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# Risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer

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ABSTRACT

*Background:* Lymph node metastases from papillary thyroid cancer is believed to disseminate sequentially, first to the central neck and later to the lateral neck. Skip metastases of papillary thyroid cancer, however, are defined as lateral lymph node metastasis without central lymph node metastasis. The aim of this study was to investigate the risk factors for skip metastases and lateral lymph node metastasis of papillary thyroid cancer.

*Methods:* We reviewed 721 papillary thyroid cancer patients undergoing total thyroidectomy with central lymph node dissection and lateral lymph node dissection during 2013 to 2018. Multivariate logistic regression analysis was performed to identify clinicopathologic risk factors for skip metastasis and lateral lymph node metastasis of papillary thyroid cancer.

*Results:* The rate of skip metastases was 7.4% (42 of 567 patients). Multivariate analysis showed that female sex and papillary thyroid microcarcinoma ($\leq$ 1 cm) were independent risk factors for skip metastases, with odds ratios ([OR], 95% confidence interval [CI]) of 2.29 (1.02–5.16) and 2.84 (1.46–5.16), respectively. Intrathyroidal spread of papillary thyroid cancer and an increased number of central lymph nodes dissected were inversely associated with skip metastases with ORs (95% CI) of 0.13 (0.02–0.99) and 0.88 (0.83–0.94), respectively. In contrast, a greater tumor size, central lymph node metastasis, an increased number of central lymph nodes dissected, and an increased number of lateral lymph nodes dissected were associated with a lateral lymph node metastasis risk of papillary thyroid cancer, with ORs (95% CI) as follow: 1.67 (1.08–2.59), 3.07 (1.71–5.52), 1.25 (1.14–1.37), and 1.07 (1.04–1.10), respectively, by multivariate analysis.

*Conclusion:* Greater tumor size, central lymph node metastasis, and an increased number of both central lymph nodes and lateral lymph nodes dissected were predictors for lateral lymph node metastasis of papillary thyroid cancer. In addition, papillary thyroid microcarcinoma was an independent risk factor for skip metastases. A complete and comprehensive central compartment dissection may decrease the false-positive detection of skip metastases of papillary thyroid cancer.



Papillary thyroid cancer (PTC) is one of the fastest increasing malignancies.[1] PTC has a better prognosis compared with other types of cancer; however, central lymph node metastasis (CLNM) is common, and nearly 50% of PTC patients present with CLNM when routine (prophylactic) central lymph node dissection (CLND) is performed.[2,3] This observation does not mean that lateral lymph node metastasis (LLNM) is an uncommon event. The rate of LLNM was as great as 74.9% among PTC patients, with an indication for LLNM by preoperative imaging examination.[4]

It has been indicated that disease persistence and recurrence and distant metastasis are significantly more frequent in PTC patients with LLNM (N1b) compared with patients of CLNM (N1a) and clinically negative for lymph nodes (cN0).[5] According to the guidelines of the American Thyroid Association, an lateral lymph node dissection (LLND) should be performed on patients with biopsy-proven, metastatic lateral cervical lymphadenopathy,[6] and fine-needle aspiration cytology (FNAC) with washout for thyroglobulin measurement was recommended for suspicious lymph nodes. The incidence of occult, level III metastases was 30% among patients without evidence of cervical lymph node metastasis when

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a prophylactic, level III dissection was performed.[7] Furthermore, the incidence of occult LLNM was reported as great as 55% among PTC patients without clinical LLNM but with verified CLNM.[8] Lim et al[9] found that the rate of recurrence in the lateral lymph nodes was 4.5% with a median follow-up of 49 months among PTC patients without clinical evidence of LLNM undergoing total thyroidectomy and CLND alone. Therefore, developing methods to predict LLNM is one of the key components to control nodal metastasis and recurrence of PTC.

Cervical lymph node metastasis of PTC is believed to disseminate sequentially first to the central neck and only later to the lateral neck. Some patients, however, develop LLNM without the involvement of CLNM, which has been referred to as skip metastasis. Although more advanced diagnostic tools are now available, skip metastases remain difficult to predict. The reported rate of skip metastasis varies considerably, ranging from 6.8% to 27.8%,[10,11] which might result from the small sample size of these studies. We found that the number of dissected lymph nodes in the central neck can affect the diagnosis of skip metastasis; however, the status of the CLND was not well investigated and not evaluated in the multivariate analysis to identify the risk factor for skip metastases from PTC previously.[4,12] In addition, studies investigating LLNM and skip metastases of PTC simultaneously were limited.

To better identify risk factors for skip metastasis and LLNM of PTC, we investigated the potential predictors in terms of clinicopathologic characteristics, and we found many differences among them, which may facilitate clinical decisions and benefit patients with PTC.

## Patients and Methods

### *Patient collection*

This study was approved by the Ethics Committee of Union Hospital, Wuhan, China. We reviewed the medical records and pathologic results of patients who, from November 2013 to March 2018, met the following requirements: had undergone total thyroidectomy combined with bilateral CLND and unilateral or bilateral LLND as their first operation and had a final pathology of PTC. Patients with tumor foci located in the isthmus, a family history of thyroid cancer, or radiation exposure in the head and neck were excluded. Finally, a total of 4,192 patients were diagnosed with PTC, of whom 721 PTC patients (17.2%) underwent LLND. Clinicopathologic features of interest, such as sex, age, tumor size, tumor number, bilaterality of tumor foci, capsular invasion, extracapsular extension, intrathyroidal spread, CLNM, the number of CLNM, the number of central lymph nodes dissected, the number of LLNM, and the number of lateral lymph nodes dissected were collected.

### *Thyroidectomy*

Thyroid surgery was performed by experienced surgeons who had 5–20 years of experience. Intraoperative frozen section was performed on all patients to determine nodule malignancy. Bilateral CLND was routinely performed on these PTC patients. The inclusion of an LLND was performed based on preoperative imaging results, tumor characteristics, and intraoperative exploration. The central neck refers to level VI; whereas the lateral neck includes levels II, III, IV, and V in the present study. Informed consents were obtained from all patients preoperatively.

### *Pathologic diagnosis*

Routine pathologic diagnosis was performed on the specimens of the thyroid and fatlike tissues with 2- to 3-μm sections. Hematoxylin and eosin (HE) staining combined with or without immunohistochemistry was performed to determine the pathologic types. Papillary thyroid microcarcinoma (PTMC) was defined as tumors ≤1 cm in largest diameter. Solitary focus means only one tumor in the thyroid, and multiple foci mean two or more foci limited to the thyroid. Bilaterality is defined as the presence of PTC foci in the right and left lobes of the thyroid. Capsular invasion means that the tumor invades up to and possibly into the thyroid capsule but does not penetrate it. In contrast, extracapsular extension is defined as when the tumor penetrates through the capsule and into the strap muscle or perithyroidal fibrofatty tissues. Intrathyroidal spread means that the primary tumor spreads to the other parts of the ipsilateral thyroid.[13]

### *Literature review of studies with skip metastases in PTC*

Because there were only 42 of the 567 patients presenting with skip metastasis in our study, we performed a literature overview on skip metastasis from PTC. We used the following strategies to retrieve studies: “skip metastasis*” as well as “papillary” and “thyroid” in titles or abstracts from June 2008 to June 2018 in databases including PubMed, EMBASE, and Cochrane Library. In addition, references of the identified articles were searched manually for relevant studies.

Studies that reported the rate of skip metastasis were included. We excluded studies not involving PTC neoplasms, those not reported in English, those including patients undergoing reoperation, or those with fewer than three patients with skip metastasis. The eligible studies were reviewed and the following data were extracted: the first author, year of publication, study type, sample size, the rate of skip metastasis, number of central lymph nodes dissected, number of LLNM, and risk factors for skip metastasis. Studies were presented according to the presence of multivariate logistic regression analysis or not.

### *Statistical analysis*

Statistical analyses were performed using SPSS v 22.0 (SPSS, Chicago, IL, USA). Category variables were analyzed using the $\chi^2$ test or the Fisher exact test. The number of metastatic lymph nodes or lymph nodes dissected were expressed as mean ± standard deviation and compared with the Student’s $t$ test. Multivariate logistic regression analysis was performed to identify risk factors for skip metastasis and LLNM of PTC. Statistical differences were set at a two-sided $P$ value < .05.

## Results

### *Clinicopathologic features for LLNM risk of PTC patients*

To investigate the predictors for LLNM, we first investigated the association between the clinicopathologic features and the risk of LLNM by univariate analysis. The following characteristics of patients were more likely to present with LLNM: male sex, (odds ratio [OR] = 1.54; $P$ = .038); a younger age (< 55 years), (OR = 1.66; $P$ = .040); a greater tumor size (> 1 cm), (OR = 2.87; $P$ < .001); and intrathyroidal spread (OR = 3.63; $P$ < .001). In addition, those with capsule invasion and extracapsular extension were more likely to present with LLNM compared with the corresponding groups without these degrees of invasion or extension (OR = 1.83 and 2.10, respectively; $P$ = .003 for both; Table I). Of note, when examining the central compartment, patients with CLNM were also more likely to present with LLNM (OR = 10.42; $P$ < .001), and the number of metastatic lymph nodes in the central compartment was positively associated with the risk of LLNM of PTC (OR = 1.47; $P$ < .001). The number of harvested lymph nodes in the central compartment

**Table I**
Clinicopathologic characteristics for LLNM risk of PTC patients by univariate analysis ($n = 721$)

| Category | Non-LLNM ($n = 154$) | LLNM ($n = 567$) | OR (95% CI) | *P* value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 37 (16.7) | 186 (83.3) | 1.54 (1.03–2.32) | .038 |
| Female | 117 (23.5) | 381 (76.5) | | |
| Age (years) | | | | |
| <55 | 126 (20.1) | 500 (79.9) | 1.66 (1.02–2.69) | .040 |
| ≥55 | 28 (29.5) | 67 (70.5) | | |
| Tumor size | | | | |
| ≤1 cm | 84 (33.5) | 167 (66.5) | 2.87 (2.00–4.14) | < .001 |
| >1 cm | 70 (14.9) | 400 (85.1) | | |
| Tumor number | | | | |
| Single | 76 (23.9) | 249 (76.6) | 1.24 (0.87–1.78) | .229 |
| Multiple | 78 (19.7) | 318 (80.3) | | |
| Capsule invasion | | | | |
| No | 50 (29.8) | 118 (70.2) | 1.83 (1.23–2.71) | .003 |
| Yes | 104 (18.8) | 449 (81.2) | | |
| Extracapsular extension | | | | |
| No | 132 (23.9) | 420 (76.1) | 2.10 (1.29–3.42) | .003 |
| Yes | 22 (13.0) | 147 (87.0) | | |
| Bilaterality | | | | |
| No | 91 (22.4) | 316 (77.6) | 1.15 (0.80–1.65) | .456 |
| Yes | 63 (20.1) | 251 (79.9) | | |
| Intrathyroidal spread | | | | |
| No | 146 (23.6) | 473 (76.4) | 3.63 (1.72–7.64) | .001 |
| Yes | 8 (7.8) | 94 (92.2) | | |
| CLNM | | | | |
| No | 70 (62.5) | 42 (37.5) | 10.42 (6.67–16.28) | < .001 |
| Yes | 84 (13.8) | 525 (86.2) | | |
| CLND number* | 12.2 ± 7.5 | 13.1 ± 6.5 | 1.02 (1.00–1.05) | .110 |
| CLNM number† | 1.8 ± 3.0 | 6.1 ± 4.9 | 1.47 (1.36–1.60) | < .001 |
| LLND number‡ | 14.0 ± 8.5 | 20.5 ± 11.3 | 1.08 (1.06–1.11) | < .001 |

Note: Data are expressed as number (%) or mean ± standard deviation.
* Number of central dissected lymph nodes.
† Number of central metastatic lymph nodes.
‡ Number of lateral dissected lymph nodes.

was similar among patients with or without LLNM ($P > .05$). Patients with LLNM had more metastatic lymph nodes in the central neck than patients without LLNM (6.1 ± 4.9 vs 1.8 ± 3.0, $P < .001$). In addition, we found that the number of lateral lymph nodes dissected was positively associated with the risk of LLNM of PTC patients (OR = 1.08, $P < .001$) (Table I ).

*Risk factors for LLNM of PTC by multivariate analysis*

To identify risk factors for LLNM of PTC, variables with statistical differences were included in a multivariate model. We found the following risk factors for LLNM: a large tumor size (> 1 cm) with an OR (95% confidence interval [CI]): 1.67 (1.08–2.59); CLNM with an OR (95% CI): 3.07 (1.71–5.52); the number of metastatic lymph nodes in the central neck with OR (95% CI): 1.25 (1.14–1.37); and the number of dissected lymph nodes in the lateral neck with an OR: 1.07 ($P < .001$; Table II).

**Table II**
Multivariate analysis of the risk factors for LLNM of PTC ($n = 721$)

| Variables | OR (95% CI) | *P* value |
|---|---|---|
| Sex | 1.13 (0.69–1.86) | .630 |
| Age | 1.20 (0.68–2.15) | .529 |
| Tumor size | 1.67 (1.08–2.59) | .022 |
| Capsule invasion | 1.11 (0.67–1.85) | .681 |
| Extracapsular extension | 1.58 (0.88–2.84) | .124 |
| Intrathyroidal spread | 1.39 (0.60–3.25) | .439 |
| CLNM | 3.07 (1.71–5.52) | < .001 |
| CLNM number* | 1.25 (1.14–1.37) | < .001 |
| LLND number† | 1.07 (1.04–1.10) | < .001 |

Note: Category variables, such as sex (male versus female), age (< 55 years versus ≥ 55 years), tumor size (> 1 cm versus ≤ 1 cm), capsule invasion, extracapsular extension, intrathyroidal spread, CLNM (yes versus no), and the continuous variable CLNM number and LLND number were included in the multivariate model.
* Number of metastatic central lymph nodes.
† Number of dissected lateral lymph nodes.

*Clinicopathologic features for risk of skip metastases among PTC patients with LLNM*

Next we reviewed skip metastasis from PTC. In contrast to male patients with LLNM, patients of female sex (OR = 2.18; $P = .053$), small tumor sizes (≤ 1 cm; OR = 2.60; $P = .003$), and the absence of intrathyroidal spread (OR = 8.83; $P = .033$), were more likely to present with skip metastases. Of note, the number of dissected lymph nodes in the lateral neck was similar between patients with and without skip metastasis ($P > .05$). In contrast, patients with skip metastasis had less LLNM (2.4 ± 1.8 vs 5.3 ± 4.7; $P < .001$), and the number of metastatic lymph nodes in the lateral neck was inversely associated with skip metastasis risk (OR = 0.67; $P < .001$). Furthermore, fewer central lymph nodes were dissected among patients with skip metastasis than those in the nonskip metastasis group (9.5 ± 6.4 vs 13.4 ± 6.4, $P < .001$), and the number of central lymph nodes dissected was negatively associated with skip metastasis (OR = 0.89, $P < .001$; Table III).

*Risk factors for skip metastasis of PTC with LLNM by multivariate analysis*

To identify risk factors for skip metastasis of PTC, variables with the statistical differences were included in the multivariate model. We found that female sex with an OR ([95% CI] 2.29 [1.02–5.16]) and smaller tumor size (≤ 1 cm) with an OR (2.84 [1.46–5.16]),

**Table III**
Clinicopathologic features for skip metastasis risk of PTC patients with LLNM by univariate analysis ($n = 567$)

| Category | Skip metastasis | | OR (95% CI) | *P* value |
|---|---|---|---|---|
| | Absent ($n = 525$) | Present ($n = 42$) | | |
| Sex | | | | |
| Male | 178 (95.7) | 8 (4.3) | 2.18 (0.99-4.81) | .053 |
| Female | 347 (91.1) | 34 (8.9) | | |
| Age (years) | | | | |
| < 55 | 464 (92.8) | 36 (7.2) | 1.27 (0.51-3.13) | .607 |
| ≥ 55 | 61 (91.0) | 6 (9.0) | | |
| Tumor size | | | | |
| ≤ 1 cm | 146 (87.4) | 21 (12.6) | 2.60 (1.38-4.90) | .003 |
| > 1 cm | 379 (94.8) | 21 (5.3) | | |
| Tumor number | | | | |
| Single | 234 (94.0) | 15 (6.0) | 1.45 (0.75-2.78) | .268 |
| Multiple | 291 (91.5) | 27 (8.5) | | |
| Capsule invasion | | | | |
| No | 106 (89.8) | 12 (10.2) | 1.58 (0.78-3.19) | .201 |
| Yes | 419 (93.3) | 30 (6.7) | | |
| Extracapsular extension | | | | |
| No | 385 (91.7) | 35 (8.3) | 1.82 (0.79-4.19) | .160 |
| Yes | 140 (95.2) | 7 (4.8) | | |
| Bilaterality | | | | |
| No | 294 (93.0) | 22 (7.0) | 0.86 (0.46-1.62) | .650 |
| Yes | 231 (92.0) | 20 (8.0) | | |
| Intrathyroidal spread | | | | |
| No | 432 (91.3) | 41 (8.7) | 8.83 (1.20-64.98) | .033 |
| Yes | 93 (98.9) | 1 (1.1) | | |
| LLND number* | 20.5 ± 11.4 | 20.0 ± 9.9 | 1.00 (0.97-1.03) | .782 |
| LLNM number† | 5.3 ± 4.7 | 2.4 ± 1.8 | 0.67 (0.56-0.82) | < .001 |
| CLND number‡ | 13.4 ± 6.4 | 9.5 ± 6.4 | 0.89 (0.84-0.95) | < .001 |

Note: Data are expressed as number (%) or mean ± standard deviation.
* Number of lateral dissected lymph nodes.
† Number of lateral metastatic lymph nodes.
‡ Number of central dissected lymph nodes.

**Table IV**
Multivariate analysis of the risk factor for skip metastasis of PTC patients ($n = 567$)

| Variables | OR (95% CI) | *P* value |
|---|---|---|
| Sex | 2.29 (1.02–5.16) | .045 |
| Tumor size | 2.84 (1.46–5.16) | .002 |
| Intrathyroidal spread | 0.13 (0.02–0.99) | .049 |
| CLND number | 0.88 (0.83–0.94) | < .001 |

Note: Category variables, such as sex (female versus male), tumor size (≤ 1 cm versus > 1 cm), and intrathyroidal spread, and the continuous variable CLND number were included in the multivariate model.

were separately and independently associated with a risk of skip metastases risk; however, intrathyroidal spread was inversely associated with a risk of skip metastasis (OR = 0.13, $P = .049$). Of note, the number of dissected lymph nodes in the central compartment was inversely associated with skip metastasis, with OR ([95% CI] 0.88 [0.83–0.94]; Table IV).

*Literature review on skip metastasis of PTC*

The literature screening process is presented in the Figure. We identified 50 records through searching the databases. After excluding duplicates ($n = 17$) and ineligible studies ($n = 18$), a total of 15 studies were eventually included, with 5 studies evaluating the predictors for skip metastasis and 10 studies reporting the rate of skip metastasis of PTC. The characteristics of the included studies are presented in Tables V and VI.

The frequency of skip metastasis in our study was 7.4%, which was the lowest percentage and with the largest sample size among the 6 studies with multivariate analysis (Table V). The ratio of

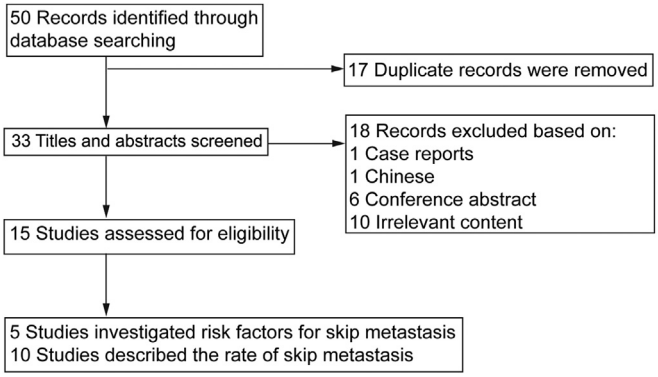


**Figure.** Flowchart of the searching process of the literatures on skip metastasis of papillary thyroid cancer (PTC).

female to male patients with skip metastasis was about 4:1. The number of dissected lymph nodes in the central neck was not discussed in 4 studies.[4,11,12,15]

We also present the literatures reporting the frequency of skip metastasis from 2008 to 2018 in studies that did not subject their results to a multivariate analysis. A total of 5 studies were abstracts from meetings,[16–20] and the remaining were research articles.[10,21–24] The frequency of skip metastasis ranged from 4% to 21.4% (Table VI).

## Discussion

In the present study, we evaluated the predictors for skip metastasis and LLNM of PTC. We found that female sex and tumors less than 1 cm (PTMC) were risk factors for skip metastasis. In contrast, intrathyroidal spread and an increased number of lymph

**Table V**
Literature overview on skip metastasis of PTC analyzed by multivariate analysis

| Study (First author) | Skip (*n*) | M/F (*n*) | Total (*n*) | Skip rate | LLNM number* | CLND number* | Risk factors for skip metastasis |
|---|---|---|---|---|---|---|---|
| Zhao (our study) | 42 | 8/34 | 567 | 7.4% | 2.4 ± 1.8 vs 5.3 ± 4.7 | 9.5 ± 6.4 vs 13.4 ± 6.4 | Tumor size ≤ 1 cm; female sex, non-intrathyroidal spread; decreased CLND number |
| Jin (2018)[12] | 44 | 10/34 | 355 | 12.4% | 2.1 ± 1.5 vs 3.4 ± 2.9 | NA | Tumor size ≤ 1 cm; upper lobe; abnormal margin; extrathyroidal extension |
| Nie et al[4] | 30 | 6/24 | 203 | 14.8% | NA | NA | Tumor size ≤ 0.5 cm |
| Lei et al[14] | 39 | 12/27 | 450 | 8.7% | 5.4 ± 2.2 vs 6.5 ± 2.9 | 10.8 ± 2.9 vs 11.0 ± 3.0 | Tumor size ≤ 1 cm; upper pole; capsule invasion |
| Ryu et al[15,†] | 35 | NA | 154 | 22.7% | NA | NA | Tumor size ≤ 1 cm; ≥ 45 years |
| Park et al[11] | 32 | 6/26 | 115 | 27.8% | 3.3 ± 2.5 vs 5.8 ± 3.5 | NA | Tumor size ≤ 1 cm; upper pole |

*NA*, not available.
* Data are expressed as mean ± standard deviation of the number of lymph nodes in the order of skip metastasis or not.
† Extracted from a meeting abstract.

**Table VI**
Literature overview of skip metastasis of PTC among studies without multivariate analysis

| Study | Skip (*n*) | Total (*n*) | Skip metastasis rate (%) | Study type |
|---|---|---|---|---|
| Dzodic et al[16] | NA | NA | ≈ 4 | Meeting abstract |
| Su et al[17,*] | 42 | 320 | 13.1 | Meeting abstract |
| Tae et al[18] | 12 | 119 | 10.1 | Meeting abstract |
| Ryu[19] | 74 | 346 | 21.4 | Meeting abstract |
| Lee et al[10,*] | 9 | 131 | 6.8 | Research article |
| Kim et al[20] | 21 | 126 | 16.7 | Meeting abstract |
| Lim and Koo[21] | 17 | 90 | 18.9 | Research article |
| Kliseska and Makovac[22] | 8 | 42 | 19.0 | Research article |
| Xiao and Gao[23,*] | 9 | 64 | 14.1 | Research article |
| Chung et al[24,*] | 3 | 39 | 7.7 | Research article |

* Skip metastasis rate was calculated as the number of patients with skip metastasis divided by the number of patients with LLNM.

nodes dissected in the central compartment were inversely associated with skip metastasis risk. Concerning LLNM, larger tumor size (>1 cm), CLNM, and an increased number of CLNM were risk factors for LLNM of PTC. In addition, the number of dissected lymph nodes in the lateral neck was positively associated with the risk of LLNM from PTC.

Lymph node metastasis from PTC involves the central compartment first, followed by the ipsilateral lateral neck and then the contralateral neck. The frequency of LLNM from PTC was 78.6% (567 of 721 patients undergoing a LLND in our study), which was similar with the reported rate of LLNM of 74.9% (203/271), based on preoperative imaging diagnosis by Nie et al.[4] Lim et al[9] reported that larger tumor size (>1 cm) and CLNM were independent predictors for lateral lymph node recurrence of PTC. Similarly, we found that tumors >1 cm and CLNM were associated with the risk of LLNM from PTC. We found further that the number of CLNM was positively associated with the risk of LLNM from PTC. The OR for the risk of LLNM was 1.24, with each additional metastatic lymph node identified in the central neck. In addition, extranodal extension of a metastatic central lymph node from PTC was an independent risk factor for lateral lymph node recurrence,[9] suggesting the close relationship between CLNM and LLNM.

We found that patients < 55 years of age were more likely to present with LLNM. Age < 55 years, however, was not associated with LLNM risk of PTC. The increase in the age cutoff from 45 to 55 years of age at diagnosis downstaged a significant number of patients into stage I without significantly altering the mortality associated with the various stages.[25] We further found that the number of lymph nodes dissected in the lateral neck was positively associated with LLNM of PTC. Therefore, patients who are of a younger age and have a larger tumor size and CLNM should be examined carefully in the lateral neck, and the implementation of standardized and comprehensive LLND can facilitate the eradication of metastatic lymph nodes in the lateral neck.

Skip metastases of PTC are defined as the presence of LLNM in the absence of CLNM. Therefore, the elimination of CLNM is a prerequisite in the diagnosis of skip metastasis, highlighting the necessity of a bilateral CLND. We found that the number of lymph nodes dissected in the central neck was inversely associated with the risk of skip metastasis (OR = 0.88, $P < .001$). A limited number of dissected lymph nodes in the central neck might lead to the overestimation of the frequency of skip metastasis.[4] A complete CLND might eradicate all CLNM and thereby decrease the false-positive detection of skip metastasis. After reviewing earlier studies on skip metastasis, we found that the status of CLNM was poorly described, and some variables with statistical differences and other confounders were not adjusted in the investigation of risk factors for skip metastasis.[14] The ratio of female to male patients with skip metastasis might also contribute to the heterogeneity between studies.[14]

With the increased diagnosis and recognition of PTC, a growing number of patients with PTMC have been detected. PTMC appears to account for the majority of the increased incidence of thyroid cancer.[26,27] Earlier studies found PTMC to be a risk factor for skip metastasis,[11,12,14,15] which was consistent with our results; however, PTMC was inversely associated with LLNM of PTC. The potential mechanisms involved in skip metastasis are obscure. Contrary to the common understanding of lymph node metastasis from PTC, believed to be first to the central neck and later to the lateral neck, skip metastasis appears to be able to bypass the central lymph nodal drainage through lymphatic channels.

Earlier studies reported that younger age, male sex, larger tumor size, and extrathyroidal extension were independent risk factors for CLNM from PTC.[28,29] We also found that patients with capsular invasion, extracapsular extension, or intrathyroidal spread were more likely to present with LLNM. Therefore, the predictors for CLNM were more like the risk factors for LLNM. In contrast, Lim and Koo[21] found that patients with tumors that had less lymphovascular invasion and extracapsular spread were more likely to present with skip metastasis. We found that intrathyroidal spread was inversely associated with skip metastasis risk. The different risk factors between skip metastasis and LLNM might account for the

different tendencies for lymph node metastasis. We found further that the mean and median ages of patients with PTMC were older than those with tumor size > 1 cm (data not presented). We thus expected that some PTCs may not develop from PTMCs, and the metastatic trend of some PTMCs may be different from PTCs, suggesting that some "genetic regulators" were involved in their oncogenesis and metastasis by activating these intracellular or extracellular processes in a certain period.[30]

Some studies have reported that tumor location in the upper pole is a predictor for skip metastasis.[11,12,14] Nie et al[4] reported that the primary tumor location (upper pole) was not significantly different between the skip-positive group and skip-negative group. We were unable to investigate the relationship between tumor location and skip metastasis because of our inability to localize the primary PTC based on the imaging reports we had available. However, in other reports, tumor location was not specific for skip metastasis, and tumor location in the upper pole was also positively associated with LLNM risk of PTC.[4,31] The most frequently involved skip area was level III,[10,11,21,22] which was different from level II as found by other researchers.[12,14] It might be expected that the upper pole of thyroid is more closely linked with the lateral lymph nodes through lymphatic passage compared with other parts of the thyroid. Therefore, tumors located in the upper pole should be evaluated carefully for possible LLNM and skip metastasis of PTC, including PTMC. Age $\geq$45 years was found to be a risk factor for skip metastasis.[15] However, we did not find that age $\geq$55 years was associated with skip metastasis.

In the present study, we investigated the predictors for skip metastasis and LLNM and found many risk factors that were different from earlier studies. However, the risk factors we identified were based on our retrospective design and the relatively small number of patients with skip metastasis, and thus may need further exploration. In addition, our study has no information about follow-up evaluation of the patients for potential development of future metastases and there may be other potential confounding factors (ie, comorbidities, clinical history) not taken into account in our analysis. Indeed, one potentially important factor not taken into account in our study is the time to CLNM or LLNM metastasis.

In conclusion, PTMC and female sex were risk factors for skip metastasis, and intrathyroidal spread was inversely associated with skip metastasis. In contrast, larger tumor size, CLNM, and an increased number of CLNM number were independent risk factors for LLNM of PTC. A comprehensive and standardized CLND and LLND might decrease the detection of the false-positive skip metastasis and increase the removal of lateral metastatic lymph nodes of PTC.

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## Conflicts of interest

The authors do not have financial interests or conflicts to report. This research was performed independent of any outside funding or support.

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