension negatively affects survival rates. Mao et al.[27] found that thyroid capsular invasion is a risk factor for increasing lymph node metastasis. Extrathyroidal extension was also found to positively affect the number of LNMs[31]. Our results showed that capsule invasion is an independent risk factor for LLNM ($P = 0.001$, odds ratio 1.468). However, no significant correlation was found between capsule invasion and recurrence, indicating that microscopic invasion of the thyroid capsule may not affect recurrence.

Recently, Feng[15] and colleagues suggested that an increase in the number of tumor foci was significantly associated with cervical lymph node metastasis and advanced TNM stage of PTC, and that the number of tumor foci independently predicted lateral lymph node metastasis. Increased tumor number seemed to be associated with higher rates of capsular invasion, extrathyroidal extension, and lymph node metastasis[32]. Previous studies showed that the presence of psammoma bodies is a useful predictor of prognosis and aggressive tumor behavior in PTC patients[33].

Mao et al.[27] identified several factors associated with lymph node metastasis in thyroid carcinoma, including age (< 1 year), sex (male), multifocality, tumor size (> 1 cm), tumor location (upper 1/3), capsule infiltration, and extrathyroid extension. However, bilateral tumors and Hashimoto's thyroiditis were not associated with lymph node metastasis. In this study, lobe dissemination (+), psammoma bodies (+), and multifocality were significantly associated with CLNM and LLNM in the univariate analysis ($P < 0.01$). However, only lobe dissemination (+) was an independent risk factor for LLNM ($P = 0.000$, odds ratio 3.411). Additionally, in the Cox regression analysis, multifocality ($P = 0.000$, odds ratio 2.916) and lobe dissemination (+) ($P = 0.005$, odds ratio 2.051) were found to negatively impact the prognosis of PTC patients.

Recent studies suggest that the location of the primary tumor within the thyroid gland may influence lymph node metastasis in PTC patients, though its exact role remains controversial[27,34]. A particularly high likelihood of lateral LNM was observed in T1a PTC patients with tumors located in the upper lobe of the thyroid gland, especially those > 5 mm in size, which could be considered a risk factor for lateral LNM in the clinical management of T1a PTC[35]. Liu[36] also found that tumors located in the upper 1/3 of the lobe were more susceptible to LLNM and skip metastasis. Patients with tumors in the lower or middle poles seemed to have a higher risk of CLNM than those in the upper pole[37,38]. In our study, we found that LLNM rates in the upper pole were significantly higher than in other groups, while no significant difference in CLNM rates was found between the groups based on tumor location. Furthermore, tumor location was not included in the multivariate or Cox regression analyses due to incomplete data.

Based on the independent risk factors identified, we developed a risk-scoring model to predict LLNM. A predictive model not only elucidates the effect of each predictor on the probability of response but also allows for quick estimation of response probability for individual subjects. This risk-scoring model demonstrated good discriminative power, with a sensitivity of 75.80% and a specificity of 74.20% when the cut-off point was set at 5. The model is simple and efficient to implement in clinical practice and can help surgeons identify high-risk groups objectively. Combining this model with imaging examinations enables surgeons to make more comprehensive and accurate decisions pre- and intra-operatively, avoiding incomplete treatment in the lateral compartment. Due to the high risk of LLNM, we advocate prophylactic LLN dissection in patients with a total score greater than 5 according to the risk-scoring model.

Our study results indicated that tumor size > 1.0 cm, lobe dissemination (+), multifocality, CLNM, and LLNM were significant risk factors for recurrence. The DFS rate in patients with more than four factors was significantly lower than in other groups, indicating that patients with a larger number of risk factors are more vulnerable to recurrence. Therefore, more aggressive treatment and more frequent follow-up should be considered for patients with more than four risk factors.

This study has several limitations. Firstly, it was a single-center retrospective study. Secondly, we assumed that patients who were radiologically LLN-negative will be considered LLN-negative in subsequent studies based on ultrasound and CT scans. However, conducting large-scale prospective studies on LLN metastasis is both challenging and impractical, making retrospective studies a feasible alternative. Due to the large patient cohort

and extended duration of the study, as well as the limited availability of CT imaging in the early stages of data collection, some patient data are incomplete. Thirdly, some factors, such as surgical approach and postoperative RAI ablation therapy, were not included in our evaluation of recurrence risk factors and should be considered in future studies.

Conclusion

In summary, patients who are male, have a tumor size > 1.0 cm, lobe dissemination (+), capsule invasion (+), and CLNM (+) are more vulnerable to LLNM. Based on these five independent risk factors, a risk-scoring model was designed to predict LLNM. Patients with a total score ranging from 0 to 5 were categorized into the low-risk group for LLNM, while those with a total score greater than 5 were categorized into the high-risk group. Additionally, tumor size > 1.0 cm, lobe dissemination (+), multifocality, CLNM, and LLNM may increase the risk of recurrence and potentially decrease survival. Therefore, we recommend that for patients with a total score greater than 5, clinicians should conduct more thorough examinations and consider all relevant factors comprehensively. It is also essential to engage in detailed communication with the patient, ensure close follow-up, and, when necessary, consider preventive neck lymph node dissection. And more aggressive treatment and more frequent follow-up should be considered for patients with tumor size > 1.0 cm, lobe dissemination (+), multifocality, CLNM, and LLNM.

Data availability

The datasets analyzed during the current study are not publicly available due to patient privacy concerns, but are available from the corresponding author on reasonable request.

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Author contributions

Y.-h. Guo, Y.-y Liu and W.-d Teng made major contributions in the preparation of the figures, interpretation of the results and writing of the manuscript. Y. Pan, L.-z.Zhang, D.-d. Feng, J.-f. Wang, J.-j. Xu, C.-m. Zheng. X.-h. Zhu provided technical assistance and data processing and Z. Tan reviewed and revised the manuscript. L.-h. Jiang guided for research and organized the work.

Declarations

Competing interests

The authors declare no competing interests.

Ethics statement

This retrospective study was approved by the medical ethics review committee in Zhejiang Provincial People's Hospital (Approval No. [Zhe Ren Yi Lun Shen 2024 Other [259]). And patient informed consent was waived. Furthermore, it adhered to the ethical standards set forth by the World Medical Association's Declaration of Helsinki.

Additional information

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