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Unilateral papillary thyroid carcinoma treated with contralateral central lymph node dissection
A nomogram to aid in decision-making

Wenjie Chen, MD, Zhihui Li, MD, Jingqiang Zhu, PhD, Jianyong Lei, PhD, Tao Wei, MD*

Abstract

The central lymph nodes of the neck are the most common sites of papillary thyroid carcinoma (PTC) but cannot be easily diagnosed preoperatively. Prophylactic central lymph node dissection (CLND), especially contralateral CLND, is not recommended in various guidelines due to its high risk. The aim of our study was to establish an objective point score based on preoperative and intraoperative data to guide the selection of patients for contralateral CLND.

We retrospectively evaluated 1085 consecutive patients with PTC treated by thyroidectomy for inclusion in this study (the training cohort). Variables of contralateral central lymph node macro-metastasis (CLNMM) were investigated using univariate and multivariate analyses; subsequently, nomograms were developed and then validated in an independent cohort of patients (n = 326, the validation cohort).

Univariate and multivariate analyses indicated that preoperative fine needle aspiration-proven ipsilateral lateral lymph node metastasis (LNM) (odds ratio [OR] 4.888, 95% confidence interval [CI] 1.587–41.280, $P < .001$) and cases with frozen-section pretracheal LNM (OR 19.015, 95% CI 2.949–186.040, $P < .001$) or Delphian LNM (OR 4.494, 95% CI 1.503–54.128, $P < .001$) were the 3 risk factors for contralateral CLNMM. A receiver operating characteristic curve indicated a cutoff value of 1 for the frozen-section pretracheal LNM number or the Delphian LNM number as a predictor of contralateral central lymph node metastasis (CLNM). The nomogram was then generated according to the 3 risk factors and well validated in the external cohorts, and the intraoperative frozen-section results were highly consistent with the postoperative pathological results.

The proposed nomogram based on the 3 factors showed a good prediction of contralateral CLNMM in PTC.

Abbreviations: ATA = American Thyroid Association, CI = confidence interval, CLND = central lymph node dissection, CLNM = central lymph node metastasis, CLNMM = central lymph node macro-metastasis, cN0 = clinically node-negative, FNA = fine needle aspiration, LNM = lymph node metastasis, OR = odds ratio, PTC = papillary thyroid carcinoma, ROC = receiver operating characteristic.

Keywords: central lymph node dissection, lymph node metastasis, nomogram, papillary thyroid carcinoma, unilateral

1. Introduction

The incidence of thyroid cancer has increased dramatically worldwide.[1–3] It is the most common endocrine malignancy, accounting for 94.5% of total new endocrine cancers and 65.9% of deaths due to endocrine cancers.[4] Papillary thyroid carcinoma (PTC) accounts for more than 80% of thyroid carcinomas.[1] Despite the excellent overall prognosis, up to 70% of PTC patients exhibit lymph node metastasis (LNM) in the central neck (level VI) at the time of surgery, in the pathological specimens or during the course of follow-up.[5] Cervical LNM is commonly associated with an increased rate of loco-regional recurrence and distant metastasis.[6,7]

Generally, therapeutic central compartment neck dissection is well accepted for all PTC patients with proven preoperative ultrasonographic scans, fine needle aspiration (FNA) cytology or Tg level examinations. However, prophylactic central lymph node dissection (CLND) is less favored in the 2015 American Thyroid Association (ATA) guidelines[8] due to its higher rate of postoperative complications, including recurrent nerve paralysis and temporary or permanent hypoparathyroidism.[4,9] Ipsilateral prophylactic CLND is recommended for selected clinically node-negative (cN0) PTC patients in the ATA and National Comprehensive Cancer Network guidelines[8,10] and is recom-
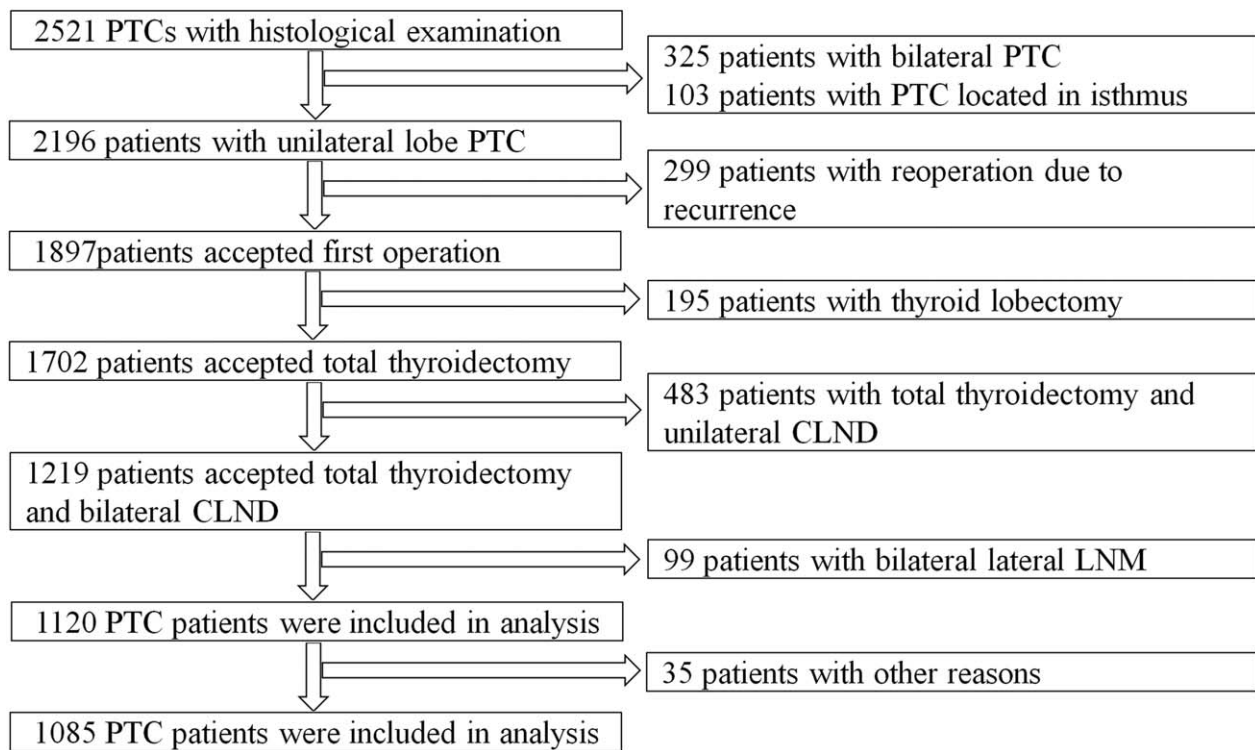
Figure 1. Flow chart of the inclusion and exclusion criteria of this study. In total, 1085 papillary thyroid carcinoma patients were included in the present study.

mended for all cN0 PTC patients by the Japanese Society of Thyroid Surgeons, the Japanese Association of Endocrine Surgeons[11] and Chinese guidelines.[12] Prophylactic contralateral CLND is not recommended in all guidelines; therefore, precisely predicting contralateral central lymph node metastasis (CLNM), especially central lymph node macro-metastasis (CLNMM; metastatic lymph node diameter larger than 2 mm), is essential for reducing complications and recurrence in PTC patients.

To date, only a few studies have detected the risk factors of contralateral CLNM[13–15]; however, none of these studies have established a nomogram system to predict contralateral CLNM. Although Hei et al[16] attempted to build a nomogram to predict contralateral CLNM, the 142 PTC patients they included did not constitute a sufficient sample to generate an objective predictive model; meanwhile, they included contralateral lymph node micro-metastasis, which may lead to less necessity for contralateral CLND. Furthermore, frozen sections of the pretracheal and Delphian lymph nodes were not taken into consideration, and no validation group was used to validate this nomogram. In our study, we aimed to develop and validate a nomogram system to help predict contralateral CLNMM based on preoperative and intraoperative data.

2. Patients and methods

2.1. Study population

The medical records of unilateral PTC patients who underwent total thyroidectomy combined with bilateral CLND were retrospectively reviewed and collected in our hospital's online

system. In total, data from 2521 PTC patients were manually reviewed, and based on the inclusion and exclusion criteria shown in Figure 1, 1085 patients were included in our analysis. In our previous study,[17] we examined the LNM characteristics of PTCs located in the isthmus and suggested that total thyroidectomy and bilateral CLND should be performed. To improve the precision of our scoring system, we excluded 103 patients with PTC located in the isthmus. PTC patients with bilateral LNM should be treated with total thyroidectomy and bilateral CLND according to guidelines. Thus, we excluded 99 PTC patients who underwent bilateral LND; prophylactic lateral neck compartment LND was not performed according to the ATA[8] and other guidelines.[10–12] Consequently, 1085 consecutive unilateral PTC patients were enrolled in this study (the training cohort).

To validate the nomogram system, which was established based on preoperative and intraoperative data, patients with unilateral PTC who underwent total thyroidectomy plus bilateral CLND in our center were consecutively and prospectively enrolled as the validation cohort. A total of 326 patients were included in the final validation cohort.

Our retrospective (training cohort) and prospective (validation cohort) studies were both approved by the Institutional Review Board of West China Hospital and adhered to the 1990 Declaration of Helsinki and its subsequent amendments. All patients signed informed consent forms.

2.2. CLND

We classified unilateral central compartments superiorly by the hyoid bone, inferiorly by the innominate vein, laterally by the carotid sheaths, dorsally by the prevertebral fascia, and medially

by the ipsilateral sidewall of the trachea. Central lymph node specimens were classified and mapped in our previous study.[18] We defined the pretracheal compartment as superior to the lower edge of the isthmus, inferior to the innominate vein, and bilateral to the sidewall of the trachea. For patients with bilateral cN1a, therapeutic bilateral CLND was performed; for patients with cN1b, bilateral CLND and ipsilateral lateral LND were performed. For patients with cN0 or unilateral cN1a, the pretracheal tissue and Delphian lymph node were harvested before the thyroidectomy and routinely sent to the pathology department for frozen-section analysis; if the result was positive for LNM, we performed contralateral CLND; if not, ipsilateral CLND was performed. The predictive value of pretracheal and Delphian lymph nodes in contralateral CLNM has been proven by our previous studies.[14,19] All surgeries were performed by 1 of 3 experienced thyroid surgeons with over 10 years of experience who performed at least 400 thyroid surgery cases annually.

Intraoperative recurrent nerve monitoring was performed from December 2008 forward and particular attention was paid to preserving the parathyroid glands in situ, with parathyroid autotransplantation performed in the sternocleidomastoid as required, mostly due to mistaken or intentional removal due to ischemic changes. Carbon nanoparticles may be used as a lymph node tracer to identify affected lymph nodes and preserve the parathyroid.[20]

2.3. Analysis variables

Participants were divided into 2 groups: group A, with contralateral CLNMM; and group B, without contralateral CLNMM. The clinical baseline and intraoperative frozen-section characteristics, which have been associated with contralateral CLNM in other reports, were comprehensively collected and analyzed. In the univariate analysis, the cutoff value for patient age was 45 years, which changed to 55 years according to the 8th American Joint Committee on Cancer system, and the cutoff values of the neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio were set to 2.7 and 105, respectively, according to our previous study.[21] Because the ipsilateral central lymph node is not routinely sent to the pathology department for frozen-section analysis in many centers (typically resulting in long wait times of 1–2 hours), other reports on the ipsilateral CLNM number or rate being used to predict contralateral CLNM are mainly based on data from the postoperative histological examination.[14] However, the aim of our study was to establish a nomogram system based on preoperative and intraoperative data to guide the selection of patients for contralateral CLND. Therefore, use of the ipsilateral CLNM number or rate to predict contralateral CLNMM was not appropriate for the present study. Furthermore, preoperative BRAFV600E and TERT mutation assays have been conducted only within the past 2 years in our center and were not included in our analysis due to the limited number of cases.

2.4. Statistical analysis

A univariate analysis was used to evaluate the relationships between contralateral CLNMM and clinical and intraoperative frozen-section factors using Pearson $\chi2$ test or Fisher exact test; variables with P values less than .05 in the univariate logistic regression analysis were included in the multivariate analysis. The

nomograms were built based on the results of the multivariate analysis of the training cohort, and the final model selection for the nomograms was performed by a backward step-down selection process using the Akaike information criterion. The nomograms were created using R i386 3.3.2 (R Core Team, 2019).

3. Results

3.1. Univariate and multivariate analysis

In the training cohort, a total of 837 patients presented with contralateral CLNMM (group A), and there were 248 patients without contralateral CLNMM (group B). As shown in Table 1, the baseline demographic data, preoperative ultrasound imaging evaluation, and intraoperative evaluation were compared between the 2 groups. Although the patients in group A were older, the difference was not statistically significant ($P > .05$). In addition, group A included more patients with nodular goiters and larger PTCs ($P < .05$). Finally, 280 of 837 (33.5%) PTC patients in group A had a contralateral CLNMM combined with preoperative FNA-proven ipsilateral lateral LNM; this proportion was significantly higher than that of group B ($P < .001$). Based on the frozen-section information, pretracheal lymph nodes and Delphian lymph nodes were routinely sent for frozen-section examination for LNM; group A exhibited a greater rate of pretracheal and Delphian LNM than group B (all $P < .001$).

All factors that exhibited a difference between the 2 groups ($P < .10$) were included in the multivariate analysis; as shown in Table 2, the rate of contralateral CLNMM was significantly higher in cases with preoperative FNA-proven ipsilateral lateral LNM ($P < .001$, odds ratio [OR] 4.888) and in cases with frozen-section pretracheal LNM ($P < .001$, OR 19.015) or Delphian LNM ($P < .001$, OR 4.494).

3.2. ROC curve analysis

Three risk factors were found in the multivariate analysis. We attempted to use a receiver operating characteristic (ROC) curve analysis to determine the cutoff value. However, because preoperative FNA was conducted only for lymph nodes with the highest risk of metastasis (often only 1 lymph node) and because the aim of our study was to predict contralateral CLNMM, an ROC curve analysis was used only to determine the cutoff value for frozen-section pretracheal LNM and Delphian LNM. As shown in Figure 2, the Youden index was highest when the frozen-section pretracheal LNM number was 1 (0.536) and when the frozen-section Delphian LNM number was 1 (0.244), based on clinical experience that the number of lymph nodes should be integers. These results indicate that when patients have a frozen-section pretracheal LNM or Delphian LNM number equal to or greater than 1, contralateral CLNMM metastasis should be evaluated.

3.3. Nomogram for predicting contralateral CLNM

A predictive nomogram based on the 3 risk factors was created, as shown in Figure 3. This nomogram integrated the results of the following 3 techniques to predict the possibility of contralateral CLNMM in individual PTC patients: drawing a vertical line from each variable axis to the point axis, summing all points to obtain the total points, and drawing a vertical line to the risk axis to determine the possibility of contralateral CLNMM for every case, as shown in Figure 3. The C-index of the nomogram was

Table 1

Univariate analysis of contralateral central lymph node macro-metastasis in unilateral papillary thyroid carcinoma patients.

Variable	Contralateral CLNMM		
	Presence (group A) 837	Absence (group B) 248	*P* value
Baseline demographic data			
Age (≤45/>45 yr)	555/282	156/92	.093
Age (≤55/>55 yr)	701/136	200/48	.063
Sex (male/female)	212/625	73/175	.682
Race (Han/other)	829/8	244/4	.207
Chronic disease (yes/no)	158/679	31/217	.608
HD (yes/no)	221/616	71/177	.712
Graves disease (yes/no)	8/829	9/239	.122
Nodular goiters (yes/no)	425/412	97/151	.049[*]
NLR (≤2.7/>2.7)	742/95	192/56	.899
PLR (≤105/>105)	588/249	160/88	.957
TSH level (≤4.2/>4.2mU/L)	692/145	196/52	.311
Preoperative US imaging evaluation			
Multifocality (yes/no)	114/723	50/198	.115
Capsule invasion (yes/no)	256/58	79/169	.105
Extrathyroid extension (yes/no)	40/797	14/234	.063
Tumor size (≤10 mm, >10mm)	391/446	115/133	.026[*]
Largest tumor size (≤10 mm, >10mm)	422/415	127/121	.201
Tumor extension (T1/T2/T3-T4)	381/456	103/145	.733
Primary tumor location (upper/middle or lower)	205/632	141/107	.144
Preoperative FNA-proven ipsilateral lateral LNM (yes/no or uncertain)	280/557	24/224	<.001[**]
Intraoperative evaluation			
Macroscopic capsule invasion (yes/no)	300/537	74/174	.191
Macroscopic extrathyroid extension (yes/no)	57/780	19/229	.294
Frozen-section pretracheal LNM (presence/absence)	598/239	32/216	<.001[**]
Frozen-section Delphian LNM (presence/absence)	390/447	48/200	<.001[**]

Chronic disease: hypertension and/or diabetes; FNA = fine-needle aspiration, HD = Hashimoto's thyroiditis, LNM = lymph node metastasis, NLR = neutrophil-lymphocyte ratio, PLR = platelet-lymphocyte ratio.
[*] $P < .05$.
[**] $P < .001$.

0.811. In the 326 external validation cohorts, the C-index of the nomogram for predicting contralateral CLNMM was 0.782 (95% confidence interval [CI]: 0.762–0.797).

3.4. Comparison of frozen-section and postoperative pathological results

Figure 4 depicts the association between the frozen-section and postoperative pathological results for pretracheal LNM and Delphian LNM. The 2 evaluation methods were consistent in 91.1% of PTC patients with a pretracheal LNM number and 87.4% of those with a Delphian LNM number. The high consistency between the intraoperative frozen sections and

postoperative pathological results indicated the rationality of using intraoperative frozen sections to evaluate the status of metastasis in pretracheal and Delphian lymph nodes and then predicting the possibility of contralateral CLNM.

4. Discussion

The incidence of LNM of PTC in the central compartment of the neck is reportedly as high as 90%,[22] even in PTC cases that are (cN0).[23] The central compartments are generally the first and most commonly involved in PTC metastasis; they exhibit a significant risk of recurrence, and the most common recurrence site is the central compartment.[24] Moreover, the surgical

Table 2

Multivariate analyses of contralateral central lymph node macro-metastasis in unilateral papillary thyroid carcinoma patients.

Variables	Odds ratio	95% CI	*P* value
Age (≤45/>45 yr)	0.554	0.421–0.862	.820
Age (≤55/>55 yr)	0.672	0.481–0.792	.569
Nodular goiters (yes/no)	1.990	1.772–14.348	.682
Tumor size (≤10 mm, >10mm)	0.807	0.412–0.882	.971
Preoperative FNA-proven ipsilateral lateral LNM (yes/no or uncertain)	4.888	1.587–41.280	<.001[**]
Frozen-section pretracheal LNM (presence/absence)	19.015	2.949–186.040	<.001[**]
Frozen-section Delphian LNM (presence/absence)	4.494	1.503–54.128	<.001[**]

FNA = fine-needle aspiration, LNM = lymph node metastasis.
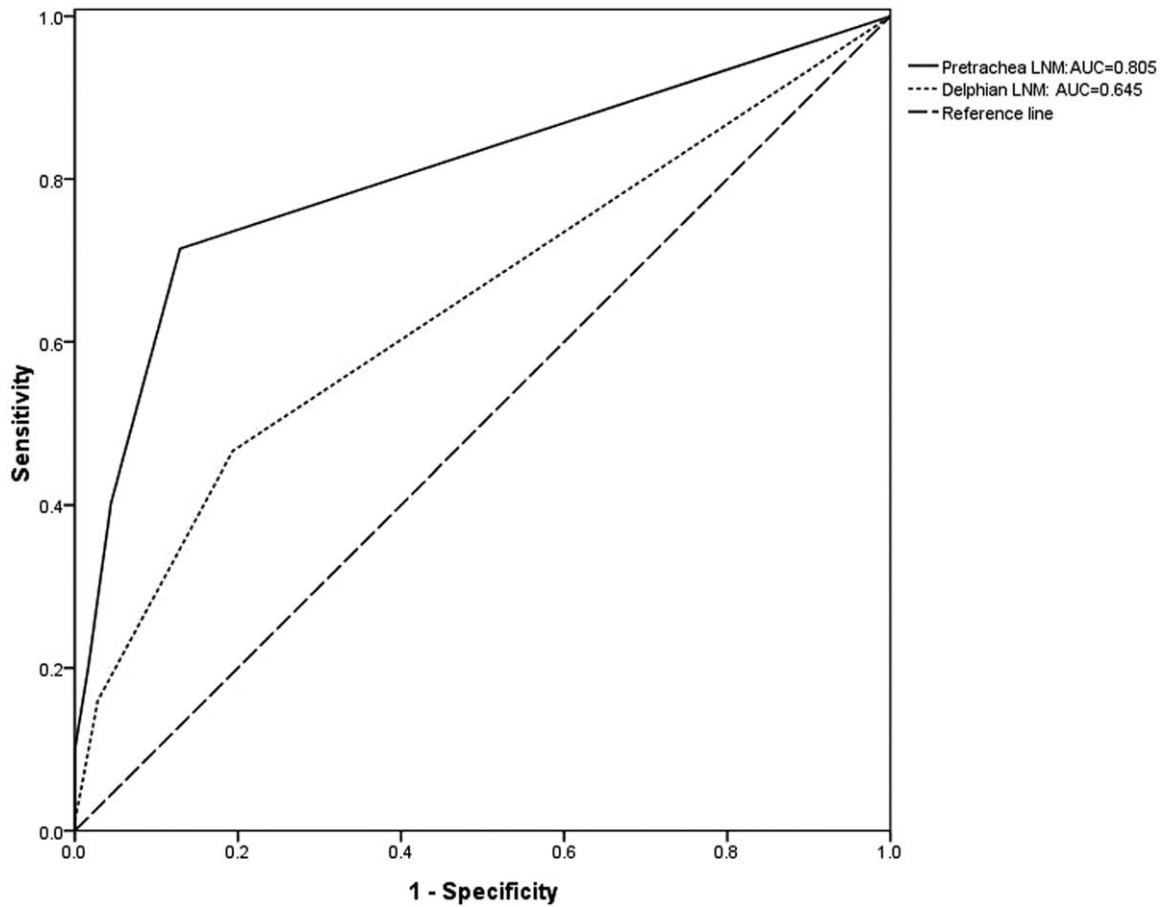[*] $P < .05$.
[**] $P < .001$.

Figure 2. Receiver operating characteristic curve analysis was used to determine the cutoff value for the pretracheal and Delphian lymph node metastasis numbers to predict contralateral central lymph node metastasis , resulting in a cutoff value of 1.
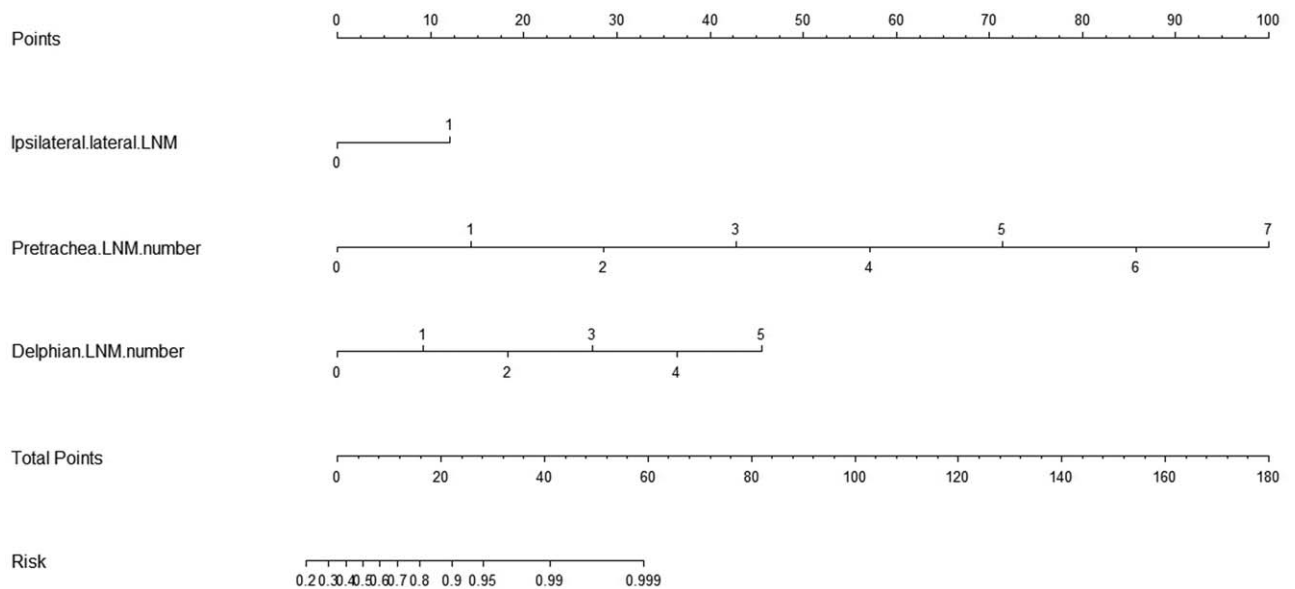

Figure 3. Nomogram for predicting the risk of contralateral central lymph node metastasis based on the 3 risk factors.
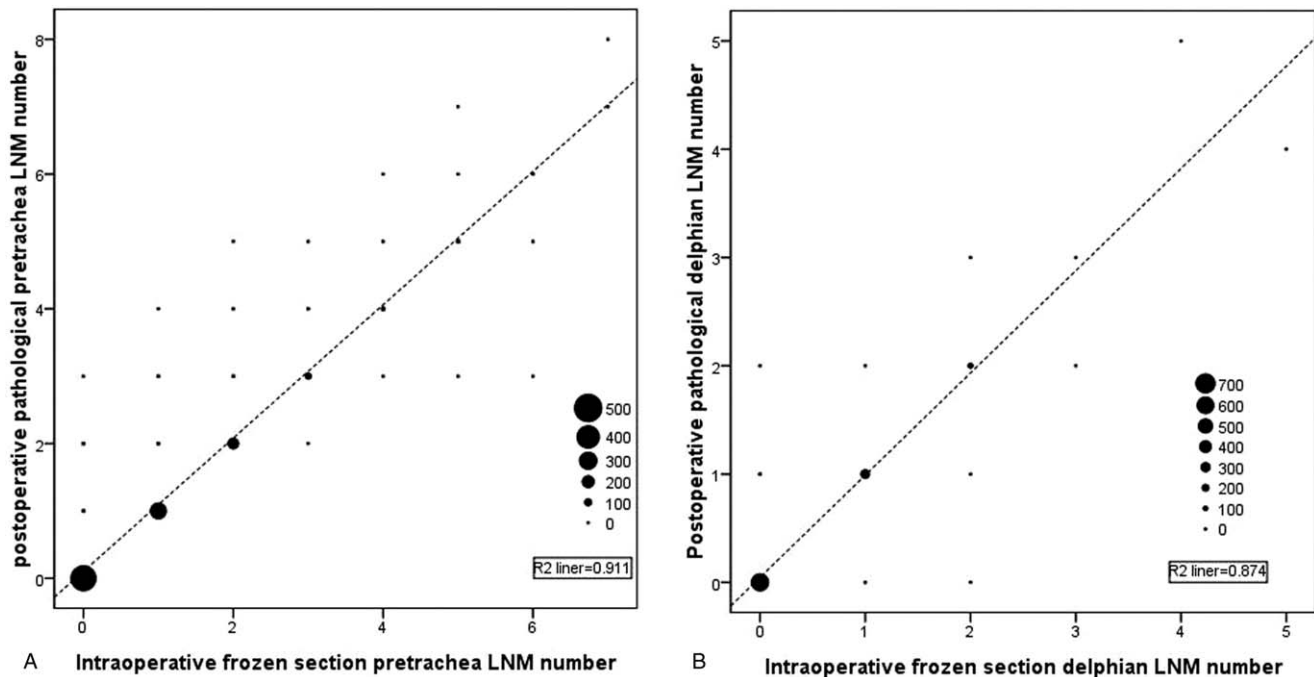
Figure 4. Linear correlation between the intraoperative frozen-section data and postoperative pathological examination of the pretracheal (A) and Delphian (B) lymph node metastasis numbers.

procedure is more difficult for reoperation in the central compartment and has a high rate of postoperative complications.[25,26] Routine CLNM examinations may also provide useful and accurate pathological N-staging information that may guide subsequent treatment and follow-up. This may enhance the effect of radioiodine ablation therapy by removing potentially positive nodes,[27] preventing recurrence, and improving survival.[28–30] However, prophylactic CLND is controversial due to a possible increased risk of hypoparathyroidism or recurrent laryngeal nerve injury, especially in bilateral CLND cases.[31] PTC patients may benefit from ipsilateral CLND according to certain guidelines due to the limited risk of complications[8,11,12]; however, prophylactic bilateral CLND has not been recommended for PTC patients. Therefore, it is clinically important to identify or predict patients with contralateral level VI LNM, which may facilitate decision-making regarding contralateral CLND, especially for cN0 cases.

Previous studies[14,32] have evaluated the rate of contralateral CLNM and detected the clinicopathological factors predictive of contralateral CLNM in clinical node-negative neck PTCs. The inclusion of only PTCs that are clinically lymph node-negative to detect the predictive risk factors is not precise due to the high rate of Hashimoto's thyroiditis (26.9%), which may lead to false lymphadenectasis in level VI. Therefore, we included all PTC patients in the present analysis, and our study had a homogenous population due to the inclusion of unilateral PTC patients. Moreover, we excluded patients who underwent only unilateral CLND, as well as all PTC patients who underwent elective prophylactic bilateral CLND; this selection process increased the reliability of our results.

In a previous study, the results suggested that ipsilateral central neck dissection along with lateral neck dissection was sufficient due to a low rate of contralateral CLNM (less than 9%)[33]; however, Koo et al insisted on bilateral CLND due to a high rate of contralateral CLNM (at least 34.3%).[34] Therefore, ipsilateral central neck dissection should be combined with contralateral CLND.[35] The multivariate analysis in our present study showed that preoperative FNA-proven ipsilateral lateral LNM is a predictive factor for contralateral CLNM, and our results are consistent with those of other reports. We also recommend that therapeutic lateral neck dissection should be combined with bilateral central neck dissection, even in central cN0 and lateral cN1b cases, due to the high rate of occult metastasis in region VI and the low sensitivity of preoperative imaging.[34,35]

Compared with previous studies on the prediction of contralateral CLNM,[13,14,16,19] our present study is not the first to determine the value of ipsilateral lateral LNM, pretracheal LNM, or Delphian LNM to predict contralateral CLNMM. However, compared to other studies, our study has 4 advantages. First, although the data were obtained from a single center, we included a large cohort of PTC patients, much larger than that in other reports, to detect the risk factors. Second, based on the multivariate analysis, we generated a nomogram, which provided greater visualization of individual PTC patients in clinical practice. Third, we found not only that the status of pretracheal LNM and Delphian LNM could predict contralateral CLNM but also that the cutoff value for pretracheal or Delphian LNM is 1; therefore, if only 1 LNM is present in the pretracheal or Delphian lymph node, we should assume that contralateral CLNM is present, and when the number increases, the risk may rise accordingly. Fourth, we excluded micro-metastasis, which is not an indication for lymph node dissection. Finally, unlike other studies using postoperative histological pathological data,[13,14,19] we used intraoperative frozen-section data of pretracheal lymph nodes or Delphian lymph nodes to detect the risk factors and build the nomogram, which may be more

precise. Intraoperative frozen sections of pretracheal or Delphian lymph nodes require only 30 minutes to obtain and may yield results that can facilitate decision-making regarding contralateral CLND.

There are several limitations to this study. First, the single-center nature of the study may have limited our analysis. Second, patients who underwent total thyroidectomy with unilateral CLND were excluded from the study, although the true CLNMM status of these patients is unknown, which may have caused selection bias. However, for these patients, unnecessary extensive dissection may lead to a higher rate of complications, such as hypoparathyroidism and recurrent laryngeal nerve injury. Finally, our study only established a nomogram system to predict CLNMM; the benefits and risks of prophylactic CLND remain unknown. Further long-term follow-up studies are needed to evaluate the outcomes.

5. Conclusion

In conclusion, preoperative FNA-proven ipsilateral lateral LNM and intraoperative frozen-section-positive pretracheal LNM or Delphian LNM are the 3 risk factors of contralateral CLNMM. A nomogram model was built based on these 3 risk factors to predict the possibility of contralateral CLNMM in individual PTC patients, which can facilitate decision-making for performing contralateral LND.

Author contributions

The first author of this manuscript is Wenjie Chen; Wenjie Chen performed the research and wrote the first draft. All authors contributed to the design and interpretation of the study and to further drafts. Tao Wei is the guarantor.
Conceptualization: Wenjie Chen.
Data curation: Wenjie Chen, Jianyong Lei.
Formal analysis: Wenjie Chen.
Investigation: Wenjie Chen, Jianyong Lei.
Methodology: Wenjie Chen, Jianyong Lei.
Project administration: Jingqiang Zhu, Tao Wei.
Resources: Zhihui Li.
Software: Wenjie Chen.
Validation: Jingqiang Zhu.
Visualization: Tao Wei.
Writing – original draft: Wenjie Chen.
Writing – review & editing: Zhihui Li, Jianyong Lei, Tao Wei.

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