Pathology & Oncology Research (2019) 25:1245–1251
https://doi.org/10.1007/s12253-018-0511-8

ORIGINAL ARTICLE

Predictive Factors of Lateral Lymph Node Metastasis in Papillary Thyroid Microcarcinoma

Wenjing Zhao[1] · Shaobo Chen[2] · Xianming Hou[2] · Quan Liao[2] · Ge Chen[2] · Yupei Zhao[2]

Received: 6 September 2018 / Accepted: 15 October 2018 / Published online: 26 October 2018

Abstract

This study was designed to determine the incidence and predictive factors for lateral lymph node metastasis (LNM) in patients with papillary thyroid microcarcinoma (PTMC). From January 2014 to July 2015, a retrospective review was conducted of 215 patients with PTMC who underwent total thyroidectomy and central lymph node dissection (LND) with lateral LND. Correlations of lateral LNM with clinicopathological features were examined using univariate analyses. Risk factors for lateral LNM were identified by multivariate analysis. Lateral LNM was observed in 163(75.8%) cases of 215 patients and often involved in level III (82.2%) and level IV (65.6%), with most found in two-levels (41.1%) and single-level (33.7%) models. Multivariate analyses showed that central LNM (odds ratio [OR]: 8.28, 95% confidence interval [CI]: 3.43–19.98, $p < 0.001$) and upper portion location (OR: 2.87 [CI: 1.34–6.09]; $p = 0.007$) were independent predictive factors for lateral LNM. The incidence of skip metastasis-Lateral LNM with central Lymph nodes negative-was 8.6% (14/163). Age ≥ 45 years old (OR: 4.37 [CI: 1.14–16.66]; $p = 0.031$) and upper portion location (OR: 4.34 [CI: 1.27–14.78]; $p = 0.019$) were independent risk factors for skip metastasis by multivariate analyses. Taken together, patients with PTMC with central LNM and tumor in the upper pole were more likely to present with lateral LNM. Even if there was no central LNM, patients with an age ≥ 45 years old and tumors in the upper portion of the thyroid should be evaluated carefully for possible lateral LNM.

Keywords Papillary thyroid microcarcinoma · Lateral lymph node metastasis · Skip metastasis · Predictors

Introduction

Papillary thyroid cancer (PTC) measuring less than 1 cm in its greatest dimension is defined as papillary thyroid microcarcinoma (PTMC) by the World Health Organization. With the recent developments in ultrasonography (US) and US-guided fine-needle aspiration cytology (FNAC), impalpable small-sized PTMC has been frequently detected. PTMC has an excellent prognosis after surgical treatment and radioiodine therapy, with a 15-year disease-specific survival rate as high as 99%, as well as a locoregional recurrence rate as low as 5% [1, 2]. However, many studies have shown that lymph node metastasis (LNM) in PTMC can increase the risk of locoregional recurrence and decrease the patient survival rate [1, 3, 4]. LNM is common in PTMC and usually occurs in a stepwise and continuous fashion. Primary cancer cells spreading from the thyroid gland initially metastasize to the central LN compartment and then to the ipsilateral lateral LN compartment, which is the first stop of lymphatic drainage followed by the mediastinal or contralateral lymph node compartments [5, 6]. Moreover, non-continuous metastasis, which presents only with metastasis to the ipsilateral lateral lymph node and not to the central LNM, is often defined as "skip metastasis" that occurs in a subgroup of patients [7–9].

Therefore, the detection of LNM is important for reducing recurrence. At present, many studies have analyzed the clinical and pathological factors related to central LNM. However, there are only a few clinicopathological studies that have investigated preoperative and intraoperative information to

Wenjing Zhao and Shaobo Chen contributed equally to this work

Ge Chen and Yupei Zhao were co-corresponding authors

✉ Ge Chen
pumchchenge@163.com

✉ Yupei Zhao
zhao8028@263.net

[1] Central Laboratory, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, 1 Shuai Fu Yuan Hu Tong, Beijing 100730, China

[2] Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, 1 Shuai Fu Yuan Hu Tong, Beijing 100730, China

evaluate the status of the lateral lymph node in PTMC. Our present study aimed to identify factors associated with lateral LNM in PTMC by retrospectively analyzing the clinicopathological data of patients, which may guide therapeutic decision-making for surgeons and patients.

Material and Methods

Patient Identification

Patients with PTMC who underwent simultaneous total thyroidectomy with therapeutic central compartment lymph node dissection (LND) and lateral LND between January 2014 and July 2015 at our hospital were identified. All the patients underwent US preoperatively and had confirmed PTMC by final histological examination. Patients were excluded if they had a history of thyroid or neck surgery with PTC of any size or nonthyroidal head and neck cancers. A total of 215 patients were included.

Data Collection

The clinicopathological data included age at diagnosis, gender, pathologic tumor size, multifocality, thyroiditis, extracapsular spread (ECS), preoperative clinical suspicion of cancer, tumor location, the status of central/lateral lymph nodes and numbers of central/lateral lymph nodes removed. The status of central/lateral lymph nodes was confirmed by a final histological examination. The location of the primary tumor was categorized as upper and middle/lower based on the results of ultrasonography. In multifocal cases, the largest tumor was analyzed. Lateral neck LND included levels II, III, IV, and V lymph nodes. Specifically, skip metastasis was defined as negative ipsilateral central and positive ipsilateral lateral lymph nodes in postoperative histopathological analyses.

Statistical Analysis

Based on the status of the lateral lymph nodes, we divided the analysis into two groups: lateral LNM-positive and lateral LNM-negative. Then, based on the status of central LNM, we divided the lateral LNM-positive group into two groups: skip metastasis present and skip metastasis absent. SPSS (version 24.0; SPSS, Inc., Chicago, IL) statistical software was used to perform statistical analysis. Pearson Chi-square test or Fisher's exact test was used for categorical data, and independent two-sample t test was used to compare continuous variables. Multivariate logistic regression analysis was conducted to assess independent associations of lateral LNM/skip metastasis with factors found to be statistically significant by univariate analysis. The results were presented as an odds ratio (OR) with 95% confidence interval (CI) and statistical significance set at $p < 0.05$.

Results

Patient Characteristics

Table 1 lists the clinicopathological characteristics of all patients. This study population consisted of 215 patients (75 were male and 140 were female) with a mean age of 42 ± 11 years. The mean size of the primary thyroid tumor (greatest dimension) was 0.69 ± 0.27 cm. Multifocal tumors were found in 96 patients (44.7%). ECS was found in 104 patients (48.4%), Hashimoto's thyroiditis was found in 68 patients (31.6%) and nodular goiter was found in 55 patients (25.6%). Primary tumor located in the upper portion of the thyroid was detected in 101 patients (47.0%), while tumor in the middle/lower lobe of the thyroid gland was detected in 114 patients (53.0%). Of all 215 patients, 182 had histologically positive central LN (84.7%) and 163 had histologically positive lateral LN (75.8%). Of these 182 patients with histologically positive central LN, 130 had a metastasis ratio of CLNM >25% (71.4%), 77 had a metastasis ratio > 50% (42.3%) and 34 had a metastasis ratio > 75% (18.7%). The mean number of central lymph nodes removed was 10.54 ± 7.14, and the number of lateral lymph nodes removed was 22.83 ± 14.03.

The Patterns of Lateral LNM

From the 163 patients with lateral LNM, a mean of 25.12 ± 14.39 lateral lymph nodes was removed, and 4.83 ± 4.51of these were positive nodes. Table 2 shows the distribution of metastatic lateral lymph node in 163 patients at the level of the neck. The most common distribution model of lateral LNM was two levels found in 67 patients (41.1%) and a single level in 55 patients (33.7%), followed by three levels in 33 patients (20.3%) and four levels in 8 patients (4.9%). Level III nodes (82.2% [134/163]) were the nodes most frequently involved in lateral LNM cases, followed by level IV nodes (65.6% [107/163]), level II nodes (38.0% [62/163]) and level V nodes (10.4% [17/163]).

Clinicopathological Factors Associated with Lateral LNM

Clinicopathological differences between patients with or without lateral LNM are compared in Table 1. Univariate analysis showed that ECS, central LNM and upper pole location of the primary tumor were significantly related with lateral LNM ($p = 0.028$, $p < 0.001$ and $p = 0.040$, respectively). Notably, the mean number of positive central lymph nodes was greater

Table 1 Clinicopathological characteristics of 215 patients with lateral LN removed

Variables	Total number ($n = 215$)	Lateral LNM		P value
		Positive ($n = 163$)	Negative ($n = 52$)	
Gender				
Male	75	58	17	0.703
Female	140	105	35	
Age(years)				
<45	122	95	27	0.420
≥45	93	68	25	
Primary tumor size(cm)				
≤0.5	58	42	16	0.479
>0.5	157	121	36	
≤0.7	106	77	29	0.284
>0.7	109	86	23	
Multifocality				
Present	96	75	21	0.477
Absent	119	88	31	
ECS				
Present	103	85	18	0.028
Absent	112	78	34	
Hashimoto's thyroiditis				
Present	68	49	19	0.382
Absent	147	114	33	
Nodular goiters				
Present	55	43	12	0.635
Absent	160	120	40	
Tumor location				
Upper	101	83	18	0.040
Middle/Lower	114	80	34	
Central LNM				
Present	182	149	33	0.000
Absent	33	14	19	
Metastatic ratio of central LN	182	149	33	
≤25%	52	34	18	0.000
>25%	130	115	15	
≤50%	105	78	27	0.002
>50%	77	71	6	
≤75%	148	117	31	0.040
>75%	34	32	2	

in patients with lateral LNM than patients without lateral LNM ([4.72 ± 4.12] vs [2.15 ± 3.51]), $p < 0.001$). In addition, the mean metastatic ratio of positive central lymph nodes (the ratio of the number of positive central lymph nodes to the number of total acquired central lymph nodes) was also greater in patients with lateral LNM than in patients without lateral LNM ([48.0 ± 31.0] % vs [19.5 ± 25.1] %, $p < 0.001$). In terms of the metastatic ratio of central lymph nodes, we set the cut-off metastatic ratio as 25%, 50% and 75%. Furthermore, the high metastatic ratio (>25%, >50% and > 75%) of an individual central lymph node was also a risk factor for lateral LNM. The patients in the lateral LNM-positive group were more likely to have a high metastasis ratio of central LN (>25%, >50% and > 75%), which was 77.2%, 47.7% and 21.5%, respectively, compared with patients in the lateral LNM-negative group, who had a ratio of 45.5%, 18.2% and 6.1%, respectively ($p < 0.001$, $p = 0.002$ and $p = 0.040$, respectively). Multivariate analysis was performed to determine the independent variables associated with the lateral LNM. The results showed that central LNM (odds ratio [OR]: 8.28,

Table 2 Distribution of metastatic lateral LNs at the levels of the neck in 163 patients

Distribution (II–V)	Number of patients
Single level	55
II/III/IV/V	5/32/17/1
Two levels	67
II + III	16
II + IV	4
III + IV	43
III + V	2
IV + V	2
Three levels	33
II + III + IV	29
II + III + V	0
III + IV + V	4
Four levels	
II + III + IV + V	8

95% confidence interval [CI]: 3.43–19.99, p < 0.001) and upper portion location (OR: 2.87 [CI]: 1.34–6.09, $p = 0.007$) significantly increased the risk of lateral LNM (Table 3). However, ECS was not significantly correlated with an increased risk for lateral LNM.

Clinicopathological Factors Associated with Skip Metastasis to the Lateral Neck

Among the total of 163 patients with lateral LNM, 149 were found to have continuous metastasis (both central and lateral LNM) and 14 had only lateral LNM, resulting in an 8.6% rate of skip metastasis in the lateral neck. The distribution of skipped metastatic lymph nodes is shown in Table 4. Level III nodes (13 of 14) were the nodes most frequently involved in skip metastasis cases, followed by level IV nodes (8 of 14), level II nodes (4 of 14), and level V nodes (1 of 14; Table 4).

Table 5 demonstrates the relationship between clinicopathological factors and skip metastasis. The univariate analysis showed that the incidence of skip metastasis to the lateral neck was greater in patients with an age ≥ 45 years old ($p = 0.018$) and primary tumor located in the upper pole of the thyroid ($p = 0.030$). As shown in Table 6, multivariate analysis indicated that the two findings were independent predictors of skip metastasis. The

Table 3 Multivariate analysis of the association of lateral LNM with clinicopathological characteristics

Variables	OR	95% CI	P value
Upper portion location	2.87	1.34–6.09	0.007
ECS	1.82	0.91–3.66	0.091
Central LNM	8.28	3.43–19.99	0.000

Table 4 Distribution of skipped metastatic LN to the lateral neck in 14 patients at the levels of the neck

Distribution (II–V)	Number of patients
Single level($n = 7$)	
III	6
IV	1
Two levels ($n = 3$)	
III + IV	3
Three levels (n = 3)	
II + III + IV	3
Four levels (n = 1)	
II + III + IV + V	1
Total	14

ORs of significant factors were 4.37 ([CI:1.14–16.66], $p = 0.031$) and 4.34([CI]: 1.27–14.78, $p = 0.019$) for age ≥ 45 years old and upper pole location, respectively.

Discussion

This study was conducted to investigate the clinicopathological features predictive of lateral LNM in patients with PTMC, with the aim of forming appropriate treatment protocols for individual patients. The incidence of LNM in PTMC differed in previous studies, with that of central LNM and lateral LNM ranging from 32% to 64% [10, 11] and 3.7% to 55%, respectively [10, 12–14]. In our study, the rate of central and lateral LNM of PTMC was 84.7% and 75.8%, respectively, which was higher compared to previous reports. In our hospital, prophylactic lateral LND is not recommended, and therapeutic lateral (II-V levels) cervical LND was performed on patients during the initial operation only when suspicious lateral LNM was identified by preoperative (imaging or FNAC) and intraoperative examination, which may account for the relatively high rate of lateral LNM in our center. LNM usually occurs in a stepwise and continuous fashion, where lateral LNM is commonly found after the central compartments; thus, the rate of central LNM was found to increase as the rate of lateral LNM increased.

Lateral LNM is most commonly observed at level III (134/163, 82.2%), followed by level IV (107/163, 65.6%), level II (62/163, 38.0%), and level V (17/163, 10.4%), indicating that levels III, IV, and II were the most frequently involved sites, which was supported by findings of previous studies [15, 16]. In addition, multilevel lateral LNM was common, which was also determined in previous studies [15, 16].

Then, we compared the clinicopathological characteristics predictive of lateral LNM in patients with PTMC. Univariate analysis revealed that lateral LNM was significantly associated with ECS, upper pole location of the primary tumor and

Table 5 Relationship of clinicopathological factors of skip metastasis

Variables	Total number (n = 163)	Skip metastasis		P value
		Present (n = 14)	Absent (n = 149)	
Gender				
Male	58	2	56	0.147
Female	105	12	93	
Age(years)				
<45	95	4	91	0.018
≥45	68	10	58	
Primary tumor size(cm)				
≤0.5	42	3	39	0.945
>0.5	121	11	110	
≤0.7	77	5	72	0.366
>0.7	86	9	77	
Multifocality				
Present	75	6	69	0.804
Absent	88	8	80	
ECS				
Present	85	6	79	0.467
Absent	78	8	70	
Hashimoto's thyroiditis				
Present	49	6	43	0.431
Absent	114	8	106	
Nodular goiters				
Present	43	3	40	0.902
Absent	120	11	109	
Tumor location				
Upper	83	11	72	0.030
Middle/lower	80	3	77	

central LNM. However, multivariate analyses indicated that only upper portion location and central LNM were independent predictors for lateral LNM in PTMC patients.

Tumor size is an important prognostic factor of PTC. Lee et al. [17, 18] reported that tumor size (>7 mm or 5 mm) was significantly correlated with central LNM in PTMC. Yon et al. [11] reported that the primary tumor size is a significant factor associated with lateral LNM in PTMC. However, Kwak et al. [16, 19] found that tumor size was not significantly associated with lateral LNM in patients with PTMC. Similar to the above reports, in the presents study, we found no significant correlation between tumor size (cut-off tumor size of 5 mm and 7 mm) and lateral LNM in PTMC.

It has been reported that extracapsular extension is an independent risk factor for central compartment LNM and associated with poor prognostic outcome in PTC. Our results indicated that ECS was not an independent factor of lateral LNM in PTMC patients (OR:1.82; $p = 0.091$), although univariate analysis revealed significant results. A recent study has reported that a contact of 25% with the adjacent capsule of PTMC on US, and not only the contact with the adjacent capsule of PTMC, was an independent factor in predicting lateral LNM [16]. Moreover, a previous study has reported that a contact of >25% with the adjacent capsule of PTMC could be the most accurate US feature in predicting pathologic extrathyroidal extension [20]. Unfortunately, we could not quantify the contact with the adjacent capsule identified by US because of the limitation of data collection, and thus we only analyzed the status of whether ECS was present or not. Further studies are needed to evaluate the association of ECS and lateral LNM.

In several studies, central LNM was proven to be an important factor for lateral LNM in PTMC [16, 21, 22], and our study also confirmed the correlation between them ($p <$

Table 6 Multivariate analysis of the association between skip metastasis and clinicopathological characteristics

Variables	OR	95% CI	P value
Age ≥ 45	4.37	1.14–16.66	0.031
Upper pole location	4.34	1.27–14.78	0.019

0.001), thus indicating that central LNM could serve as an intraoperative factor for predicting lateral LNM.

The quantitative evaluation of positive central lymph nodes could be conducted in the form of a mean number or metastatic ratio. Lim et al. [21] reported that the mean number, and not the metastatic ratio, of positive central lymph nodes was significantly associated with the lateral LNM. Furthermore, we analyzed the mean number and metastatic ratio of central lymph nodes and set the cut-off metastatic ratio as 25%, 50% and 75%. Univariate analysis showed that both the mean number and metastatic ratio of positive central lymph nodes were all significantly associated with the lateral LNM. In addition, patients with a high metastatic ratio (>25%, >50% and > 75%) of the central lymph node were at significantly higher risk of having lateral LNM compared with patients with a low metastatic ratio (≤ 25%, ≤ 50% and ≤ 75%, respectively).

Previous studies reported that upper pole location of PTMC was significantly associated with lateral LNM [16, 22, 23]. The present study also showed that upper pole location was an independent risk factor for lateral LNM, thus indicating that carcinoma cells from the upper region are more likely to be transported to the lateral lymph nodes by lymphatic flow along the superior thyroid artery, as reported by a previous study.

LNM usually occurs first to the central compartment and subsequently to the lateral compartment. The presence of positive lateral lymph nodes with negative lymph nodes in the central compartment (skip metastasis) is common. In the study, a total of 149 of the 163 (91.4%) patients with positive lateral LNM had positive central LN, and 14 of the 163 patients (8.6%) had skip metastasis. The ratio of skip metastasis in our study was 8.6%, which was lower than previously reported values (3%–37.5%) [7, 12, 15, 24]. This can be accounted for partly by the difference in the inclusion criteria of population and sample size in individual studies, especially previously studies that included patients with PTC and did not extract patients with PTMC.

With univariate and multivariate analyses, we confirmed that an age ≥ 45 years old and the upper pole location were independent predictors of skip metastasis. Verburg FA et al. [25] reported that long-term survival of PTC patients aged 45 years or older with lateral LNM is greatly affected. Therefore, for patients aged 45 years or older with upper pole location of the tumor, preoperative lateral lymph node examination should be more detailed and comprehensive, with appropriate indication of lateral lymph node FNAC.

However, this study had limitations. First, we did not collect all the US characteristics, such as the quantification of contact of >25% with the adjacent capsule and calcifications due to the limitation of US data collection. Furthermore, given the limited number of cases, as well as the retrospective and single-institution design, our evidence in the discussion of lateral LNM in PTMC is limited; therefore, more data from prospective, multicenter and large cohort trails are needed to determine the predictive factors for lateral LNM in PTMC.

In conclusion, our study identified two statistically significant independent predictive factors for lateral LNM in PTMC: central LNM and upper location of the primary tumor. It seems that lateral LNM in patients with no preoperative evidence of LNM can be predicted by the nodal status of central compartment and tumor location. The incidence of skip metastasis is low; however, with an age ≥ 45 years old and primary tumor location in the upper pole, it is crucial to pay attention to the possibility of LNM in the lateral compartment, even in the absence of central LNM.

Acknowledgements This work was supported by the grants from the CAMS Innovation Fund for Medical Sciences (CIFMS, 2016-I2M-3-005).

Compliance with Ethical Standards

Conflict of Interest All the authors declare that they have no conflict of interest.

Ethics Approval The study protocol was approved by the Institutional Review Board of the Peking Union Medical College Hospital and conducted in accordance with Helsinki's Declaration.

Informed Consent Informed consent was obtained from all patients included in the study.

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