

The Extent of Therapeutic Central Compartment Neck Dissection in Unilateral cT1N1a or cT2N1a Papillary Thyroid Carcinoma

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Purpose: Papillary thyroid carcinomas (PTCs) frequently metastasize to the central neck compartment. Therapeutic central compartment neck dissection (CCND) is a well-established treatment for PTC nodal metastases; however, the extent to which therapeutic CCND should be performed remains controversial. In this study, we investigated the predictive risk factors for contralateral paratracheal lymph node metastasis (LNM) in unilateral cT1N1a or cT2N1a PTC.

Patients and Methods: In this case-control study, which was conducted at a single center, demographic and pathological data from unilateral cT1N1a or cT2N1a PTC patients were collected from January 2017 to March 2019. All patients were treated with total thyroidectomy and bilateral CCND.

Results: Two hundred thirty-seven patients met the inclusion criteria. Forty-nine patients (20.7%) were diagnosed with positive lymph nodes in the contralateral paratracheal region. Male sex ($p=0.003$), T2 disease (21–40 mm) ($p<0.001$), inferior pole tumor ($p=0.011$), near isthmus tumor ($p<0.001$), aggressive pathology ($p<0.001$), intraglandular dissemination ($p=0.009$), pretracheal LNM ($p<0.001$), >5 metastatic lymph nodes ($p<0.001$) and extranodal invasion ($p=0.003$) were significantly associated with contralateral paratracheal LNM in univariate analysis. Multivariate analysis showed that male sex ($p=0.005$, OR=17.545), T2 disease ($p=0.003$, OR=34.317), inferior pole tumor ($p=0.022$, OR=8.289), near isthmus tumor ($p=0.001$, OR=40.229), aggressive pathology ($p=0.027$, OR=48.063), pretracheal LNM ($p=0.002$, OR=14.235) and >5 metastatic lymph nodes ($p=0.025$, OR=23.426) were independent risk factors for contralateral paratracheal LNM.

Conclusion: Male sex, T2 disease, a tumor located near the isthmus or inferior pole, aggressive pathology, pretracheal LNM and >5 metastatic lymph nodes were predictive factors for contralateral paratracheal LNM in unilateral cT1N1a or cT2N1a PTC. These data may be useful to identify targets for surveillance or develop therapeutic interventions for patients with CCND.

Keywords: papillary thyroid carcinoma, central compartment neck dissection, predictive factor, lymph node metastasis

Introduction

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland. The incidence of PTC has increased significantly over the past several decades.^{1–3} An increasing number of small PTCs (T1 or T2) are being diagnosed due to the development of high-resolution ultrasound and widespread health screening. Regional lymph node metastases (LNMs) are present at the time

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of diagnosis in a majority of patients with PTC,^{4–6} and the most common site of nodal metastasis is the central neck compartment (level VI). The central neck compartment consists of the ipsilateral and contralateral paratracheal compartments, the prelaryngeal compartment and the pretracheal compartment. In previous studies, central lymph node metastasis (CLNM) was identified in 40–70% of patients with PTC and was detected even in patients with small PTCs.^{7–11} Contralateral paratracheal LNM was observed in 9.8–27.3% of patients with cN0 unilateral PTC.^{12–15} Lymph node metastasis is commonly associated with an increased rate of local recurrence and distant metastasis.^{16–19}

The extent of thyroid resection that should be performed has been the subject of contentious debate regarding the surgical management of PTC.²⁰ Therapeutic central compartment neck dissection (CCND) is commonly performed for the treatment of PTC nodal metastases in patients with cN1a disease because CCND is associated with improved outcomes, both in terms of recurrence and survival. The American Thyroid Association (ATA) guidelines suggest that therapeutic CCND should accompany total thyroidectomy in patients with clinically involved central nodes to ensure clearance of disease from the central neck region.² However, the extent to which therapeutic CCND that should be used for unilateral cN1a disease remains unclear. Bilateral CCND has a high rate of postoperative complications, such as temporary or permanent hypoparathyroidism. Therefore, bilateral CCND should only be performed in unilateral cN1a PTC patients with a high risk of contralateral paratracheal LNM.

Some studies have reported that a tumor size >1 cm, extrathyroidal extension and lateral lymph node metastasis may be important factors for predicting contralateral paratracheal LNM.^{15,21–25} However, few studies have examined contralateral paratracheal LNM in unilateral cT1N1a or cT2N1a PTC patients. Therefore, we aim to determine the incidence of occult contralateral paratracheal LNM in unilateral cT1N1a or cT2N1a PTC patients and identify the risk factors associated with contralateral paratracheal LNM.

Patients and Methods

Patient Selection

We performed total thyroidectomy (TT) and bilateral CCND in unilateral cT1N1a or cT2N1a PTC patients from January 2017 to March 2019. Patients with more

than five metastatic lymph nodes or with the largest involved lymph node measuring >3 cm in diameter were treated with radioactive iodine. High-resolution ultrasound and computed tomography (CT) scans were performed preoperatively. All patients underwent fine needle aspiration (FNA) before surgery. A solid hypoechoic nodule measuring >5 mm with a highly suspicious sonographic pattern (irregular margins, microcalcifications, taller-than-wide shape, or evidence of extrathyroidal extension) were subjected to FNA to refute or confirm malignancy. In this study, nodules measuring <5 mm were not subjected to FNA or surgery. If ipsilateral paratracheal lymph nodes that were sonographically suspicious for PTC (microcalcifications, cystic aspect, round shape, peripheral vascularity, or hyperechogenicity) were detected by ultrasound, FNA of the suspicious lymph node was performed for cytology and washout for thyroglobulin (Tg) assessments. The CT scans were mainly used to detect superior mediastinal lymph nodes (level VII). Histological examinations were routinely performed postoperatively.

This study complies with the Declaration of Helsinki. All patients were provided with a description of the study in written and oral forms and signed an informed consent document to participate. This case-control study was reviewed by the Medical Ethics Committee of Qilu Hospital of Shandong University (project identification code: 2018149) and registered in the Research Registry (UIN: researchregistry5292). Reporting followed the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) criteria.²⁶ The study design is depicted in Figure 1. With the exception of the surgeons and surgical assistants, all of the study members were blinded to the surgical method used for each patient to minimize bias.

The inclusion criteria for this study were as follows: (1) the absence of a previous history of thyroidectomy; (2) unilateral PTC verified by histological examination; (3) stage T1 or T2 primary carcinoma (tumor size ≤4 cm in the largest dimension and without gross extrathyroidal extension);²⁷ (4) tumor not located within the isthmus or pyramidal lobe; (5) contralateral lobe without nodes or benign contralateral nodes confirmed by a postoperative pathological assessment; (6) unilateral cN1a disease (ipsilateral paratracheal lymph node metastases verified by preoperative imaging and FNA or by inspection at the time of surgery);²⁷ and (7) the absence of distant metastasis. Patients with multifocal unilateral PTC were included. Patients who met the inclusion criteria were

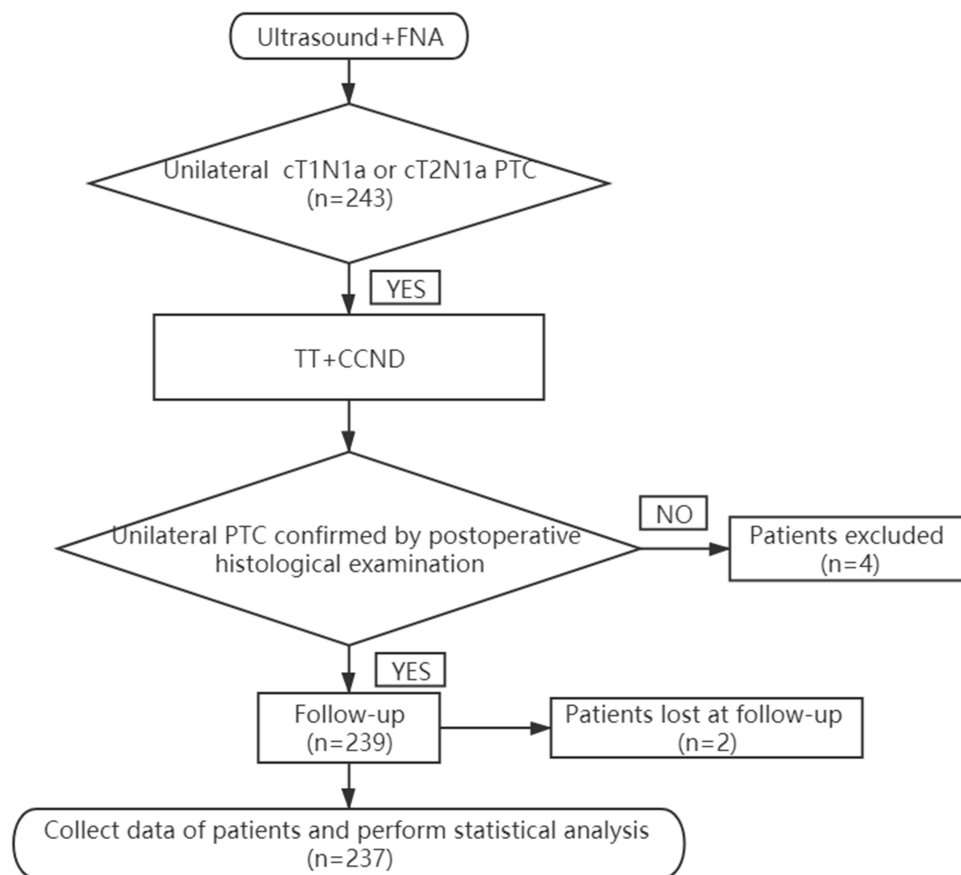


Figure 1 Flow chart of the study protocol.

Abbreviations: FNA, fine needle aspiration; PTC, papillary thyroid carcinoma; TT, total thyroidectomy; CCND, central compartment neck dissection.

divided into two groups based on the status of the contralateral paratracheal LNM.

Surgical Procedure

All surgeries were performed by the same surgical team, which included two experienced thyroid surgeons. To ensure comprehensive removal of lymph nodes from the central compartment, a standardized CCND was performed in accordance with the method described by Pai.²⁸ The recurrent laryngeal nerve was identified and preserved using intraoperative nerve monitoring (IONM). The parathyroid gland was routinely identified and preserved in situ or through autotransplantation. The central neck compartment was bounded superiorly by the hyoid bone, inferiorly by the innominate artery, laterally by the carotid artery and dorsally by the prevertebral fascia. The central compartment was further divided into the prelararyngeal, pretracheal and paratracheal regions (Figure 2). For accurate compartmentalization, the boundary of each

region was marked by suturing prior to CCND. The specimens were isolated and sent for histological examinations.

Clinical Assessment

The following data were recorded: patient age; patient sex; primary tumor site; primary tumor size (measured as the longest diameter of the largest lesion); whether the pathology was aggressive; multifocality; microscopic extrathyroidal extension; intraglandular dissemination; the number of metastatic lymph nodes in the ipsilateral paratracheal, pretracheal and paratracheal regions; the total amount of metastatic lymph nodes in these three regions; underlying conditions of chronic lymphocytic thyroiditis (CLT); and the presence of a proto-oncogene B-Raf mutation (*BRAF* V600E).

The tumor site was further divided into the following regions: left lobe or right lobe, inferior pole or superior pole, and far isthmus or near isthmus region (Figure 2). Inferior pole tumors were located in the lower half of the

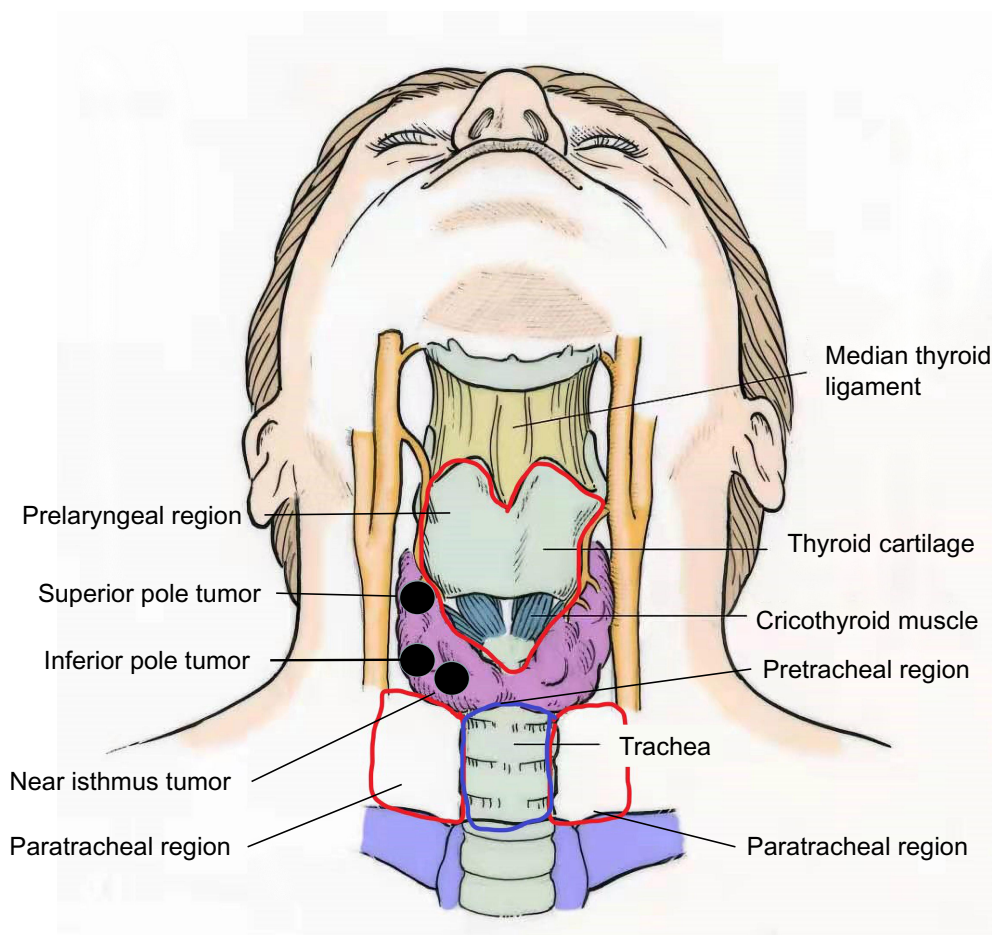


Figure 2 Schematic representation of the subsites of the central compartment and the primary tumor site.

thyroid gland lobe. The borders of the near isthmus tumors were in contact with the isthmus lateral boundary. In contrast to the near isthmus tumors, the far isthmus tumors were those whose boundaries did not contact the isthmus lateral boundary. Microscopic extrathyroidal extensions were detected only by histological examination. Multifocality was defined as the presence of two or more lesions in a single lobe. Intraglandular dissemination was defined as cancerous embolisms in the lymphatic vessels surrounding a major thyroid carcinoma, with features of heterotypic cells and psammoma bodies.²⁹ The aggressive pathologies included the hobnail variant, columnar cell variant, solid variant and tall cell variant.

Statistical Analysis

Based on our own clinical experience, the rates of contralateral paratracheal LNM reported in previous publications,^{12–15} and an estimated 10% loss to follow-up rate, we calculated that 243 total patients would be needed to achieve 90% power at the 5% significance level.

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, N.Y., USA). Continuous variables were reported as mean \pm standard deviation. A *t*-test or Mann–Whitney *U*-test was used to compare continuous variables, while a Chi-square test or Fisher's exact test was used for categorical variables. Logistic regression was used for multivariate analysis, and independent risk factors were defined as those with an odds ratio (OR) >1 . Before logistic regression analysis, correlation analyses and collinearity tests were used for variable selection. P-values <0.05 indicated statistical significance.

Results

Of the 243 patients initially enrolled in this study, two patients were lost at follow-up. Four patients were excluded due to contralateral papillary thyroid microcarcinoma (PTMC) confirmed by postoperative histological examination. Two hundred thirty-seven patients (179 females and 58 males, age 45.9 ± 9.3 years, range 25–68)

Table 1 Demographic, Tumor and Lymph Node Characteristics of Patients

Characteristics	Patient n=237	(%)
Age (min-max)	45.9±9.3 (25–68)	
Sex		
Male	58	24.5
Female	179	75.5
Primary tumor size (mm)	14.3±7.8(6–40)	
Primary tumor size stage		
T1a (0–10 mm)	110	46.4
T1b (11–20 mm)	75	31.6
T2 (21–40 mm)	52	22.0
Multifocality	42	17.7
Intraglandular dissemination	21	8.9
Microscopic extrathyroidal extension	58	24.5
Aggressive pathology		
Tall cell	10	4.2
Hobnail	2	0.9
Primary tumor site		
Right lobe	170	20.7
Inferior pole tumor	67	28.3
Near isthmus tumor	25	10.5
CLNM (pN1a)		
Contralateral paratracheal LNM	49	20.7
Pretracheal LNM	95	40.1
Prelaryngeal LNM	54	22.7
Size of the largest involved lymph node (mm)	18.8±9.4	
Extra-nodal invasion	87	36.7
CLT	50	21.1
BRAF mutation (+)	85	35.9

Abbreviations: LNM, lymph node metastasis; CLNM, central lymph node metastasis; CLT, chronic lymphocytic thyroiditis.

met the inclusion criteria. The patient, tumor and lymph node characteristics are shown in Table 1. The size of the primary tumor ranged from 6 to 40 mm (average 14.3 ±7.8 mm). Forty-nine patients (49/237, 20.7%) had metastatic lymph nodes in the contralateral paratracheal region. In addition, 95 patients (40.1%) had positive LNM in the pretracheal region, while 54 (22.7%) had positive LNM in the prelaryngeal region (Table 1). A total of 1557 T1 or T2 PTC patients (86.5%) undergoing simultaneous surgeries had cN0 stage.

The follow-up period was 3–12 months (median 8 months). The rate of structural lymph node recurrence in the neck after the first surgery was 1.3% (3/237 patients).

The time to recurrence among the 3 patients was 5.3±1.2 months (4 months, 5 months, and 7 months). All of these patients experienced recurrence in the ipsilateral lateral neck region. Among the 237 patients, seven had temporary recurrent laryngeal nerve injury confirmed by IONM and laryngoscopy within 7 days after surgery, and nerve function recovery was verified with laryngoscopy after 3 months. Eighteen patients had permanent hypoparathyroidism, and their parathyroid hormone (PTH) levels remained below the lower limit of the normal range at 3 months after surgery.

In the univariate analysis, a larger number of male patients ($p=0.003$) were diagnosed with contralateral paratracheal LNM. The patients with contralateral paratracheal LNM had larger tumors ($p<0.001$) and more commonly had T2 diseases (21–40 mm) ($p<0.001$). More patients in the contralateral paratracheal LNM (+) group had metastatic lymph nodes in the pretracheal region ($p<0.001$) but not in the prelaryngeal region. In the contralateral paratracheal LNM (+) group, a larger number of patients had more than five metastatic lymph nodes. Contralateral paratracheal LNM was more likely to occur in patients with aggressive pathology ($p<0.001$), inferior pole ($p=0.011$) or near isthmus ($p<0.001$) tumors, extranodal invasion ($p=0.003$) and intraglandular dissemination ($p=0.009$) (Table 2). Age, multifocality, microscopic extrathyroidal extension, the size of the largest involved lymph node, CLT and *BRAF* gene mutations were not associated with contralateral paratracheal LNM. In the final multivariate analysis, the male sex ($p=0.005$, OR=17.545), T2 disease ($p=0.003$, OR=34.317), an inferior pole ($p=0.022$, OR=8.289) or near isthmus tumor ($p=0.001$, OR=40.229), aggressive pathology ($p=0.027$, OR=48.063), pretracheal LNM ($p=0.002$, OR=14.235) and having more than five metastatic lymph nodes ($p=0.025$, OR=23.426) were independent predictive factors of contralateral paratracheal LNM (Table 3).

Discussion

Bilateral CCND has many advantages, including the fact that it leads to a low local recurrence rate because other potentially metastatic lymph nodes are removed in the process.^{21,22} However, unilateral CCND can obviate the possibility of bilateral recurrent laryngeal nerve injury and permanent hypoparathyroidism because it does not involve exploration of the contralateral central neck compartment. Therefore, it is very important to evaluate preoperative and intraoperative predictive factors of contralateral

Table 2 Univariate Analysis of Clinical and Pathological Factors Related to Contralateral Paratracheal LNM

Characteristics	Contralateral Paratracheal LNM (+) n=49	Contralateral Paratracheal LNM (-) n=188	P value
Age (min-max)	44.4±9.8 (28–64)	46.4±9.1 (25–68)	0.194
Male, n (%)	20 (40.8%)	38 (20.2%)	0.003*
Primary tumor size (mm)	19.2±9.9	13.0±6.7	<0.001*
Primary tumor size stage			<0.001*
T1a (0–10mm), n (%)	15 (30.6%)	95 (50.5%)	a
T1b (11–20mm), n (%)	12(24.5%)	63 (33.5%)	a
T2 (21–40mm), n (%)	22 (44.9%)	30 (16.0%)	b
Primary tumor site			
Right lobe	26(53.1%)	114(60.6%)	0.337
Inferior pole tumor	21 (42.9%)	49 (26.1%)	0.011*
Near isthmus tumor	12 (24.5%)	13 (6.9%)	<0.001*
Aggressive pathology, n (%)	8(25.0%)	4(2.1%)	<0.001*
Multifocality, n (%)	11 (22.4%)	31 (16.5%)	0.331
Intraglandular dissemination, n (%)	9 (18.4%)	12 (6.4%)	0.009*
Microscopic extrathyroidal extension, n (%)	14 (28.6%)	44 (23.4%)	0.454
Pretracheal LNM, n (%)	44	51	<0.001*
Prelaryngeal LNM, n (%)	12	42	0.749
Total number of metastatic lymph node			<0.001*
1–5, n (%)	7(14.3%)	149(79.3%)	
>5, n (%)	42(75.7%)	39(20.7%)	
Size of the largest involved lymph node (mm)	20.2±10.2	18.4±9.1	0.229
Extra-nodal invasion	27(55.1%)	60(31.9%)	0.003*
CLT, n (%)	7 (14.2%)	43 (22.8%)	0.189
BRAF mutation+, n (%)	22 (44.8%)	63(33.5%)	0.139

Notes: *P<0.05; a, b, There is a statistically significant difference in proportion between T1a and T2 ("a" versus "b") and T1b and T2 ("a" versus "b"), but there is no statistically significant difference in proportion between T1a and T1b ("a" versus "a").

Abbreviations: LNM, lymph node metastasis; CLT, chronic lymphocytic thyroiditis.

Table 3 Multivariate Logistic Regression for Contralateral Paratracheal LNM

Variables	Partial Regression Coefficient	OR	95% Confidence Interval	P
Constant	−5.600	0.004		
Male sex	2.865	17.545	2.386–129.032	0.005
T2 disease (21–40 mm)	3.536	34.317	3.256–361.704	0.003
Inferior pole tumor	2.115	8.289	1.359–50.563	0.022
Near isthmus tumor	3.695	40.229	4.257–380.185	0.001
Aggressive pathology	3.873	48.063	1.561–1480.185	0.027
Pretracheal LNM	2.725	14.235	1.471–46.662	0.002
>5 metastatic lymph nodes	2.716	23.426	5.767–293.244	0.025

Abbreviation: LNM, lymph node metastasis.

paratracheal LNM and avoid unnecessary neck dissections. In this study, contralateral paratracheal LNM was uncommon in the cN1a PTC patients (20.7%; 49/237). Other studies have reported similar rates of contralateral paratracheal LNM (9.8–27.3%) in cN0 PTC patients.^{12–15}

Previous studies have shown that PTC with a maximal diameter of >10 mm is associated with a high rate of concomitant contralateral paratracheal LNM.^{9,30–33} However, this study showed that the presence of a T2 disease (21–40 mm) was an independent predictive factor

of contralateral paratracheal LNM ($p=0.003$, $OR=34.317$). This inconsistency may be attributable to the fact that patients with tumors measuring >40 mm and gross extrathyroidal extension (stage T3 and T4) were included in previous studies. In this study, we analyzed the relationship between the primary tumor site and contralateral paratracheal LNM and observed that both inferior pole ($p=0.022$, $OR=8.289$) and near isthmus tumors ($p=0.001$, $OR=40.229$) were independent predictive factors of contralateral paratracheal LNM in T1N1a or T2N1a PTC. Previous studies have reported that patients with PTC located in the isthmus are more likely to have CLNM, especially pretracheal and prelaryngeal LNM, and bilateral CCND should be considered.^{34–36}

According to this study, male sex ($p=0.005$, $OR=17.545$) and the presence of an aggressive pathology ($p=0.027$, $OR=48.063$) were independent predictive factors of contralateral paratracheal LNM. Men are known to be at high risk for thyroid cancer.^{35,37–40} One previous study reported that male sex was associated with a high rate of contralateral paratracheal LNM.³⁰ Aggressive pathologies have also been identified as risk factors for PTC invasion and metastasis.² PTC with aggressive pathology was more likely to have extrathyroidal extension and lymph node metastasis than typical PTC.^{41–43}

Although previous studies have reported that multifocality is predictive of CLNM,^{38–40} we found that multifocality was not associated with contralateral paratracheal LNM. Genetic studies have shown that some multifocal PTC are caused by intraglandular dissemination of a single cancer focus.^{44,45} In this study, cancers with scattering foci that were detectable only by microscopy were classified as PTC with intraglandular dissemination. Previous studies have suggested that patients with intraglandular dissemination have a higher likelihood of developing LNM.⁴⁶ In this study, univariate analyses confirmed that patients with intraglandular dissemination are more likely to develop contralateral paratracheal LNM ($p=0.009$); however, intraglandular dissemination was not an independent predictor in the multivariate analysis. Patients with intraglandular dissemination are more likely to have LNM, but the specific metastatic direction may be more strongly influenced by other factors.

This study showed that pretracheal LNM ($p=0.002$, $OR=14.235$) and the presence of more than five metastatic lymph nodes ($p=0.025$, $OR=23.426$) were independent predictive factors of contralateral paratracheal LNM.

Previous studies have reported that prelaryngeal/pretracheal LNM is a potential independent predictor of concomitant contralateral paratracheal LNM.^{31,33} In this study, however, prelaryngeal LNM was not an independent predictor of contralateral paratracheal LNM. As previously reported, the presence of >5 positive nodes and extranodal invasion were associated with a moderate risk of recurrence and low disease-specific survival in pN1 patients.⁶ Some studies have reported that intraoperative frozen section examinations of ipsilateral lymph nodes have high sensitivity, specificity and accuracy in predicting the contralateral nodal status and may be useful in determining the appropriate extent of central compartment node dissection.^{47–50} The presence of extranodal invasion greatly influences the risk of contralateral paratracheal LNM.⁵¹ In this study, extranodal invasion was significant in the univariate analysis but was not an independent predictor of contralateral paratracheal LNM.

The aim of this prospective study was to identify risk factors for contralateral paratracheal LNM in unilateral cT1N1a or cT2N1a PTC; however, long-term follow-up data on the complications, recurrence, and mortality were not available. We analyzed the *BRAF* gene mutation status in this study but were unable to include other genetic factors that may impact CLNM. Our study was also limited by a small sample size and absence of randomization. A randomized controlled trial with a large sample size is necessary to verify our conclusions.

Conclusion

In conclusion, our data indicate that the male sex and the presence of a T2 disease (21–40 mm), an inferior pole or near isthmus tumor, an aggressive pathology, pretracheal LNM and >5 metastatic lymph nodes may predict contralateral paratracheal LNM in unilateral cT1N1a or cT2N1a PTC. These data may be useful for identifying targets for surveillance or therapeutic interventions for CCND in the future.

Abbreviations

PTC, Papillary thyroid carcinoma; LNM, Lymph node metastasis; CLNM, Central lymph node metastasis; CCND, Central compartment neck dissection; ATA, American Thyroid Association; TT, Total thyroidectomy; FNA, Fine needle aspiration; IONM, Intraoperative nerve monitoring; CT, computed tomography; CLT, Chronic lymphocytic thyroiditis.

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Disclosure

The authors declare that they have no conflicts of interest related to this work.

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