High-risk factors for ipsilateral lateral neck lymph node metastasis in clinically node-negative patients with papillary thyroid microcarcinoma (cT1aN0)

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Research

Keywords: Papillary thyroid microcarcinoma, Risk factors, Lateral neck, Lymph node metastasis, Clinically node negative

Posted Date: April 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-21101/v1>

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Abstract

Background: The incidence of papillary thyroid microcarcinoma (PTMC) increases yearly. There are several studies on the high-risk factors for lymph node metastasis in the central compartment of PTMC but few studies on the high-risk factors for lateral neck lymph node (LNLN) metastasis. Few studies have analyzed the high-risk factors for LNLN metastasis for clinically lymph node-negative PTMC patients in stage T1a (cT1aN0). We investigated the risk factors for LNLN metastasis in these patients.

Methods: In total, 127 PTMC (cT1aN0) patients underwent hemi- or total thyroidectomy with ipsilateral central lymph node dissection (CLND) plus lateral lymph node dissection (LLND), including levels III and IV, between 2018 and 2019 in our hospital. Univariate and multivariate analyses identified the high-risk factors for LNLN metastasis in PTMC (cT1aN0).

Results: The rate of LNLN metastasis was 21.26% (27/127). The multivariate analysis showed that capsular invasion ($p=0.027$), tumor location at the superior pole ($p=0.002$) and ipsilateral central lymph node positivity ($p=0.001$) were independent risk factors for LNLN metastasis in PTMC patients (cT1aN0), with odds ratios (ORs) of 0.181 (95% confidence interval (95% CI): 0.039-0.827), 5.994 (95% CI: 1.949-18.435) and 6.182 (95% CI: 2.193-17.425), respectively.

Conclusions: These findings indicate that capsular invasion, tumor location at the superior pole and ipsilateral central lymph node positivity are independent high-risk factors for LNLN metastasis in clinically node-negative PTMC (cT1aN0) patients. High-risk factors should be correctly evaluated to guide surgical treatment for PTMC patients.

1. Background

Papillary thyroid microcarcinoma (PTMC), defined as the maximum diameter of the tumor being 10 mm or less, has become the fastest-growing tumor of the endocrine system worldwide^[1]. Though the 10-year prognosis of patients with PTMC is excellent and is well known for its indolent natural course^[2], the probability of cervical lymph node metastasis is not low, and lymph node metastasis is associated with an increased risk of recurrence^[3]. Currently, with the increased incidence of thyroid cancer, especially with the popularization and application of high-resolution color Doppler ultrasound (US) and fine needle aspiration (FNA) cytology, the incidence of PTMC has increased. Many studies have focused on the high-risk factors for cervical lymph node metastasis in PTMC patients. These studies still have some limitations. First, studies have predicted high-risk factors for lymph node metastasis in the central lymph nodes (CLNs) rather than high-risk factors for lateral neck lymph node (LNLN) metastasis in patients with PTMC^[4]. Second, research on high-risk factors for LNLN metastasis is aimed mostly at patients with suspected clinically positive lymph nodes preoperatively (cN+) rather than patients with clinically negative lymph nodes preoperatively (cN0)^[5]. Third, some studies of high-risk factors for lymph node metastasis have focused only on tumor size (≤ 1 cm) rather than clinical stage (T1a)^[6,7]. Therefore, we

performed this retrospective study to analyze the high-risk factors for LNLN metastasis (levels III, IV) in PTMC patients with clinically negative nodes in clinical stage cT1aN0.

2. Patients And Methods

2.1 Patients:

The study subjects were patients who received surgical treatment at the Affiliated Cancer Hospital of Zhengzhou University, China, between October 2018 and November 2019. A total of 127 patients were included according to the following criteria: (1) The patients were diagnosed with PTMC by FNA preoperatively; (2) No previous thyroid surgery; (3) Patients with unilateral PTMC whose cancer was confined to one lobe; and (4) Patients with clinical stage cT1aN0 after preoperative color Doppler US and a computed tomography (CT) evaluation. Finally, a total of 127 patients were included in this study. This research was approved by the Medical Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University, China.

2.2 Surgical Treatment:

Patients with a definitive diagnosis of unilateral PTMC (clinical stage cT1aN0M0) underwent primary thyroid surgery (hemi- or total thyroidectomy with ipsilateral central lymph node dissection (CLND) plus lateral lymph node dissection (LLND) including levels III and IV) at our hospital. A flow chart of the surgical options for PTMC is presented in Fig. 1.

Clinical and pathological factors, including sex, age, tumor size, tumor site, microscopic or visible thyroid capsule invasion without extrathyroidal extension (ETE), and ipsilateral central lymph node positivity, were retrospectively collected and analyzed. Among these factors, tumor site was grouped as follows: superior third, middle third, and inferior third. Tumor size was defined as the largest diameter of the primary tumor measured by preoperative US imaging. Unilateral multifocality was defined as two or more PTMC tumors located in the same lobe, and unifocality was defined as only one PTMC tumor found in the whole thyroid gland. Pathological T stage was classified according to the 8th edition of the American Joint Committee on Cancer/International Union for Cancer Control (AJCC/UICC) tumor node metastasis (TNM) staging system (2018) [8].

2.3 Statistical Analysis:

The data were analyzed by SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA). Data are expressed as the mean $\pm$ standard deviation (SD). Differences between categorical variables were analyzed by the chi-squared (χ^2) test. Multivariate logistic regression analysis was performed to identify risk factors for lateral lymph node metastasis (levels III, IV). A p-value < 0.05 was considered statistically significant.

3. Results

The demographic and tumor characteristics of the patients are presented in Table 1. The mean age of all patients was 46.05 ± 10.98 years. The mean tumor size, defined as the maximal diameter, of this cohort was 6.30 ± 1.94 mm. The total metastasis rate of the ipsilateral central neck compartment was 24.41% (31/127). The total metastasis rate of the lateral lymph node was 21.26% (27/127); 11.02% (14/127) of patients had metastasis only in level III, 5.51% (7/127) of patients had metastasis only in level IV, and 4.72% (6/127) of patients had metastasis in both levels III and IV. A total of 14.59% (14/96) of patients demonstrated skip metastasis as lateral lymph node metastasis (LLNM) without central lymph node metastasis (CLNM).

Risk factors for LLNM in PTMC included the following. ☐ Location: Tumor location at the superior pole was statistically significant compared with tumor location at the middle and inferior poles ($p = 0.002$), with an odds ratio (OR) of 5.357 (95% confidence interval (95% CI): 1.724–16.650). ☐ Capsular invasion: The metastasis rate of capsular invasion was 30.43% (21/69), and that of noninvolvement was 10.49% (6/58), which were significantly different ($p = 0.006$), with an OR of 0.264 (95% CI: 0.098–0.709). ☐ Ipsilateral central lymph node positivity: The LLNM rate was 41.94% (13/31) when the ipsilateral CLN was positive, and the LLNM rate was 14.58% (14/96) when the ipsilateral CLN was negative, which were significantly different ($p = 0.001$), with an OR of 4.23 (95% CI: 1.701–10.521). The univariate analysis showed that LLNM was significantly associated with tumor location at the superior pole, capsular invasion and ipsilateral CLNM. The variables without a significant association with LLNM included sex, age, tumor size and multifocality (Table 2).

For the multivariate analysis, three variables were included in the logistic regression model. The results are shown in Table 3. In our model, the multivariate analysis showed that capsular invasion ($p = 0.027$), tumor location at the superior pole ($p = 0.002$), and ipsilateral CLNM ($p = 0.001$) were independent risk factors for LLNM, with ORs of 0.181 (95% CI: 0.039–0.827), 5.994 (95% CI: 1.949–18.435) and 6.182 (95% CI: 2.193–17.425), respectively.

4. Discussion

Lymph node metastasis is very common in PTC patients^[9]. Following the central compartment, the lateral neck is regarded as the second most common region involved^[9]. Lateral neck metastasis occurs in 25%-65% of PTC patients^[10, 11]. The lateral neck contains levels II through V^[12], among which, levels III and IV are more commonly involved than levels II and V^[9, 13]. However, some studies have shown that the prevalence of LNLN metastasis among patients with PTMC is relatively low, ranging from 1.1 to 9.4%^[14, 15]. Although other studies have shown that the rate of LNLN metastasis is low in patients with PTMC, an important risk factor for a high recurrence rate and a low survival rate in patients with thyroid cancer is neck lymph node metastasis^[16], especially LNLN metastasis^[17]. At present, there are many studies on the predictive factors of cervical lymph node metastasis in papillary thyroid carcinoma. A meta-analysis by So.YK et al showed that ETE, tumor multifocality, the male sex, an upper pole location, tumor size ≥ 1.0 cm, lymphovascular invasion and tumor bilaterality were significantly associated with LNLN

metastasis. The most frequently affected areas were levels III and IV^[18]. However, the above studies on the high-risk factors for cervical lymph node metastasis in PTMC have the following limitations. 1. Preoperative clinical T staging of included cases: Although some patients have clinically negative lymph nodes (cN0) preoperatively, clinical T staging includes not only stage T1a but also stages T1-T4 (with extrathyroidal invasion, which belongs to stage T3 rather than stage T1). 2. Preoperative clinical N staging of included cases: Some of the patients included in the studies were patients with suspected positive cervical lymph nodes (cN+), not cN0. Therefore, there have been few studies on the risk factors for LNLN metastasis in PTMC patients with clinical stage cT1aN0.

Therapeutic lateral neck lymph node dissection (LND) is recommended for PTC patients with the clinically positive lateral neck (cN1b) ^[2], and prophylactic lateral neck LND is not routinely recommended for patients with the clinically negative (cN0) lateral neck. However, some patients with the cN0 lateral neck might need secondary operations due to positive nodes in lateral compartments during surveillance. Because of the current harsh medical environment in China^[19], suspicious metastatic LNLNs are found via color Doppler US examinations during the follow-up period after the first operation (subsequent years). On the one hand, a second surgery may be needed. On the other hand, the patient is likely to believe that the lesion was caused during the first operation and would not be satisfied with the initial treatment results, which may cause resistance or resentment to the doctor who performed the first treatment. Therefore, this retrospective analysis is not intended to recommend prophylactic LNLN dissection for PTMC patients with clinical stage cT1aN0 but to provide a reference for clinicians to make a decision regarding the management of the lateral cervical lymph nodes in PTMC patients with clinical stage cT1aN0. It is important that the high-risk factors for LNLN metastasis be explained to patients and that appropriate clinical decisions are made.

Level III and IV LNLNs are the most common areas of metastasis in addition to level VI. Therefore, we performed ipsilateral level III, IV and VI lymph node dissection on PTMC patients with clinical stage cT1aN0. In our study, the metastasis rate of LNLNs was higher than that in previous studies by other scholars. The total lateral neck metastasis rate was 21.26%, which is higher than that in other studies ^[14, 15]. Capsular invasion is an independent high-risk factor for lateral neck metastasis, and this risk factor has not been mentioned in other studies. Most research results show that ETE is a high-risk factor for LNLN metastasis. However, the clinical stage of ETE belongs to T3, so we excluded ETE in this study. Tumor location at the superior pole and ipsilateral central lymph node positivity are also independent high-risk factors for lateral neck metastasis in PTMC patients, consistent with other studies ^[20, 21]. However, our study did not find that sex, multifocality or age were high-risk factors for LNLN metastasis. Therefore, the likelihood of LNLN metastasis will be increased for PTMC patients with capsular invasion, a tumor located at the superior pole and ipsilateral CLNM. Thus, there should be appropriate communication with the patients, and an appropriate treatment plan should be selected.

Population-based studies from the past 5 years have demonstrated that an increasing number of incidental thyroid nodules are being identified based largely on an expansion in the use of diagnostic

imaging^[22]. Preoperative ultrasonography examinations have been widely adopted to assess the metastatic risk of lymph nodes and assist clinicians in decision-making^[2]. Although some authors have reported that ultrasonography performed by a skilled operator can accurately detect neck lymphadenopathy^[23], the sensitivity and specificity of ultrasonography for the detection of LNLN metastases are only 65–80.3% and 72–84.8%, respectively^[24, 25]. Another disadvantage of ultrasonography is that it is not sensitive enough to detect deep lymph nodes. Moreover, ultrasonography is a subjective assessment and highly dependent on the experience of the operator^[25, 26], and its diagnostic accuracy in low-volume institutions decreases dramatically, making the results less valuable. However, occult LNLN metastases are not rare in clinically N0 PTC patients^[27]. Because of the limitation of color Doppler ultrasonography in the diagnosis of metastatic lymph nodes, we cannot rely entirely on preoperative color Doppler ultrasonography to assess the presence of suspected LNLN metastases. Although color Doppler US cannot completely detect suspected metastatic lymph nodes in the lateral neck, it can uncover the relationship between tumors and thyroid capsules. Our study shows that tumor capsular invasion is a high-risk factor for ipsilateral LNLN metastases. Therefore, when color Doppler US reveals that the tumor is closely related to the thyroid capsule, we should pay close attention to these patients, and it is of clinical significance to stratify patients according to their risk of LNLN metastases and to distinguish high-risk PTMC patients from low-risk PTMC patients. This will assist in tailoring treatment options for PTMC patients with clinical stage cT1N0.

There are many controversies regarding the clinical treatment of PTMC. Little controversy exists concerning therapeutic LND, which is recommended for patients with biopsy-proven metastatic nodes in the lateral neck^[2]. However, much controversy exists concerning whether to perform prophylactic LND for patients with the clinical negative lateral neck (cN0)^[2, 28, 29]. Opposition to prophylactic LNLN dissection is based mainly on the following aspects: 1. Prophylactic neck lymph node dissection will increase the operation time and may increase surgical complications^[30], such as chyle leaks and spinal accessory nerve dysfunction; 2. Prophylactic LNLN dissection does not provide patients with significant survival benefits^[12]; and 3. Even if LNLN recurrence is found during the follow-up, the progression of lymph node metastasis is slow due to its indolent character, and it can be removed easily by reoperations. Support for prophylactic LND is based mainly on the following aspects: 1. Preventive LND can reduce the chance of recurrence and secondary surgery^[28, 31–34]; 2. If treated by an experienced surgeon, its long-term complications are uncommon^[30, 35], and prophylactic, selective LND of levels III and IV may bring few postoperative complications^[36]; 3. Recent articles claim that the presence of metastatic lymph nodes is associated with poor prognosis^[32, 37]; and 4. Due to the limitations of US, suspicious positive lymph nodes cannot be fully evaluated before surgery^[11, 38]. Some scholars have created a nomogram estimation of the metastatic risk for each patient that can help guide clinicians in decision-making regarding whether to perform lateral LLND^[39]. However, according to the metastasis prediction model, its scoring criteria are based mainly on suspicious high-risk factors, such as ETE and the number of positive lymph nodes, so it is not suitable for lymph node-negative patients with PTMC in stage cT1a

preoperatively. Therefore, patients with PTMC in stage cT1N0 should be evaluated separately, and treatment decisions should be individualized for patients with high-risk factors.

There are some limitations to this study. First, because of its retrospective nature and single-center analysis, it is difficult to design surgical treatment and collect patient information and other items in advance. Prospective and multicenter clinical trials should be performed to identify the predictive factors of LNLN metastases in PTMC patients in future research. Second, the sample size was not large enough, with only 127 patients ultimately identified. Larger sample sizes are needed in further studies to provide supporting evidence with greater reliability.

In conclusion, LNLN metastasis in patients with PTMC in clinical stage cT1aN0 is not rare. Capsular invasion, tumor location at the superior pole and ipsilateral central lymph node positivity are independent risk factors for LNLN metastases in clinically node-negative patients with PTMC in the T1 clinical stage (cT1aN0). The combinational use of these risk factors will help surgeons devise an appropriate surgical plan preoperatively.

Abbreviations

PTMC: Papillary thyroid microcarcinoma; **US:** ultrasound; **FNA:** fine needle aspiration; **CLNs:** central lymph nodes; **LNLN:** lateral neck lymph node; **CT:** computed tomography; **CLND:** central lymph node dissection; **LLND:** lateral lymph node dissection; **ETE:** extrathyroidal extension; **SD:** standard deviation; **LLNM:** lateral lymph node metastasis; **CLNM:** central lymph node metastasis; **OR:** odds ratio; **CI:** confidence interval; **LND:** lymph node dissection.

Declarations

Acknowledgments:

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in this manuscript.

We appreciate all the staff involved in the preparation of the study.

Author contributions:

Bin Zhou did the conception and design, collection and assembly of data, data analysis and interpretation.

Lin Wei did the provision of study materials or patients.

Jianwu Qin did the conception and design and administrative support.

All authors did the manuscript writing and final approval of manuscript

Funding: No

Availability of data and materials: Not applicable.

Ethics approval and consent to participate:

Approved by the Ethics Committee of The Affiliated Cancer Hospital of Zhengzhou University.

Consent for publication: We have consent for publication from the patient.

Competing interests: No.

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Tables

Table 1 Tumor characteristics of PTMC (cT1aN0M0)			
Characteristic		No.	%
Sex			
	Male	33	25.98
	Female	94	74.01
Age(years)			
	n<55	105	82.68
	n≥56	22	17.32
Primary tumor size(unifocality)			
	≤5mm	38	36.19
	5mm<n≤10mm	67	63.81
Tumor location(unifocality)			
	Superior	16	15.24
	Mid	57	54.29
	Inferior	32	30.48
Capsular invasion			
	yes	58	45.67
	no	69	54.33
Multifocality			
	yes	22	17.32
	no	105	82.68
PTMC: Papillary thyroid microcarcinoma			

Table 2 Statistical analyses of LNLN metastasis in patients with PTMC (cT1aN0M0)														
		All patients		With LNM		Without LNM		Level III LNM		Level IV LNM		Level III+IV LNM		p value
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	
Sex														
	Male	33	25.98	10	30.3	23	69.7	6	60	2	20	2	20	0.14
	Female	94	74.02	17	18.09	77	81.91	8	47.06	5	29.41	4	23.53	
Age (years)														
	n<55	105	82.68	22	20.95	83	79.05	13	59.09	4	18.18	5	22.73	0.853
	n≥55	22	17.32	5	22.73	17	77.27	1	20	3	60	1	20	
Tumor location (unifocality)														
	Superior	16	15.24	8	50	8	50	5	62.5	2	25	1	12.5	0.002
	Mid	57	54.29	8	14.04	49	85.96	4	50	1	12.5	3	37.5	
	Inferior	32	30.48	6	18.75	26	81.25	3	50	1	16.67	2	33.33	
Multifocality														
	Yes	22	17.32	4	18.18	18	81.82	1	25	2	50	1	25	0.919
	No	105	82.68	23	21.9	82	78.1	13	56.52	5	21.74	5	21.74	
Capsular invasion														
	yes	69	54.33	21	30.43	48	69.57	12	57.14	4	19.05	5	23.81	0.006
	no	58	45.67	6	10.34	52	89.66	2	33.33	3	50	1	16.67	
Tumor size (unifocality)														
	≤5mm	38	36.19	9	23.68	29	76.32	6	66.67	1	11.11	2	22.22	0.74
	5mm<n≤10mm	67	65.71	14	20.9	53	79.1	7	50	4	28.57	3	21.43	
Ipsilateral level VI														
	Ipsilateral level VI LN+	31	24.41	13	41.94	18	58.06	6	46.15	4	30.77	3	23.08	0.001
	Ipsilateral level VI LN-	96	75.59	14	14.58	82	85.42	8	57.14	3	21.43	3	21.43	

PTMC: Papillary thyroid microcarcinoma ; LNLN: Lateral neck lymph node ; LN: Lymph node ; LNM: Lymph node metastasis

Table 3. Univariate and multivariate analyses of high-risk factors for LNLN metastasis in patients with PTMC						
	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Capsular invasion	0.264	0.098-0.709	0.006	0.181	0.039-0.827	0.027
Tumor location (unifocality)	5.357	1.724-16.650	0.002	5.994	1.949-18.435	0.002
Ipsilateral level VI	4.23	1.701-10.521	0.001	6.182	2.193-17.425	0.001
Multifocality	1.262	0.389-4.099	0.919	Not selected		
Age (years)	0.901	0.299-2.714	0.853	Not selected		
Sex	1.969	0.793-4.890	0.14	Not selected		
Tumor size (unifocality)	1.175	0.453-3.044	0.74	Not selected		

PTMC: Papillary thyroid microcarcinoma; LNLN: Lateral neck lymph node ; OR: Odds ratio ; CI: Confidence interval

Figures

Figure 1

Flow chart of surgical options for PTMC. PTMC: Papillary thyroid microcarcinoma; US: Ultrasonography; CT: Computed Tomography