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Predictive Factors of Skip Metastasis in Papillary Thyroid Cancer

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Background: Skip metastasis is defined as metastasis incident to the lateral compartment without involvement of the central compartment, and is generally unpredictable in papillary thyroid cancer (PTC). The present study aimed to investigate the frequency and predictor value of skip metastasis in PTC patients.

Material/Methods: A total of 355 patients diagnosed with thyroid cancer who had received a prior complete thyroidectomy with bilateral central neck and ipsilateral lateral neck lymph node dissection were enrolled in this study. The clinicopathological and ultrasound features were analyzed. A univariate and multivariate analysis were performed to identify the risk factors of skip metastasis.

Results: The frequency of skip metastasis was 12.4% (44/355). The PTC patients with skip metastasis exhibited fewer lymph node metastasis, which was more commonly detected in tumor size ≤1 cm (OR 9.354; p=0.001; 95% confidence interval (CI) 1.865–26.735), tumors located in upper pole (OR 3.822; p<0.001; 95% CI 1.935–7.549), without a well-defined margin (OR 2.528; p=0.016; CI 1.191–5.367), and extrathyroidal extension (OR 2.406; p=0.013; CI 1.691–4.367).

Conclusions: Skip metastasis was common in PTC. The PTC patients with a tumor size ≤1.0 cm, located in the upper pole, without a well-defined margin and extrathyroidal extension should be carefully evaluated for skip metastasis.

MeSH Keywords: Lymphatic Metastasis • Neoplasm Metastasis • Thyroid Neoplasms

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Background

Thyroid cancer is among the top five most common cancers that occur in women. In the United States, 56,870 new cases were estimated in 2017 [1]. Among these cases, papillary thyroid cancer (PTC) is rapidly increasing in incidence worldwide, and is the most common histological type [2]. To date, it is estimated that 30%–80% of PTC patients have regional lymph node metastasis [3], which brings an element of risk in recurrence, distant metastasis, and reduced survival [4–6]. Central and lateral cervical, as well as mediastinal compartments, are all common metastatic sites. While lymphatic drainage is observed to occur primarily in the central lymphatic compartment, the second most common site of PTC metastasis is the lateral compartment [7,8].

Skip metastasis is defined as metastasis within the lateral compartment without central compartment participation. Although more advanced diagnostic tools are now available, skip metastasis remains unpredictable [9]. While previous studies reported the incidence of skip metastasis as 7–38% [10–12], these studies had unclear clinical significance due to small sample size. Therefore, the present study aimed to evaluate the clinical characteristics of PTC with skip metastases in PTC.

Material and Methods

Patients

The present study included 355 thyroid cancer patients who had received complete thyroidectomy with bilateral central neck and ipsilateral lateral neck lymph node dissection at the First Affiliated Hospital of Wenzhou Medical University from January 2014 to December 2016. The patients were separated into two groups: the skip metastasis group and the control group. Retrospective reviews of electronic clinical and pathologic records were conducted to collect clinicopathological information. Clinical evidence obtained from patients confirmed a positive lateral neck preoperative via a fine-needle aspiration biopsy or thyroglobulin measurement in fine-needle aspiration (no prophylactic lateral lymph node dissection). The exclusion criteria were as follows: history of neck surgery or irradiation, negative lateral lymph node metastases, and other types of thyroid cancer. Research approval was obtained from the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Central compartment lymph node dissection was performed superiorly to the thyroid cartilage notch, laterally to the carotid sheaths, posteriorly to the prevertebral fascia, and inferiorly to the innominate vein. The lateral compartment delimited superiorly to the posterior belly of the digastric muscle, inferiorly to the subclavian vein, and laterally to the anterior border of the trapezius muscle. The surgery was performed by the same operation team.

Parameters analyzed

Ultrasonography and/or neck computed tomography (CT) was performed to assess tumor characteristics such as size, position, and nodal metastases. The images were evaluated by two experienced radiologists. Multifocal PTC was defined as more than one lesion in a paraffin section and the lesion with the maximum diameter was analyzed. Shape was classified as either regular or irregular. Internal composition was classified as totally solid or largely solid (proportion of solid components ≥50%), cystic. Margin was divided into well-defined and without well-defined margin. Tumor position was divided into four areas (upper, middle, lower, and isthmus).

Statistics

An independent two-sample Student's *t*-test was conducted to compare data displayed on a normal distribution. Categorical variables were expressed as percentage and compared with the results of chi-square test or Fisher's exact test, as appropriate. Variables with $p<0.05$ in the univariate analysis were progressed to multivariate analysis using forward stepwise selection. The findings were considered as odds ratio (OR) having 95% confidence interval (CI) and as *p*-value. Each *p*-value was two-sided. Moreover, $p<0.05$ was regarded as statistically significant. Statistical analysis was performed with SPSS software version 22.0 (SPSS, Chicago, IL, USA).

Results

Of the 5,633 patients, 355 met our study criteria and their medical records were reviewed and analyzed. The present study included 112 males and 243 females. The average age was 48.80±12.51 years (range, 15–85 years). The average size of a primary tumor was 1.91±1.02 cm (range, 0.1–5.0 cm), including 142 cases of papillary thyroid microcarcinoma (≤1.0 cm). The mean number of total harvested central lymph nodes was 9.81±5.31 (range, 1.0–28.0), of which 6.87±3.97 (range, 1.0–20) were observed to have metastasis. The mean number of harvested lateral lymph nodes was 15.73±8.22 (range,1.0–49.0), of which 5.63±4.30 (range, 1.0–21.0) were observed to have metastasis. Among these patients, skip metastasis was observed in 44 (12.4%).

The distributions of pathologic lymph node according to neck level are summarized in Table 1. The clinicopathological features between two groups (presence versus absence of skip metastases) were compared to determine the clinical features related

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Table 1. Distributions of pathologic lymph node according to neck level.

Neck level	No.
Level II	140
Level III	251
Level IV	254
Level V	131
Level VI	311

to skip metastases. PTC patients with skip metastases tended to be older patients (50.45±12.79 versus 45.05±12.12 years, p=0.006), smaller size of tumor (1.15±0.80 versus 1.44±0.84 cm, p=0.03), upper portion (p<0.001), without well-defined margin (p=0.032), and extrathyroidal extension (p=0.032) (Table 2). The tumor size ≤1 cm (p=0.002) was more commonly observed in the skip metastasis group. Also, Hashimoto's thyroiditis was more commonly observed in the skip metastasis group; however, the incidence was not observed to be statistically significant. Other clinical and ultrasound features such as multifocality, shape, intact capsule, composition, being longer than wide, and vascularization were not observed as having any significant differences between the two groups. The skip metastases group had fewer lateral node metastases (2.11±1.47 versus 3.41±2.89, p=0.001) in the case of similar harvested lateral lymph nodes.

For the multivariate logistic regression, the following variables were independently associated with skip metastases (Table 3): tumor size ≤1 cm (OR 9.354; p=0.001; 95% CI 1.865–26.735), tumor located in the upper pole (OR 3.822; p<0.001; 95% CI 1.935–7.549), without well-defined margin (OR 2.528; p=0.016; CI 1.191–5.367), and extrathyroidal extension (OR 2.406; p=0.013; CI 1.691–4.367)

Discussion

To date, it has been reported that 30–80% of patients diagnosed with PTC also had some form of lymph node metastasis [3]. For certain patients, nodal involvement in PTC was observed to be commonly associated with local recurrence and cancer specific mortality [13,14]. Re-operation for recurrence may increase operative complications, including (but not limited to) hypothyroidism and recurring laryngeal nerve injury. Therefore, it is necessary to predict lymph node metastasis in preoperative terms for surgeons to precisely determine neck dissections.

Surgeons may advocate routine central lymph node dissection given that the central lymph node is the first site of metastasis, followed by the lateral lymph node. Also, current imaging modalities, such as ultrasound and CT, are observed to have high false negative rates. However, to what extent PTC patients with skip metastasis can manage their disability is a perplexing situation for physicians. For example, whether dissection should be performed on the central lymph node in this subgroup is a commonly encountered dilemma. Therefore, the present study evaluated the incidence and detailed characteristics associated with skip metastasis.

The incidence of skip metastasis in a previous study was observed to range from 3% to 38% [10–12,15–17], which could be explained by different regions and sample sizes. Most of these studies were limited by a small sample size. The present study utilized a sufficient number of patients, with the incidence of skip metastasis observed at 12.4% (44/355).

The risk factors associated with skip metastasis were explored. Similar to the results obtained from a previous study [11], tumors present in the upper pole thyroid were observed to increase metastasis risk. Each lobe of the thyroid has its own lymphatic system. For example, a tumor located in the upper pole thyroid may migrate along the superior thyroid artery to lateral lymph nodes and bypass central lymph nodes. Lateral lymph node metastasis frequently involves level 3, after which levels 4, 2, and 5 follow [16]. In the present study, the rate of level 2 metastasis was observed at 68.2% within the skip metastasis subgroup, which was a higher rate than the other levels. As such, the tumor located in the upper pole tended to metastasize to upper levels. In addition, skip metastasis was observed to be more frequent in tumors no larger than 1 cm, which agrees with a previous finding in which skip metastasis was observed to be more recurrent in less aggressive forms of PTC [18]. Furthermore, the number of positive lymph nodes in the present study was observed to be inversely correlated to skip metastasis. Finally, ultrasound features, the absence of well-defined margin, and extrathyroidal extension were observed to be more common in PTC with skip metastasis.

The significance of skip metastasis in relation to PTC remains unknown. Skip metastasis is a well-known form of metastatic spread to regional lymph nodes and has a positive effect on prognosis in non-small-cell lung cancer and colorectal cancer [19,20]. However, a recent study analyzed the survival rates of 450 PTC patients between 39 patients exhibiting skip metastasis and 411 patients without skip metastasis [21]. The results showed no significant difference between the two groups for tumor free survival. However, these results remain to be verified.

The reasons for skip metastasis are as follows: first, nodal metastasis was observed to bypasses the normal anatomical lymphatic channels; second, neck treatment alters the normal

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Table 2. Comparison of clinicopathological facors between two groups of patients with PTC.

Characteristics	Skip metastasis		P value
	Present (n=44)	Absent (n=311)	
Age at diagnosis(years)	50.45±12.79	45.05±12.12	0.006
≤45 (n, %)	18 (40.9%)	160 (51.4%)	0.191
>45 (n, %)	26 (59.1%)	151 (48.2%)	
Tumor size(mm)	11.50±7.97	14.44±8.44	0.030
≤10 (n, %)	27 (61.4%)	115 (37.0%)	0.002
>10 (n, %)	17 (38.6%)	196 (63.0%)	
Sex			0.179
Male (n, %)	10 (22.7%)	102 (32.8%)	
Female (n, %)	34 (77.3%)	209 (67.2%)	
Multifocality(n, %)			0.272
Yes (n, %)	32 (72.7%)	200 (64.3%)	
No (n, %)	12 (27.3%)	111 (35.7%)	
Bilaterality			0.669
Yes (n, %)	10 (22.7%)	80 (25.7%)	
No (n, %)	34 (77.3%)	231 (74.3%)	
Hashimoto's thyroiditis			0.051
Yes (n, %)	16 (36.4%)	71 (22.8%)	
No (n, %)	28 (63.6%)	240 (77.2%)	
Tumor location			<0.001
Upper (n, %)	23 (52.3%)	71 (22.8%)	
Lower/middle/isthmus (n, %)	21 (47.7%)	240 (77.2%)	
Taller than wide			0.244
Yes (n, %)	9 (20.5%)	43 (13.8%)	
No (n, %)	35 (79.5%)	268 (86.2%)	
Calcification			0.151
Calcification (n, %)	35 (79.5%)	272 (87.5%)	
Absence (n, %)	9 (20.5%)	39 (12.5%)	
Margin			0.032
Well-defined (n, %)	32 (72.7%)	173 (55.6%)	
Without a well-defined margin (n, %)	12 (27.3%)	138 (44.4%)	
Shape			0.864
Regular (n, %)	30 (68.2%)	215 (69.1%)	
Irregular (n, %)	14 (31.8%)	96 (30.9%)	

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Table 2 continued. Comparison of clinicopathological facors between two groups of patients with PTC.

Characteristics	Skip metastasis		P value
	Present (n=44)	Absent (n=311)	
Intact capsule			0.822
Yes (n, %)	8 (18.2%)	61 (19.6%)	
No (n, %)	36 (81.8%)	250 (80.4%)	
Extrathyroidal extension			0.035
Yes (n, %)	18 (40.9%)	80 (25.7%)	
No (n, %)	26 (59.1%)	231 (74.3%)	
Composition			0.572
Solid (n, %)	41 (93.2%)	296 (95.2%)	
Cystic or mixed (n, %)	3 (6.8%)	15 (4.8%)	
Vascularization			0.512
Present (n, %)	4 (9.1%)	39 (12.5%)	
Absence (n, %)	40 (90.9%)	272 (87.5%)	
Lateral neck node metastasis LN number			
Harvested	11.25±6.71	11.32±7.14	0.95
Metastatic	2.11±1.47	3.41±2.89	0.001
Lateral neck node metastasis LN cases			
Level II	30 (68.2%)	110 (35.4%)	<0.001
Level III	22 (50.0%)	229 (73.3%)	0.002
Level IV	2 (4.5%)	252 (81.0%)	<0.001
Level V	1 (2.3%)	130 (41.8%)	<0.001
Single lateral neck level involvement	30 (68.2%)	51 (16.4%)	<0.001

Table 3. Multivariate analysis between the clinicopathologic factors and skip metastasis.

Characteristic	OR	95% CI	P value
Tumor size (≤1.0 cm)	9.354	1.865–26.735	0.001
Tumor location	3.822	1.935–7.549	<0.001
Margin	2.528	1.191–5.367	0.016
Extrathyroidal extension	2.406	1.691–4.367	0.013

lymphatic channels and induce skip metastasis; and third, false negative findings due to inadequate lymph node sampling are a factor in the inaccurate staging of esophageal cancer [22]. The present study included patients without neck surgery or neck irradiation, and collected equivalent numbers of lymph nodes. Therefore, we concluded that skip metastasis can bypassed the central lymph node through normal lymphatic channels.

The present study may have been limited by its retrospective nature. For example, patients were only enrolled in this study if they had received a therapeutic lateral node dissection. It is recommended that patients who received a prophylactic lateral node dissection be included in studies to detect latent lateral metastases [23]. Finally, additional factors to predict skip metastasis should be identified after prophylactic lateral node dissection.

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Conclusions

In this study, 12.4% of PTC cases were found to have skip metastasis. Therefore, it is recommended that PTC patients with tumor size ≤1.0 cm, located in the upper pole, without a well-defined margin and extrathyroidal extension should be carefully evaluated for skip metastasis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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