ORIGINAL ARTICLE

Risk stratification for lateral involvement in papillary thyroid carcinoma patients with central lymph node metastasis

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Abstract

Purpose To effectively predict lateral neck lymph nodes (LLN) metastasis in papillary thyroid carcinoma (PTC) patients with central lymph nodes (CLN) invasion, and devise targeted treatment strategies.

Methods Four hundred and thirty-four PTC patients with CLN metastasis from two medical centers were retrospectively analyzed. A new statistical model was established for predicting LLN involvement in these patients to guide lymph nodes management strategies.

Results Patients with more than five positive CLN metastasis appeared to have extremely high risk (83.0%) of LLN involvement. For patients with five or less positive CLN invasion, multivariate logistic analyses were applied. Independent risk factors for LLN involvement were determined to be: age over 40, maximum tumor diameter of no less than 1.0 cm, existence of thyroid capsular invasion, and tumor with ipsilateral nodular goiter (iNG). These factors were used to construct a predictive nomogram. The accuracy and validity of our newly built model were verified by C-index 0.761 (95% CI, 0.707–0.815) in development cohort and 0.759 (95% CI, 0.745–0.773) in validation cohort and calibration curve. The patients were stratified into three groups based on their nomogram risk scores. Possible LLN involvement rates for low-risk, moderate-risk, and relatively high-risk subgroups were 8.9%, 22.8%, and 48.2%, respectively.

Conclusions Our newly established model can effectively predict possible LLN metastasis in PTC patients, and a new strategy selection flow chart was created for patients with positive CLN invasion. For patients in high-risk group, prophylactic LLN dissection is recommended, if not, adjuvant radioactive iodine or a closer follow-up scheme should at least be conducted. For those in low-risk group, surgical intervention is unnecessary and regular follow-up is recommended.

Keywords Papillary thyroid carcinoma · Lateral lymph node metastasis · Predictive model · Treatment strategy · Risk stratification

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Introduction

Papillary thyroid carcinoma (PTC) is the predominant pathological type of thyroid malignancy [1] with satisfactory long-term survival outcome due to less aggressive behavior [2]. However, incidence of local lymph nodes metastasis is high, especially central lymph node involvement, which proved to be correlated with poorer recurrence and survival outcomes after initial surgical intervention [3–5]. Therefore, cervical lymph node management is of vital importance in patients with PTC. Usually, metastasis occurs first in central lymph nodes (CLN) and then in the node of the lateral compartment. The Japanese Society of Thyroid Surgeons recommends that CLN dissection should be performed [6], and this recommendation has been gaining the support of many surgeons [7]. In general, for patients with evidence of CLN metastasis through

preoperative ultrasonography or fine-needle aspiration (FNA) pathology, surgical managements including primary tumor and central lymph node dissection are conducted in initial operation worldwide. But for patients with negative lymph node findings preoperatively, substantial variations may exist across regions. In some countries such as Japan and China, prophylactic CLN dissection may be performed, which is not the case for countries such as the U.S. In addition, almost no consensus has been reached on the lymph node dissection outside the central neck for patients with positive CLN metastasis. Generally, lateral lymph node (LLN) dissection is only conducted on patients with evidence of metastasis through preoperative ultrasonography or FNA pathology [8], which makes the occult metastatic nodes a recurrence risk for patients with PTC. Several studies have revealed that certain indicators such as number of CLN metastasis and tumor size were independent factors for LLN metastasis [4, 9, 10], but the traditional methods of discovering relationships with LLN involvement were qualitative based, with no existing literature measuring LLN metastasis risk quantitatively for PTC patients with positive findings of CLN. The present retrospective study was designed to synthetically predict and stratify the risk of LLN metastasis in patients with CLN metastasis, to decide the LLN individualized management for patients in different risk groups.

Materials and methods

Patient cohort

Between 2017 and 2019, 488 thyroid carcinoma patients were treated with surgery in Department of General Surgery at Ruijin Hospital of Shanghai Jiao Tong University School of Medicine, and Department of Otorhinolaryngology, Head and Neck Surgery at the Eye, Ear, Nose, and Throat Hospital of Fudan University. These patients were confirmed to have CLN metastasis by postoperative pathology. Patients with any of the following criteria were excluded from our study: (1) non-PTC proven by postoperative pathology ($N = 35$); (2) having received thyroid surgery previously ($N = 13$); (3) with history or coexisting of other head and neck cancer ($N = 6$). Following these criteria, a total of 434 patients were included and analyzed. This study was approved by the Institutional Ethics Committee of the Eye and ENT Hospital of Fudan University and the Ruijin Hospital of Shanghai Jiao Tong University School of Medicine.

Surgical methods and data collection

Clinicopathological information including demographic features, blood examination reports, surgical treatments, and postoperative pathological diagnoses were collected to establish our retrospective database. All patients received a total thyroidectomy or thyroid lobectomy, along with CLN dissection performed therapeutically or prophylactically. LLN dissection was conducted in those with clinically positive LLN metastasis detected by preoperative ultrasonography or FNA, or had high suspect of lateral metastasis during operation. The pathological diagnoses were confirmed by at least two board-certified pathologists. For patients who did not receive LLN dissection, if positive LLN metastasis is found by ultrasonography and FNA within 6 months after initial surgical treatment, they will be considered as having occult lateral involvement at the time of operation.

Statistical analysis

Chi-square and independent t-test were used to make comparisons between categorical and continuous variables. Logistic univariate and multivariate regression analyses were used to screen risk factors that were significantly associated with LLN metastasis using the SPSS 24.0 package (SPSS Inc., Chicago, IL, USA). Factors with P value < 0.05 from the univariate logistic regression were enrolled in the multivariate logistic regression. Variables screened by multivariate logistic analysis were used for the construction of a risk prediction model—Nomogram, conducted by R software (version 3.5.1; R Development Core Team). Then the discrimination and consensus degree of our newly established predictive model were tested by the concordance index (C-index), receiver operating characteristic (ROC) curve, and the calibration curve. The individual risks of LLN were quantified as risk scores according to our nomogram and each patient was stratified into different subgroups based on their calculated LLN metastasis risk scores.

Results

Demographics, clinicopathological characteristics, and LLN metastases of our cohort

A total of 434 newly diagnosed PTC patients were enrolled in this study. Among them, 157 (36.2%) were male and 277 (63.8%) were female. The mean age of all patients was 40.22 ± 11.87 years (ranging from 14 to 78). All patients received a total thyroidectomy or thyroid lobectomy. Prophylactical CLN dissection was performed routinely for all patients in our study independent of whether metastases were detected before surgery. However, LLN dissection was performed only for those with positive or highly suspicious LLN metastases during pre- or intraoperative
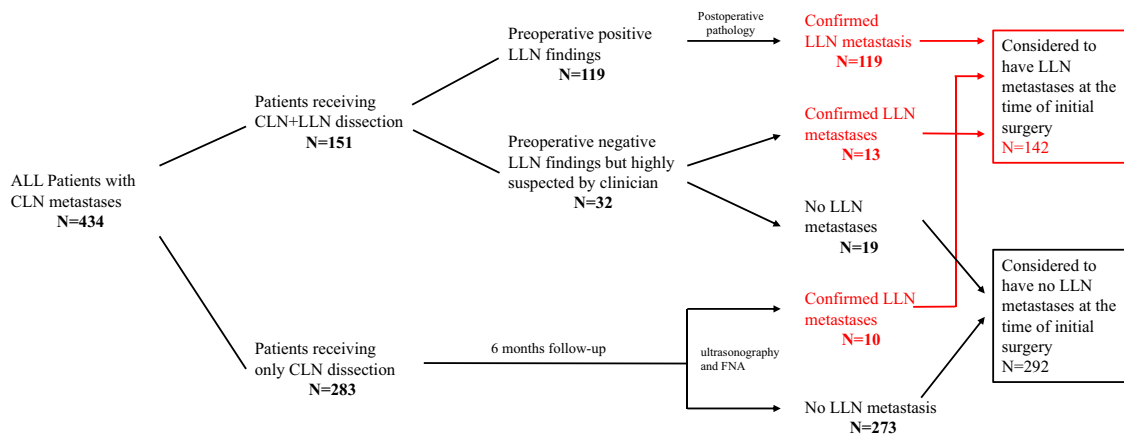
ALL Patients with CLN metastases **N=434**

Patients receiving CLN+LLN dissection **N=151**

Patients receiving only CLN dissection **N=283**

Preoperative positive LLN findings **N=119**

Preoperative negative LLN findings but highly suspected by clinician **N=32**

Postoperative pathology → Confirmed LLN metastasis **N=119**

Confirmed LLN metastases **N=13**

No LLN metastases **N=19**

6 months follow-up → ultrasonography and FNA → Confirmed LLN metastases **N=10**

No LLN metastasis **N=273**

Considered to have LLN metastases at the time of initial surgery **N=142**

Considered to have no LLN metastases at the time of initial surgery **N=292**

Fig. 1 Surgical managements, postoperative pathology, and follow-up information for patients enrolled

phases. As a result, LLN dissection was conducted for 151 (34.8%) patients. From these, 119 had pre-operative confirmed metastases, and 32 of them were considered high-risk LLN metastases during operation with 13 confirmed by postoperative pathology. Among those receiving CLN dissection alone, ten were detected to have LLD metastases within half a year in post-operation follow-up. In total, 142 (32.7%) patients were considered as having LLN metastases before surgery in our research (shown in Fig. 1). The maximum tumor diameter ranged from 0.15 to 6.0 cm, with a mean of 1.06 ± 0.77 cm. Main clinicopathological characteristics of our cohort were shown in Table 1. Patients in LLN group had significantly bigger tumor size than those in Non-LLN group. In addition, thyroid capsular invasion (TCI) and tumor with ipsilateral nodular goiter (iNG) were significantly more common in LLN Group. We also investigated the complication rates and length of hospital stay for our patients. We conducted blood tests for every patient receiving surgical treatment both on postoperative day 1 and 1 month after surgery. Patients with serum potassium lower than 3.5 mmol/L were considered to have temporary postoperative hypopotassemia which may have originated from the length of operation time. Patients with blood parathyroid hormone (PTH) lower than 15.0 pg/mL were considered to have postoperative hypoparathyroid hormone. For those that were detected to have hypoparathyroid hormone on postoperative day 1 yet had their blood PTH return to normal 1 month after surgery, we regarded them as having developed a temporary postoperative hypoparathyroid hormone. This indicates partial parathyroid damage during operation that can be compensated by normal parathyroid tissues. However, those who had low blood PTH both on day 1 and after 1 month were considered to have at least three parathyroid glands damaged and could not be compensated. These patients were regarded as having permanent postoperative hypoparathyroid hormone. Among 151 patients receiving LLN

Table 1 The clinicopathological characteristics of patients

	All patients		Non-LLN group		LLN group		
	$n = 434$	%	$n = 292$	%	$n = 142$	%	P value
BMI (mean ± SD)	23.92 ± 4.09		24.12 ± 4.17		23.34 ± 3.78		0.107
Maximum tumor diameter (mean ± SD)	1.06 ± 0.77		0.94 ± 0.64		1.39 ± 0.97		0.000
Age							0.014
>40	177	40.8	131	44.9	46	32.4	
≤40	257	59.2	161	55.1	96	67.6	
Gender							0.352
Male	157	36.2	110	37.7	47	33.1	
Female	277	63.8	182	62.3	95	66.9	
History of smoking							0.166
No	394	90.8	269	92.1	125	88.0	
Yes	40	9.2	23	7.9	17	12.0	
History of alcoholism							0.739
No	400	92.2	270	92.5	130	91.5	
Yes	34	7.8	22	7.5	12	8.5	
History of hypertension							0.107
No	361	83.2	237	81.2	124	87.3	
Yes	73	16.8	55	18.8	18	12.7	
History of diabetes							0.648
No	416	95.9	279	93.4	137	94.1	
Yes	18	4.1	13	6.6	5	5.9	
Thyroid capsular invasion							0.000
No	172	39.6	135	46.2	37	26.1	
Yes	262	60.4	157	53.8	105	73.9	
Bilateral disease							0.753
Absent	325	74.9	220	75.3	105	73.9	
Present	109	25.1	72	24.7	37	26.1	
Multifocality							0.254
Absent	234	53.9	163	55.8	71	50.0	
Present	200	46.1	129	44.2	71	50.0	
PTC with ipsilateral Hashimoto thyroiditis							0.450
No	355	81.8	236	80.8	119	83.8	
Yes	79	18.2	56	19.2	23	16.2	
PTC with ipsilateral nodular goiter							0.000
No	326	75.1	238	81.5	88	62.0	
Yes	108	24.9	54	18.5	54	38.0	

dissection, 13 (8.6%) had temporary postoperative hypopotassemia, and 35 (23.2%) had temporary postoperative hypoparathyroid hormone. Only seven (4.6%) were found to have permanent postoperative hypoparathyroid hormone. In addition, 6 of 151 (4.0%) patients had hoarseness after surgery, and 1 of these 6 patients also had mediastinal emphysema after surgery. Lymphatic fistula occurred on 4 of 151 (2.6%). In total, only 17 (11.3%) patients were found to have developed relatively severe postoperative complications including permanent postoperative hypoparathyroid hormone, hoarseness, and lymphatic fistula among all patients that received LLN dissection in our study. The average length of hospital stay was 6.44 days for LLN dissection patients and 3.29 days for only CLN dissection patients. A comparison of complication rates between patients receiving CLN dissection and receiving only CLN dissection was made and shown in Table 2. Actually, the relatively severe complication rate was higher in LLN dissection group than in only CLN dissection group (11.3% vs 4.6%, $P = 0.009$). Patients in LLN dissection group also had longer hospital stays than those in only CLN dissection ($P = 0.000$)

Number of positive central lymph nodes was significantly associated with lateral lymph node metastases

Previous studies had reported that number of central lymph node metastasis was a predictor for lateral involvement in patients with thyroid carcinoma [11, 12]. In this research, all 434 patients with CLN metastases were divided into two groups based on the number of pre- or intraoperative positive CLN found—more than five or five and less. The relationship between CLN and LLN metastasis among these two groups were shown in Table 3. The rate of LLN metastasis in patients with more than five positive CLN was significantly higher (44 of 53, 83.0%), than those with less CLN metastases (98 of 381, 25.7%). Thus, we classified those with more than five CLN involvements as extremely high-risk group and recommended them for routine CLN dissection.

Construction of the nomogram for patients with five or less CLN involvements

In patients with five or less CLN involvements, univariate and multivariate logistic regression analyses were conducted to screen for variables associated with LLN involvement. Factors significantly associated with LLN metastases by univariate logistic analysis were found to be: age no more than 40 years old, maximum tumor diameter no less than 1.0 cm, TCI and PTC with iNG. These were then enrolled in the multivariate logistic analysis. Following a backward stepdown process with regard to the Akaike information criterion, these four variables were further confirmed as independent factors for LLN metastases and were applied to construct the nomogram (shown in Fig. 2).

**Table 2** Length of hospital stay and postoperative complications

	All patients		Receiving CLN + LLN dissection		Receiving CLN dissection only		
	$n = 434$	%	$n = 283$	%	$n = 151$	%	P value
Length of hospital stay (mean ± SD)	5.40 ± 1.62		6.44 ± 1.15		3.29 ± 0.67		0.000
1. Temporary postoperative hypopotassemia							0.132
No	407	93.8	269	95.1	138	91.4	
Yes	27	6.2	14	4.9	13	8.6	
2. Temporary postoperative hypoparathyroid hormone							0.894
No	335	77.2	219	77.4	116	76.8	
Yes	99	22.8	64	22.6	35	23.2	
3. Permanent postoperative hypoparathyroid hormone							0.143
No	421	97.0	277	97.9	144	95.4	
Yes	13	3.0	6	2.1	7	4.6	
4. Postoperative hoarseness							0.262
No	422	97.2	277	97.9	145	96.0	
Yes	12	2.8	6	2.1	6	4.0	
5. Lymphatic fistula							0.033
No	429	98.8	282	99.6	147	97.4	
Yes	5	1.2	1	0.4	4	2.6	
Relatively severe postoperative complications (including 3, 4, 5)							0.009
No	404	98.8	270	95.4	134	88.7	
Yes	30	1.2	13	4.6	17	11.3	

Table 3 Risk stratification of PTC patients with CLN metastasis

| | More than five (N = 53, %) | No more than five (N = 381, %) | P value | No more than five positive CLN metastasis | | | P value |
				Low risk (N = 124, %)	Moderate risk (N = 145, %)	Relatively high risk (N = 112, %)	
LLN metastasis	44 (**83.0**)	98 (25.7)	0.000	11 (**8.9**)	33 (**22.8**)	54 (**48.2**)	0.000
No LLN metastasis	9 (17.0)	283 (74.3)		113 (91.1)	112 (77.2)	58 (51.8)	

The bold values were to emphasize the LLN metastasis rates of different groups

Fig. 2 Univariate (**a**) and multivariate (**b**) logistic regression analyses of factors associated with LLN metastasis. BIL bilateral PTC, CEA carcinoembryonic antigen, Cr serum creatinine, TSH thyroid-stimulating hormone, RBC red blood cell count, Mon monocyte, Neu neutrophil, WBC white blood cell count, MTD maximum tumor diameter, TCI thyroid capsular invasion, iNG ipsilateral nodular goiter, iHT ipsilateral Hashimoto thyroiditis, BMI body mass index
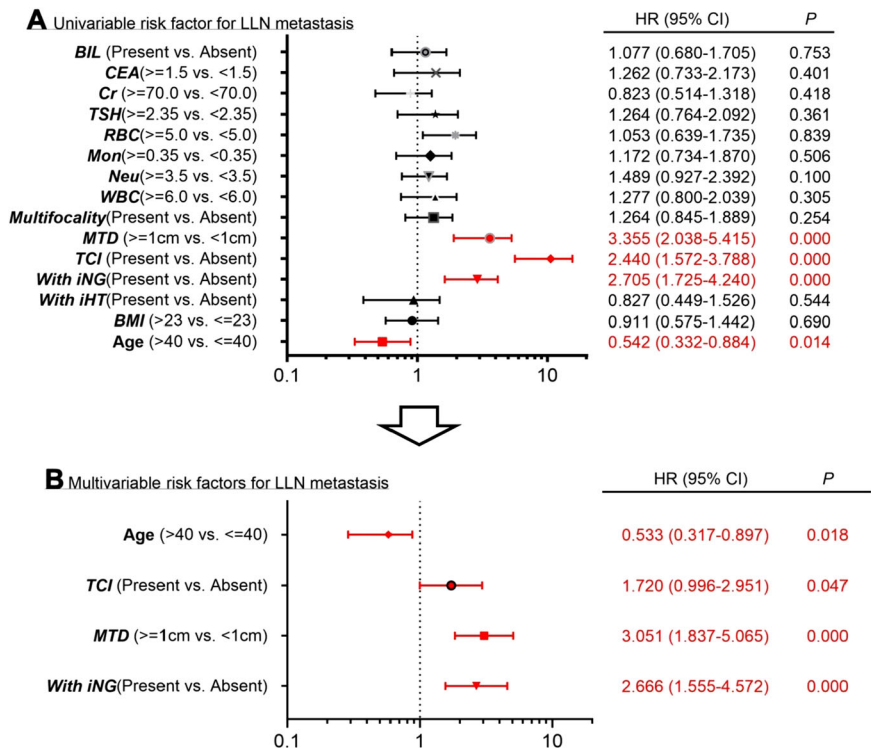
Evaluation and validation of the nomogram

A nomogram incorporating the above-mentioned four variables was established to predict the existence of PTC patients with CLN metastases (Fig. 3a). An internal validation was performed by 1000 bootstrap resamples for evaluating its precision in terms of C-index. As a result, C-index was found to be 0.761 (95% CI, 0.707–0.815), and 0.759 (95% CI, 0.745–0.773) after bootstrapping, demonstrating favorable accuracy of our newly built model's LLN involvement prediction ability. The ROC curve was also constructed for our cohort shown in Fig. 3b. Furthermore, the calibration plot was created and the actual and estimated probability of LLN metastases were in fair agreement (shown in Fig. 3c).

Novel risk stratification according to the scores obtained by the nomogram

The variables that constituted the nomogram had their corresponding risk points. We then summed up the LLM metastasis risk scores of each variable for all patients according to our nomogram. Based on distribution of the total risk score, two cutoff values were chosen to stratify patients with five or less positive CLM involvements into three subgroups:

(1) a low-risk group (patients with LLN metastasis risk score of ≤90, n = 124),
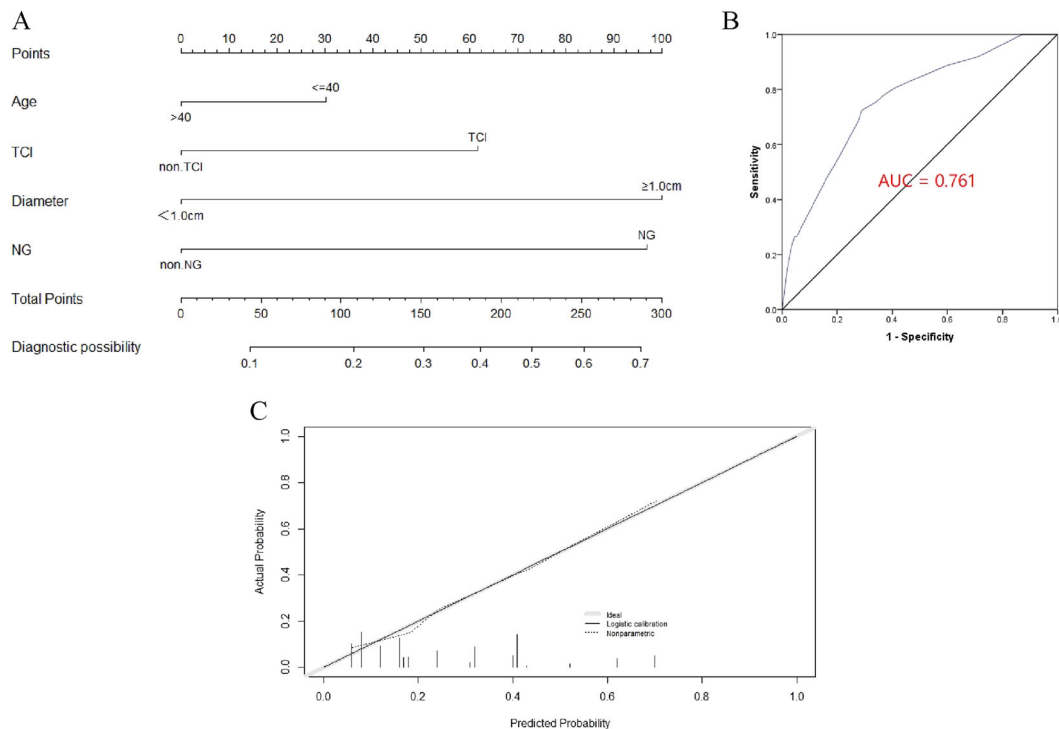(2) a moderate-risk group (patients with a risk score of 90–180, n = 145),

Fig. 3 Construction, evaluation, and validation of the nomogram. **a** The nomogram for predicting risk of possible LLN metastasis in PTC patients with CLN metastasis. **b** The ROC curve and AUC of the nomogram; ROC receiver operating characteristics. **c** The calibration curve of the nomogram for predicting possible LLN metastasis. Actual probability is plotted on the y-axis, and nomogram predicted probability on the x-axis

(3) a relatively high-risk group (patients with a risk score of ≥180, $n = 112$).

The rates of LLN metastases increased gradually from low-risk to relatively high-risk group (8.9%, 22.1%, and 49.1% for low-risk, moderate-risk, and relatively high-risk group, respectively), and chi-square test showed a significant difference among these three subgroups ($P = 0.000$, shown in Table 3).

Discussion

PTC is the most common endocrine malignancy on the globe. Although it appears to have a favorable long-term survival prognosis [13], the lymph node metastasis rate is extremely high, ranging from 32% to 80% [14–17]. Reports concluded that existence of positive lymph node metastasis was associated with poor prognosis [13, 18]. Thus, the management of cervical lymph nodes is of vital importance in patients with PTC.

The cervical lymph node metastasis of PTC occurs firstly in the central compartment and then infiltrates to the lateral region in general [19]. For cN0 patients, a "wait and see" strategy is applied in some clinical centers, and central lymph node dissection is also conducted routinely in several regions considering high rate of level VI lymph nodes involvement, and relatively low risk of surgery-related complications. However, LLN dissection was performed only for those with clinically positive LLN metastasis in most medical institutions. Prophylactic LLN dissection was not recommended by most clinical guidelines including the American Thyroid Association guidelines due to the low metastasis rate in this region as well as the high incidence of postoperative complications including chyle leakage, hemorrhage, nerve damage, shoulder ache, and limited mobility, which makes the meticulous preoperative examinations and assessments more crucial in LLN management.

Normally, ultrasonography is recognized as effective means for detecting metastatic lymph nodes. Yet, reported sensitivities of ultrasonography for cervical lymph node metastasis was 37–84% [9] and ranged from 65.0 to 80.3% for LLN metastasis [20, 21], which falls a bit short of being reliable. Moreover, the insensitivity of assessing deep lymph nodes such as those in the retropharyngeal region also limits the usage of this technology. Subclinical LLN metastasis may also exist in some of patients with PTC especially those with positive CLN metastasis. Ito et al. [22] conducted prophylactic LLN dissection for PTC patients and found that LLN metastasis rate was as high as 40.5% in microcarcinoma and may be even higher in carcinoma enlargement. Several studies also revealed higher LLN

involvement rates than what was previously estimated [23], providing further evidence that the existence of LLN occult metastasis was underestimated.

Considering the negative effect of LLN metastasis on tumor recurrence and survival, more aggressive intervention for patients with high LLN metastasis risk appears to be of great importance. Given that skip metastasis (LLN involved without positive CLN metastasis) was extremely rare for patients with PTC [4, 24], most LLN metastasis occurs in cases where CLN metastasis exist. Thus, we focused on those patients in our study. Previous studies had screened out some independent factors that were significantly correlated with LLN involvement for patients with CLN metastasis such as number of CLN involved and tumor size [25]. However, those studies only revealed qualitative relationship between risk factors and LLN metastasis. Research on quantifying the risk of LLN metastasis for individual patients is hard to find. Therefore, creating a predictive model to stratify patients using a more granular level of LLN metastasis risk can help low-risk patients avoid unnecessary surgical morbidity brought by prophylactic LLN, and can be used to direct optimal individual management for high-risk patients.

Bohec [26] reported that patients with more than five positive CLN metastasis had a significantly high risk of LLN involvement and could be predictive for LLN metastasis. Here in our research, the incidence of LLN metastasis both clinical and subclinical was over 80 percent (83.0%) in patients with more than five clinically found positive CLN metastasis. In contrast, incidence was 25.7% for those with ≤5 positive CLN metastasis. In view of this, we classified those with more than five CLN metastasis as extremely high-risk group and LLN dissection should be recommended for patients with this feature independent of clinical evidences in LLN metastasis.

Among patients with five or less positive CLN metastasis, the association between some clinicopathologic factors and LLN metastasis has been evaluated. Age, maximum tumor diameter, existence of TCI, and PTC with iNG were proven to be independent risk factors for LLN involvement in the present research.

Previous studies have proved that young age [27–29] and large tumor size [30] were CLN metastasis predictors. However, to our knowledge, it is the first report where young patients appeared to be more vulnerable to LLN metastasis in patients with CLN metastasis. The cell viability of young patients is relatively strong which means stronger capability for invasion and metastasis. Larger size often means more aggressive tumor and is associated with lymph node metastases. Our research showed that patients with tumor equal to or greater than 1.0 cm were more prone to LLN metastasis than patients with smaller tumors. Bilateral disease was reported to be predictive for CLN

metastasis [29], but the relationship between this clinical feature and LLN metastasis remains unknown. In our research, the connection between these two was analyzed and the result indicated that in respect to PTC patients, bilateral disease showed no tendency to be involved in LLN involvement compared with unilateral carcinoma. It illustrates that bilateral carcinoma may contribute little to LLN metastasis in PTC patients despite high occurrence rate of CLN invasion. Extrathyroidal extension was widely reported to be related with central lymph node metastasis. According to our clinical observation and experience, patients with tumor directly underlie the boundary of the thyroid and adjacent tissues also showed a high lymph node invasion rate. Thus, we expanded the concept and defined tumor clinging closely to the junction of thyroid and adjacent soft tissue, and invading beyond thyroid and surrounding fibrous tissue, fat tissue, and even skeletal muscle as TCI. As a result, clinical CLN metastasis patients with TCI exhibited higher LLM involvement rate than those without. This result hints that although invasion did not reach outside of the thyroid tissue, the existence of close infiltration to the capsular of thyroid can also lead to high LLN metastasis risk. Interestingly, tumor with ipsilateral Hashimoto thyroiditis (iHT) and with iNG were both analyzed in our research and only iNG was proven to be positively related with LLN metastasis, which has not been reported before. This implies that the coexistence of nodular goiter portends a more aggressive tumor.

Nomogram is a tried and true method to create models for clinical disease diagnosis [31] and is characterized by its ability in combining multiple independent variables and quantifying their respective impact for the whole model. No such model has been constructed for predicting possible LLN metastasis in controversial patients who were proven to have few CLN metastasis. In our research, a nomogram for predicting possible LLN involvement in patients with few CLN metastasis was established based on the independent risk factors we screened out and was proved to be efficacious. All the factors included could be detected pre- or intraoperatively: age should already be known, tumor size can be measured by preoperative ultrasonography, and TCI and iNG can be proven by preoperative ultrasonography and intraoperative frozen biopsy. Furthermore, the risk scores for LLN involvement were calculated in line with the nomogram and each patient in our group had their individual risk-evaluation scores determined. Three subgroups were then formed by two cutoff points: low (≤90), moderate (90–180), and relatively high risk (≥180) groups. The incidences of LLN metastasis were 8.9%, 22.8%, and 48.2%, respectively ($P < 0.001$), confirming the rationality and validity of our classification. For patients in the low-risk subgroup, the incidence rate of positive LLN involvement is extremely low, so unless obvious clinical

Fig. 4 Treatment strategy selection flow chart for patients with positive CLN metastasis
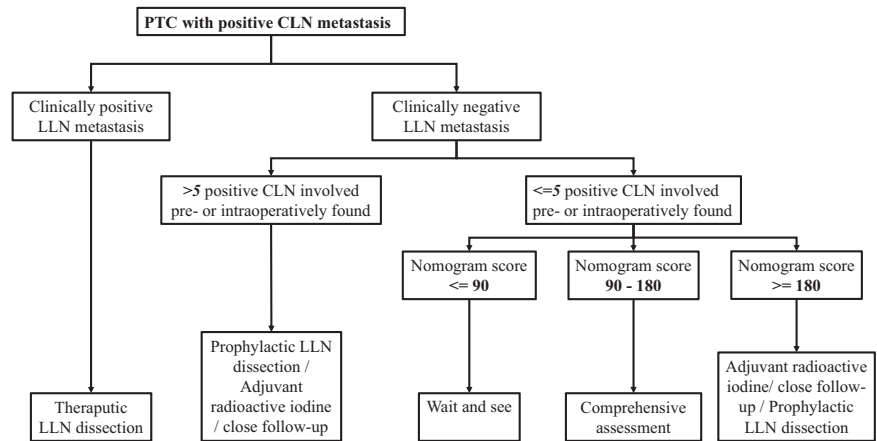
evidence is present, "wait and see" is recommended for these patients, and prophylactic LLN dissection is not required as it contributes to higher surgery-related postoperative complication rate. For patients in the moderate-risk group, patient's general status and preference as well as clinician's judgment should be comprehensively considered for individual treatment strategy. With nearly 50% LLN transfer rate, close follow-up or adjuvant radioactive iodine is recommended, prophylactic LLN dissection can also be considered in conjunction with patient's preference. For patients in the extremely high-risk group in which the incidence of occult LLN metastasis reaches up to 83% and the incidence of surgery-related complication rate was only 11.3%, prophylactic LLN dissection is recommended, if not, adjuvant radioactive iodine or a closer follow-up scheme should at least be conducted. Finally, a detailed treatment selection flow chart is created by our team and shown in Fig. 4.

Limitations

Our research has several potential limitations. First, it is a retrospective study and nonrandomized features are inevitably produced. Second, some molecular markers such as Braf mutation are not included in our analysis, which may limit the application of our nomogram. Thus, more reliable prediction models containing more details information are expected in the future.

Compliance with ethical standards

References

1. M.A. Rosenbaum, C.R. McHenry, Contemporary management of papillary carcinoma of the thyroid gland. Expert Rev. Anticancer Ther. **9**(3), 317–329 (2009)
2. S.A. Hundahl, I.D. Fleming, A.M. Fremgen, H.R. Menck, A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995 [see comments]. Cancer **83**(12), 2638–2648 (1998)
3. Y.D. Podnos, D. Smith, L.D. Wagman, J.D. Ellenhorn, The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am. Surg. **71**(9), 731–734 (2005)
4. J.W. Feng, X. H. Yang, B. Q. Wu, D. L. Sun, Y. Jiang, Z. Qu. Predictive factors for central lymph node and lateral cervical lymph node metastases in papillary thyroid carcinoma. Clin. Transl. Oncol. (2019).
5. G. Mercante, A. Frasoldati, C. Pedroni, D. Formisano, L. Renna, S. Piana, G. Gardini et al. Prognostic factors affecting neck lymph

node recurrence and distant metastasis in papillary micro-carcinoma of the thyroid: results of a study in 445 patients. Thyroid **19**(7), 707–716 (2009)

6. H. Takami, Y. Ito, T. Okamoto, A. Yoshida, Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. World J. Surg. **35**(1), 111–121 (2011)

7. X. Wu, B. Li, C. Zheng, X. He, Risk factors for central lymph node metastases in patients with papillary thyroid micro-carcinoma. Endocr. Pract. **24**(12), 1057–1062 (2018)

8. A. Machens, S. Hauptmann, H. Dralle, Lymph node dissection in the lateral neck for completion in central node-positive papillary thyroid cancer. Surgery **145**(2), 176–181 (2009)

9. X. Lan, W. Sun, H. Zhang, W. Dong, Z. Wang, T. Zhang, A meta-analysis of central lymph node metastasis for predicting lateral involvement in papillary thyroid carcinoma. Otolaryngol. Head. Neck Surg. **153**(5), 731–738 (2015)

10. M.J. Jeon, M.S. Chung, H. Kwon, M. Kim, S. Park, J.H. Baek et al. Features of papillary thyroid microcarcinoma associated with lateral cervical lymph node metastasis. Clin. Endocrinol. **86**(6), 845–851 (2017)

11. R.C. Zeng, W. Zhang, E.L. Gao, P. Cheng, G.L. Huang, X.H. Zhang et al. Number of central lymph node metastasis for pre-dicting lateral lymph node metastasis in papillary thyroid micro-carcinoma. Head Neck **36**(1), 101–106 (2014)

12. Y. Tao, C. Wang, L. Li, H. Xing, Y. Bai, B. Han et al. Clin-icopathological features for predicting central and lateral lymph node metastasis in papillary thyroid microcarcinoma: analysis of 66 cases that underwent central and lateral lymph node dissection. Mol. Clin. Oncol. **6**(1), 49–55 (2017)

13. K.A. Pathak, A. Mazurat, P. Lambert, T. Klonisch, R.W. Nason, Prognostic nomograms to predict oncological outcome of thyroid cancers. J. Clin. Endocrinol. Metab. **98**(12), 4768–4775 (2013)

14. J.D. Isaacs, T.P. McMullen, S.B. Sidhu, M.S. Sywak, B.G. Robinson, L.W. Delbridge et al. Predictive value of the Delphian and level VI nodes in papillary thyroid cancer. ANZ J. Surg. **80**(11), 834–838 (2010)

15. A.R. Shaha, Prognostic factors in papillary thyroid carcinoma and implications of large nodal metastasis. Surgery **135**(2), 237–239 (2004)

16. K.E. Lee, I.Y. Chung, E. Kang, H. Koo do, K.H. Kim, S.W. Kim et al. Ipsilateral and contralateral central lymph node metastasis in papillary thyroid cancer: patterns and predictive factors of nodal metastasis. Head. Neck. **35**(5), 672–676 (2013)

17. I.D. Hay, C.S. Grant, J.A. van Heerden, J.R. Goellner, J.R. Ebersold, E.J. Bergstralh, Papillary thyroid microcarcinoma: a study of 535 cases observed in a 50-year period. Surgery **112**(6), 1139–1147 (1992)

18. N.J. Beasley, J. Lee, S. Eski, P. Walfish, I. Witterick, J.L. Freeman et al. Impact of nodal metastases on prognosis in patients with well-differentiated thyroid cancer. Arch. Otolaryngol. Head. Neck Surg. **128**(7), 825–828 (2002)

19. A. Goropoulos, K. Karamoshos, A. Christodoulou, T. Ntitsias, K. Paulou, A. Samaras et al. Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma. World J. Surg. **28**(12), 1275–1281 (2004)

20. J.E. Ahn, J.H. Lee, J.S. Yi, Y.K. Shong, S.J. Hong, D.H. Lee et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. World J. Surg. **32**(7), 1552–1558 (2008)

21. H.S. Hwang, L.A. Orloff, Efficacy of preoperative neck ultra-sound in the detection of cervical lymph node metastasis from thyroid cancer. Laryngoscope **121**(3), 487–491 (2011)

22. Y. Ito, T. Higashiyama, Y. Takamura, A. Miya, K. Kobayashi, F. Matsuzuka et al. Risk factors for recurrence to the lymph node in papillary thyroid carcinoma patients without preoperatively detectable lateral node metastasis: validity of prophylactic mod-ified radical neck dissection. World J. Surg. **31**(11), 2085–2091 (2007)

23. L. Zhang, W.J. Wei, Q.H. Ji, Y.X. Zhu, Z.Y. Wang, Y. Wang et al. Risk factors for neck nodal metastasis in papillary thyroid microcarcinoma: a study of 1066 patients. J. Clin. Endocrinol. Metab. **97**(4), 1250–1257 (2012)

24. Y. Qiu, Y. Fei, J. Liu, C. Liu, X. He, N. Zhu et al. Prevalence, risk factors and location of skip metastasis in papillary thyroid carci-noma: a systematic review and meta-analysis. Cancer Manag. Res. **11**, 8721–8730 (2019)

25. G.W. Randolph, Q.Y. Duh, K.S. Heller, V.A. LiVolsi, S.J. Mandel, D.L. Steward et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid **22**(11), 1144–1152 (2012)

26. H. Bohec, I. Breuskin, J. Hadoux, M. Schlumberger, S. Leboul-leux, D.M. Hartl et al. Occult contralateral lateral lymph node metastases in unilateral N1b papillary thyroid carcinoma. World J. Surg. **43**(3), 818–823 (2019)

27. S.K. Kim, J.W. Woo, J.H. Lee, I. Park, J.H. Choe, J.H. Kim, Role of BRAF V600E mutation as an indicator of the extent of thyr-oidectomy and lymph node dissection in conventional papillary thyroid carcinoma. Surgery **158**(6), 1500–1511 (2015)

28. A.M. Thompson, R.M. Turner, A. Hayen, A. Aniss, S. Jalaty, D. L. Learoyd, A. Preoperative, Nomogram for the prediction of ipsilateral central compartment lymph node metastases in papil-lary thyroid cancer. Thyroid **24**(4), 675–682 (2014)

29. S.K. Kim, Y.J. Chai, I. Park, J.W. Woo, J.H. Lee, K.E. Lee, Nomogram for predicting central node metastasis in papillary thyroid carcinoma. J. Surgical Oncol. **115**(3), 266–272 (2016)

30. J.L. Roh, J.M. Kim, C.I. Park, Central lymph node metastasis of unilateral papillary thyroid carcinoma: patterns and factors pre-dictive of nodal metastasis, morbidity, and recurrence. Ann. Sur-gical Oncol. **18**(8), 2245–2250 (2011)

31. V.P. Balachandran, M. Gonen, J.J. Smith, R.P. DeMatteo, Nomograms in oncology: more than meets the eye. Lancet Oncol. **16**(4), e173–e180 (2015)