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Predicting factors of lateral neck lymph node metastases in patients with papillary thyroid microcarcinoma

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Abstract

The incidence of papillary thyroid microcarcinoma (PTMC) has increased dramatically in recent years. Compared with central lymph node metastases, lateral neck lymph node (LNLN) metastases in patients with PTMC were less studied. The aim of the present study is to analyze the predicting factors associated with LNLN metastases in patients with PTMC.

A total of 3514 patients underwent thyroid surgery at our hospital from January 2017 to December 2017, and 936 patients with PTMC were selected and assessed retrospectively. They were further divided into 2 groups based on whether LNLN metastases existed or not. The relationship between LNLN metastases and clinicopathologic features of PTMC was analyzed.

LNLN metastases were confirmed in 126 patients. Univariate and multivariate analyses found 5 independent factors associated with LNLN metastases. They were tumor size ($\geq$0.7 cm) [odds ratio (OR) = 1.960, 95% confidence interval (95% CI) 1.227–3.131; P = .005], multifocality (OR = 2.254, 95% CI 1.398–3.634; P = .001), tumor location (upper portion) (OR = 6.312, 95% CI 3.853–10.340; P < .001), thyroid cancer family history (OR = 7.727, 95% CI 2.227–26.818; P = .001), and central lymph node metastases (OR = 11.810, 95% CI 6.547–21.302; P < .001).

The findings of our study indicated that LNLN metastases were not rare in patients with PTMC, and tumor size ($\geq$0.7 cm), multifocality, tumor location (upper portion), thyroid cancer family history, and central lymph node metastases were independent factors for LNLN metastases. In order to perform individualized management, LNLN should be meticulously evaluated when these features are detected.

Abbreviations: BMI = body mass index, LNLN = lateral neck lymph node, PTC = papillary thyroid carcinoma, PTMC = papillary thyroid microcarcinoma, TSH = thyroid-stimulating hormone.

Keywords: lateral neck lymph node, metastases, papillary thyroid microcarcinoma, predicting factor, total thyroidectomy

1. Introduction

The most common carcinoma in the endocrine system is thyroid cancer, whose incidence has increased dramatically in recent years.[1] Papillary thyroid carcinoma (PTC) is the most frequent histological subtype of thyroid cancer. It is the third most common malignancy in China.[2] Papillary thyroid microcarcinoma (PTMC) is a type of PTC with a maximum tumor diameter no larger than 10 mm.[3] Most PTMCs have an indolent clinical course and an excellent prognosis, but early spread to local lymph nodes is not rare. According to AJCC 8.0, regional lymph node metastases to level VI or VII (pretracheal, paratracheal, prelaryngeal/Delphian, or upper mediastinal) lymph nodes are defined as stage N1a, and metastases to unilateral, bilateral, or contralateral lateral neck lymph node (LNLN) (levels I, II, III, IV, or V) or retropharyngeal lymph nodes are defined as stage N1b. The highest lymph node metastases rate is up to 50%.[4]

Central compartment is the most common site of lymph node metastases and several different studies have been reported to determine the predicting factors of central lymph node metastases (N1a) in patients with PTMC.[5–7] But few studies have attempted to find out the predicting factors of LNLN metastases (N1b) in patients with PTMC. LNLN metastases has been reported in approximately 21.1% of patients with PTMC.[8] Therefore, it is very important to identify the predicting factors for LNLN metastases in patients with PTMC. This would guide therapeutic decision for both surgeons and patients. The aim of the present study is to analyze the potential clinicopathological predicting factors associated with LNLN metastases in patients with PTMC.

2. Methods

2.1. Patients

From January 2017 to December 2017, 3514 patients underwent thyroid surgery at our hospital. All the medical records were

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reviewed systematically by 2 independent surgeons. Patients were selected based on the following inclusion criteria: PTMC was diagnosed by postoperative pathology, total thyroidectomy along with central lymph node dissection was performed with or without LNLN dissection, and no previous thyroid operation history. Patients who had previous radiation exposure and coexisting head and neck tumors were excluded. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Peking Union Medical College Hospital. The need for informed consent was waived due to the retrospective nature of the study.

Clinicopathological data were collected from both inpatient and outpatient medical records. A retrospective database was constructed. Demographic features, ultrasonography outcomes, thyroid function, operation details, and pathological results were analyzed. The age of 55 years was used as a watershed, and all included patients were divided into a younger group (age < 55 years) and an older group (age ≥55 years). Thyroid-stimulating hormone (TSH) levels were divided into a low group (TSH ≤4.2 mIU/L) and a high group (TSH >4.2 mIU/L). Tumor location was described as lower portion (lower of low plane of isthmus), middle portion (parallel to isthmus), and upper portion (upper of high plane of isthmus). If at least 2 foci were found in bilateral or unilateral lobes, the tumor was defined as multifocality. The largest lesion was considered as the main foci.

2.2. Treatment

Before surgery, all patients underwent routine ultrasound examination by 2 different sonographers with at least 5 years of experience in thyroid imaging. Fine-needle aspiration cytology was performed if patients were willing to accept it and tumor diameter was more than 5 mm. Because central lymph node dissection was recommended by both Chinese guidelines for thyroid nodules disease and differentiated thyroid carcinoma and Chinese experts consensus on the diagnosis and treatment of PTMC,[7] so prophylactic central lymph node dissection was performed routinely in the present study. LNLN dissection was performed only if metastases were revealed by preoperative ultrasonography. Specimens were examined by 2 different pathologists with at least 5 years of experience in thyroid pathology before the postoperative pathological diagnosis was confirmed.

All patients underwent operation under general anesthesia in the supine position with hypsokinesis of the head. No antibiotic was administered. All patients were given oral euthyrox postoperatively for suppressive therapy. The TSH level was maintained lower than 0.3 mIU/L. For patients who did not undergo LNLN dissection, ultrasonography and iodine uptake capacity test were performed half year after operation to confirm there was no metastasis in LNLN.

2.3. Statistical analysis

The Statistical Package for Social Sciences software (SPSS, version 19.0; SPSS Inc., Chicago, IL) was used to perform statistical analysis. Linear variables were described by mean ± standard deviation. Categorical variables were presented as absolute number or frequency. Differences between study groups were analyzed by the Student t test or χ^2 test as appropriate.

Table 1	
Distribution of metastases in LNLN from 126 patients with PTMC.	
Distribution (II–V)	**Number of patients**
Single level	
Left II/III/IV	2/10/6
Right II/III/IV	3/17/13
Two levels	
Left II+III/II+IV/III+IV	8/2/11
Right II+III/II+IV/III+IV	5/2/20
Left III and right IV	3
Three levels	
Left II+III+IV	6
Right II+III+IV	6
More than 3 levels	
Right II+III+IV+V	6
Left II+III+IV and right III+IV	4
Left II+III+IV and right II+III+IV	2

LNLN = lateral neck lymph node, PTMC = papillary thyroid microcarcinoma.

Logistic multivariate regression analyses were performed to identify independent predicting factors for LNLN metastases. A P value <.05 was considered statistically significant.

3. Results

A total of 936 patients with PTMC were selected. Among the total patients, 264 were male (28.2%) and 672 were female (71.8%). The mean age was 43.31 ± 9.92 years (range, 16–68 years). The mean size of tumor was 0.65 ± 0.24 cm (range, 0.1–1.0 cm). Tumors were located in the upper portion of the thyroid in 229 patients, middle portion in 412 patients, and lower portion in 295 patients. Four hundred fourteen patients had lesions in the left lobe, and 522 patients had lesions in the right lobe. A total of 494 patients had a multifocal tumor, and 406 patients had lesions in bilateral lobes. Central lymph node metastases were confirmed by pathology in 441 patients (47.1%) and LNLN metastases in 126 patients (13.5%). The distribution of LNLN metastases is presented in Table 1.

On the basis of postoperative pathology, patients were further divided into 2 groups: a LNLN metastases positive group (126 patients) and a LNLN metastases negative group (810 patients). The demographic data, pathological results, and outcomes of ultrasonography were analyzed and compared between the 2 groups (Table 2). Significant differences were found between the 2 groups for gender, body mass index (BMI), thyroid cancer family history, tumor size, multifocality, tumor location, and central lymph node metastases.

Multivariate logistic regression analyses were performed to determine the associations between select variables and LNLN metastases. Five variables proved to be independent factors associated with LNLN metastases. They were larger tumor size (≥0.7 cm), multifocality, tumor location (upper portion), thyroid cancer family history, and positive central lymph node metastases and had odds ratios of 1.960, 2.254, 6.312, 7.727, and 11.810, respectively (Table 3).

4. Discussion

Differentiated thyroid cancer accounts for more than 95% of thyroid carcinoma.[1] Due to the popularization of health examination and advancement of imaging technology, more

Table 2

Detailed data regarding demographic data, pathological results, and outcomes of ultrasonography for patients with PTMC.

	Total (n = 936)	LNLN (+) (n = 126)	LNLN (−) (n = 810)	P
Male/female (n)	264/672	48/78	216/594	.008
Age ≥55 y (n)	123	18	105	.683
BMI, kg/m^2	24.84 ± 3.38	24.03 ± 3.04	24.98 ± 3.42	.003
Thyroid cancer family history (n)	18	6	12	.032
Smoking (n)	63	12	51	.179
TSH >4.2 mIU/L (n)	99	12	87	.679
Hashimoto thyroiditis (n)	269	36	233	.964
Tumor size, cm	0.65 ± 0.24	0.74 ± 0.24	0.64 ± 0.23	<.001
Multifocal tumor (n)	494	79	415	.016
Bilateral lobes tumor (n)	406	50	356	.369
Tumor location (LL/RL) (n)	414/522	58/68	356/454	.662
Tumor location (U/M+L) (n)	229/707	66/60	163/647	<.001
Capsular invasion (n)	647	91	556	.418
Extrathyroidal invasion (n)	83	16	67	.104
Ki67 ≥3% (n)	183	30	153	.195
CLN metastases (n)	441	110	331	<.001

BMI = body mass index, CLN = central lymph node, L = lower, LL = left lobe, LNLN = lateral neck lymph node, M = middle, PTMC = papillary thyroid microcarcinoma, RL = right lobe, TSH = thyroid-stimulating hormone, U = upper.

and more microcarcinoma have been discovered and diagnosed. Lee et al[9] reported that up to 60% of all thyroid cancers are PTMCs. PTMCs grow slowly and the 2015 guidelines of the American Thyroid Association even indicated that observation with direct follow up should be conducted for a thyroid mass <1 cm.[10,11] But there are still some patients with PTMC who need operation because of lymph node metastases.[12] Although less common than central compartment lymph node metastases, LNLN metastases are found in 3.7% to 55% of patients with PTMC.[13–17] For these patients, if the initial surgery does not include LNLN dissection, a second operation is almost foreseeable. Thus, it is very important to estimate preoperatively whether LNLN metastases exist or not. Meticulous preoperative evaluations should be performed in patients with high possibility of LNLN metastases.

Preoperative ultrasonography is the preferred method of thyroid examination and detecting the absence of lymph node metastases. Metastatic lymph node often manifests as diffuse or focal hyperechogenicity, calcification, abnormal vascular pattern (peripheral or chaotic), cystic change, and round shape.[18,19] The sensitivity and specificity of ultrasonography for the detection of LNLN metastases are only 65% to 80.3% and 72% to 84.8%, respectively.[20,21] Another disadvantage of ultrasonography is that it is not sensitive enough to detect deep lymph nodes. Occult LNLN metastases are not rare in clinically N0 PTC patients.[22]

Table 3

Multivariate analyses for predicting factors of LNLN metastases for patients with PTMC.

	P	OR	95% CI
Tumor size (≥0.7 cm)	.005	1.960	1.227–3.131
Multifocal tumor	.001	2.254	1.398–3.634
Tumor location (upper portion)	<.001	6.312	3.853–10.340
Thyroid cancer family history	.001	7.727	2.227–26.818
CLN metastases	<.001	11.810	6.547–21.302
Gender (male/female)	.993		
BMI (≥25 kg/m^2)	.349		

95% CI = 95% confidence interval, BMI = body mass index, CLN = central lymph node, LNLN = lateral neck lymph node, OR = odds ratio, PTMC = papillary thyroid microcarcinoma.

So, an accurate preoperative diagnosis could hardly be achieved every time even by experienced sonographers. A new assessment method for predicting LNLN metastases need to be proposed and would be helpful in selecting patients for LNLN dissection.

The present study is among the largest sample sizes reporting on the predicting factors for LNLN metastases in PTMC. The association between several variables and LNLN metastases has been examined. Larger tumor size (≥0.7 cm), multifocality, tumor location (upper portion), thyroid cancer family history, and positive central lymph node metastases were proved to be independent risk factors.

Both larger tumor size and multifocality contribute to the tumors being more proliferative and aggressive.[23] Tumor size is an important factor related to tumor staging and LNLN metastases. PTMCs with larger tumor size are more frequently associated with LNLN metastases than those with smaller tumor size.[24,25] The present study also demonstrates that 0.7 cm is a tumor size cutoff value that could be used in predicting LNLN metastases. Some previous studies considered multifocality as intraglandular spread of the main foci.[26,27] And multifocality has been reported significantly correlated with lymph node metastases.[28,29] This may be the reason why multifocality becomes an independent predicting factor. Tumor cells from the upper portion are easily transported to the LNLN through the lymphatic flow along the superior thyroid artery than those from middle and lower portions.[17,30] This may be the main reason why upper portion increases the risk of LNLN metastases. Central lymph node metastases mean tumor cells have broken through thyroid gland and entered lymphatic circulation system. This would increase the possibility of LNLN metastases. For thyroid cancer family history, there is still no convincing explanation. Maybe familial thyroid cancer is more aggressive. Some previous studies also reported that male gender, young age, Hashimoto thyroiditis, and capsule invasion could be predicting factors of LNLN metastases.[17,31–34] In the present study, no significant association was found between LNLN metastases and the above variables.

For the included 936 patients, the rate of central lymph node metastases is as high as 47.1%, but the rate of LNLN metastases is only 13.5%. Prophylactic LNLN dissection is not recommended due to the low metastases rate and high incidence of

complications, such as cervical chylous fistulae, seroma, nerve damage, bleeding, and postoperative pain. But patients with LNLN metastases have a higher rate of tumor recurrence.[35] If unsuitable surgical approach was given to those patients, a bad prognosis is predictable. Therefore, the best choice is that selected high-risk patients should receive meticulous preoperative evaluations for LNLN metastases. On the basis of our findings, we recommend a multimodal approach and meticulous evaluations on patients with larger tumor size (≥0.7 cm), multifocality, upper portion tumor location, thyroid cancer family history, and positive central lymph node metastases.

As summarized in Table 1, level IV (81/126, 64.3%) is the most commonly observed group of LNLN metastases, followed closely by level III (78/126, 61.9%). Seventy-five patients (59.5%) have at least 2 levels been involved. Both our findings and previous studies point out that multilevel LNLN metastases are common in patients with PTMC.[13,36] Sixteen patients shown skip metastases (positive LNLN metastases without central lymph node metastases). The same phenomenon was also described in another study.[34] These findings mean preoperative examination of LNLN should be performed routinely and carefully even if no central lymph node metastasis was found. And in case of LNLN dissection, multilevel dissection was recommended.

There are some limitations to this study. First, because of its retrospective nature and single-center analysis, the registration information, patient volume, and inspection items could not be designed beforehand. Second, LNLN dissection was not performed on the patients in LNLN negative group. Subclinical lymph node metastases may exist and result in wrong grouping. Prospective and multicenter clinical trials should be performed to identify the predicting factors of LNLN metastases in patients with PTMC and provide more supporting evidence with greater reliability.

In conclusion, LNLN metastases are not rare in patients with PTMC. Tumor size (≥0.7 cm), multifocality, tumor location (upper portion), thyroid cancer family history, and central lymph node metastases are independent risk factors for LNLN metastases. In order to perform individualized management, LNLN should be meticulously evaluated when these features are detected.

Author contributions

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