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Risk factors for lateral neck lymph node metastasis in papillary thyroid ultra micro carcinoma with implications for active surveillance

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Papillary thyroid ultra-microcarcinoma (PTUMC), defined as a tumor ≤ 0.5 cm in size, can be considered for active surveillance management. However, lateral neck node metastases also occur in patients with PTUMCs. This study evaluated the clinicopathological features of PTUMC and compare the clinicopathological characteristics of patients with PTUMC with and without lateral neck lymph node metastasis. The study included 3,004 patients with PTUMC treated between January 2009 and June 2013; of these, 89 (3.0%) had lateral neck node metastasis. Clinicopathological characteristics including sex, age, size, operation type, tumor location, multiplicity, thyroiditis, microscopic extrathyroidal extension (ETE), and nodal status were compared between the two groups. Patients with PTUMC presented with significant male sex ($p = 0.014$), microscopic ETE ($p < 0.001$), multiplicity ($p < 0.001$), upper pole lesions ($p < 0.001$), psammomatous calcification, and central node metastasis ($p < 0.001$). Multivariate analysis revealed microscopic ETE ($p = 0.003$), upper pole lesions ($p < 0.001$), psammomatous calcification ($p = 0.002$), central neck node metastases ($p < 0.001$) and aggressive subtype($p < 0.001$) are independent risk factors for lateral neck metastasis in PTUMC, warranting careful consideration when deciding between active surveillance and surgical intervention in this patient population.

Keywords Thyroid cancer, Lateral neck node metastasis, Active surveillance

Papillary thyroid carcinoma (PTC) is a slowly progressing cancer[1,2]. With the technological advancement of diagnostic modalities including ultrasonography, papillary thyroid microcarcinoma has emerged as a predominant component of thyroid cancer diagnoses, accounting for 30–50% or more of cases internationally[3–5].

Papillary thyroid microcarcinoma (PTMC) is characterized by a tumor size of less than 1 cm, and active surveillance has recently emerged as a notable management strategy for these lesions[6–8]. According to published studies, the long-term outcomes of patients with PTMC managed with active surveillance demonstrate that, over 10 to 20 years of follow-up, the incidence of disease progression remains low, ranging from approximately 0.8–3.8%[9–12].

Although the incidence of lymph node metastasis during active surveillance is very low, it is important to recognize that, in clinical practice, lateral neck lymph node involvement may be present at the time of PTMC diagnosis or may be detected during the course of active surveillance[13,14].

In the present study, the authors defined papillary thyroid ultra-microcarcinoma (PTUMC) as a markedly small malignancy, measuring less than 0.5 cm in greatest dimension on imaging studies. According to the American Thyroid Association (ATA)[15] and European Thyroid Association (ETA)[16] guidelines, fine-needle aspiration (FNA) biopsy is generally not recommended for nodules smaller than 0.5 cm.

Given the characteristics of PTUMC, even when malignancy is suspected, diagnostic procedures such as fine-needle aspiration (FNA) may be deferred. Furthermore, if PTUMC is diagnosed, active surveillance is often pursued; however, there remains a possibility that lateral neck metastasis may develop during follow-up.

This study aims to identify risk factors for lateral neck LN metastasis in patients with PTUMC and to clarify which factors should be carefully evaluated before initiating active surveillance.

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Results

Clinicopathological results

Table 1 summarizes the demographics and clinical characteristics of patients with or without lateral neck LN metastasis.

A total of 3,004 patients with PTUMC were included in this study. Majority of patients were female (81.8%, $n = 2{,}458$), with a mean age of 45.8 ± 10.5 years, ranging from 13 to 81 years. The mean tumor size was 0.40 (range: 0.05–0.5) cm.

Total thyroidectomy was performed in 1,493 patients (49.7%), and the remaining 1,511 (50.3%) patients underwent less-than-total thyroidectomy. The distribution of primary tumor sites showed a relatively balanced occurrence between the right and left lobes of the thyroid gland. In total, 1,598 (50.3%) tumors were located in the right lobe, whereas 1,333 (44.4%) were located in the left lobe. A smaller proportion of tumors (73 cases; 2.4%) were identified in the isthmus. Analysis of the vertical distribution of tumors within the thyroid lobes revealed that 807 (26.8%), 1,553 (51.0%), and 664 (22.1%) cases were located in the upper, middle and lower poles, respectively. This distribution indicates a slight predominance of tumors in the middle third of the thyroid lobe.

Multifocal tumors were identified in 316 (10.5%) patients with unilateral lesions, 306 (10.2%) patients with bilateral lesions, and 2,382 (79.3%) patients with solitary lesions. The majority of the tumor types in our study

Variables	*N* = 3,004
Sex (male: female)	546:2458 (18.2%:81.8%)
Age	45.8 ± 10.5 (13–81)
Age ≥ 55 years	644 (21.4%)
Size (cm)	0.40 (0.05–0.5)
Op type	
Less than total	1511 (50.3%)
Total	1493 (49.7%)
Primary tumor site	
Right	1598 (53.2%)
Left	1333 (44.4%)
Isthmus	73 (2.4%)
Primary tumor location	
Upper	807 (26.8%)
Mid	1533 (51.0%)
Lower	664 (22.1%)
Multiplicity	
None	2382 (79.3%)
Unilateral	316 (10.5%)
Bilateral	306 (10.2%)
Tumor type	
Expanding	658 (21.9%)
Infiltrative	2345 (78.1%)
Microscopic capsule invasion	
Positive	986 (32.8%)
Negative	2018 (67.2%)
Psammomatous calcification	717 (23.9%)
Underlying thyroiditis	1021 (34.0%)
Central neck node metastasis	702 (23.4%)
Lateral neck node metastasis	89 (3.0%)
Subtype of PTC	
Conventional	2875 (95.7%)
Follicular	96 (3.2%)
Diffuse sclerosing	19 (0.6%)
Tall cell	5 (0.2%)
Solid	1 (0.0%)
Oncocytic	5 (0.2%)
Warthin like	3 (0.1%)
*Aggressive subtype	25 (0.8%)

Table 1. Demographics and clinical characteristics. PTC, papillary thyroid carcinoma; * Aggressive subtype: *Diffuse sclerosing*, *Tall cell*, *Solid*.

were classified as infiltrative, accounting for 2,345 (78.1%) patients. A total of 658 (21.9%) patients presented with the expansion-type disease. Microscopic capsular invasion was observed in 986 (32.8%) patients while 2,018 (67.2%) showed no evidence of it. Psammomatous calcification was observed in 717 (23.9%) patients. In our study, underlying thyroiditis was histologically confirmed in 1,024 (34.0%) patients, and the remaining 1,980 (65.9%) had no evidence of thyroiditis.

Overall, 702 patients revealed significant LN involvement. Central LNs metastasis was detected in 702 (23.4%) patients, whereas 89 (3.0%) had lateral LNs metastasis with or without central neck node metastasis. Aggressive subtypes such as diffuse sclerosing, tall cell, and solid variants were identified in the final pathology of 25 patients (0.8%).

Our study compared the clinicopathological variables between the lateral neck node negative and positive groups in patients with PTUMC. The results are presented in Table 2.

The lateral neck node-negative group comprised 2,915 (97.0%) patients, while the lateral neck node-positive group included 89 patients (3.0%). The mean age was lower in the lateral neck node positive group (44.7 ± 11.5 years) compared to the negative group (45.8 ± 10.5 years) ($p = 0.318$). The male sex was more prevalent in the positive group (28.1% vs. 17.9%, $p = 0.014$).

The mean tumor size was significantly larger in the lateral neck node positive group (0.44 ± 0.08 cm) than in the negative group (0.40 ± 0.10 cm) ($p < 0.001$). Microscopic extrathyroidal extension (ETE) was significantly more frequent (50.8% vs. 33.5%, $p < 0.001$) and multiplicity was more common (33.7% vs. 20.3%, $p < 0.001$) in the positive than in the negative group. The tumor location was significantly more common in the upper pole in the lateral neck node positive group than in the negative group (47.2% vs. 26.2%, $p < 0.001$). The histopathological features of psammomatous calcification were significantly more common in the lateral neck node-positive group (48.3% vs. 23.1%, $p < 0.001$). The central LNs metastasis was significantly more prevalent in the lateral neck node-positive group (64.0% vs. 22.1%, $p < 0.001$). Furthermore, Aggressive subtypes were observed at a significantly higher rate in patients with lateral neck node positivity compared to those without (9.0% vs. 0.6%, $p < 0.001$).

Predictors of lateral neck LN metastasis in patients with PTUMC

Univariate and multivariate logistic regression analyses were conducted to identify risk factors for lateral neck node metastasis in patients with PTUMC, and the results is shown in Table 3.

Univariate analysis revealed several clinicopathological factors that were significantly associated with lateral neck node metastasis in PTUMC. Male sex (odds ratio [OR], 1.795; 95% confidence interval [CI], 1.120–2.877; $p = 0.015$), tumor multiplicity (OR: 1.995, 95% CI: 1.274–3.125, $p = 0.03$), and bilaterality (OR: 2.664, 95% CI: 1.596–4.448, $p < 0.001$) increased the risk of lateral neck node involvement. Microscopic ETE was associated with a higher likelihood of lateral neck node metastases (OR, 2.586; 95% CI, 1.691–3.955; $p < 0.001$). Tumors located in the upper pole of the thyroid gland were associated with an increased risk (OR, 2.511; 95% CI, 1.643–3.839; $p < 0.001$). Moreover, the presence of psammomatous calcification was a significant predictor (OR, 3.108; 95% CI, 2.033–4.752; $p < 0.001$). The presence of central lymph node metastasis emerged as significant predictor of lateral neck node involvement. (OR, 6.269; 95% CI, 4.031–9.750; $p < 0.001$). Notably, Aggressive subtypes were the strongest predictor of lateral neck node involvement (OR, 16.837; 95% CI, 7.062–40.141; $p < 0.001$).

Multivariate logistic regression analysis identified four independent risk factors that were significantly associated with lateral neck LN metastasis in patients with PTUMC. Microscopic ETE was associated with a high

Variables	Lateral neck node Positive group (*n* = 89)	Lateral neck node Negative group (*n* = 2,915)	*P*-value
Sex (male: female)	25:64 (28.1%:71.9%)	521:2394 (17.9%:82.1%)	0.014
Age	44.7 ± 11.5	45.8 ± 10.5	0.318
Age ≥ 55 years	15 (16.9%)	629 (21.6%)	0.285
Size (cm)	0.44 ± 0.08	0.40 ± 0.10	< 0.001
Infiltrative type	75 (84.3%)	2270 (77.9%)	0.151
Microscopic ETE	49 (55.1%)	937 (32.1%)	< 0.001
Multiplicity			< 0.001
None	59 (66.3%)	2323 (79.7%)	
Unilateral	10 (11.2%)	306 (10.5%)	
Bilateral	20 (22.5%)	286 (9.8%)	
Tumor location			< 0.001
Upper pole	42 (47.2%)	765 (26.2%)	
Mid pole	38(42.7%)	1495 (51.3%)	
Lower pole	9(10.1%)	655 (22.5%)	
Psammomatous calcification	43 (48.3%)	674 (23.1%)	< 0.001
Underlying thyroiditis	35 (39.3%)	986 (33.8%)	0.280
Central LN metastasis	57 (64.0%)	645 (22.1%)	< 0.001
Aggressive subtype	8 (9.0%)	17 (0.6%)	< 0.001

Table 2. Comparison of clinicopathological variables in the lateral neck node negative and positive group in PTUMC. PTUMC, papillary thyroid ultra-microcarcinoma; ETE, extrathyroidal extension; LN, lymph node.

Independent variable	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Male sex	1.795 (1.120–2.877)	0.015	1.471 (0.888–2.438)	0.134
Multiplicity	1.995 (1.274–3.125)	0.003	0.921 (0.449–1.890)	0.822
Bilaterality	2.664 (1.596–4.448)	< 0.001	2.387 (1.052–5.414)	0.037
Microscopic ETE	2.586 (1.691–3.955)	< 0.001	1.982 (1.269–3.094)	0.003
Upper pole location	2.511 (1.643–3.839)	< 0.001	2.553 (1.634–3.989)	< 0.001
Psammomatous calcification	3.108 (2.033–4.752)	< 0.001	1.806 (1.134–2.879)	0.013
Central LN metastasis	6.269 (4.031–9.750)	< 0.001	4.516 (2.822–7.229)	< 0.001
Aggressive subtype	16.837 (7.062–40.141)	< 0.001	9.018 (3.384–24.032)	< 0.001

Table 3. Univariate and multivariate logistic regression for lateral neck node metastasis in patients with PTUMC. PTUMC, papillary thyroid ultra-microcarcinoma; ETE, extrathyroidal extension; LN, lymph node; OR, odds ratio; CI, confidence interval.

risk of lateral neck LN metastasis (OR, 1.982; 95% CI, 1.269–3.094; $p = 0.003$). Tumors located in the upper pole of the thyroid gland were also associated with an increased likelihood of lateral neck node involvement (OR, 2.553; 95% CI, 1.634–3.989; $p < 0.001$). In addition, central LN metastasis was significantly correlated with a higher risk of lateral neck node involvement (OR, 4.516; 95% CI, 2.822–7.229; $p < 0.001$). The presence of aggressive subtypes was the strongest predictor, with an OR of 9.018 (95% CI, 3.384–24.032; $p < 0.001$). Additionally, pasmmomatous calcification (OR, 1.806; 95% CI, 1.134–2.897; $p = 0.013$). and bilaterality (OR, 2.387; 95% CI, 1.052–5.414; $p = 0.037$) were identified as an independent risk factor. These findings have important implications for risk stratification and management decisions in patients with PTUMC.

Discussion

Multivariate analysis revealed that microscopic ETE, upper pole location, psammomatous calcification, and central neck node metastasis were significant risk factors of lateral neck metastasis in PTUMC. These findings are similar to those reported in previously published studies on lateral neck LN metastasis in PTMC)[13,14,17]. In this study, we aimed to address whether PTUMCs are sufficiently indolent to warrant active surveillance or whether they are overlooked during diagnosis. Notably, approximately 3% of patients with PTUMC presented with lateral neck LN metastasis, suggesting that a subset of PTUMC cases may represent more aggressive thyroid cancers and should not be disregarded.

Previous studies reported similar risk factors for lateral neck metastases in patients with PTMC[13,14,17,18]. Our findings indicate that even small PTUMCs with these risk factors can metastasize to the lateral neck, highlighting the limitations of size alone as a criterion for determining the safety of active surveillance.

Our analysis demonstrated that the presence of aggressive subtypes of PTC serves as a significant risk factor for lateral neck metastasis in patients with PTUMC. The World Health Organization (WHO) classification of thyroid tumors recognizes variants such as tall cell, columnar cell, solid/trabecular, hobnail, and diffuse sclerosing types as exhibiting more aggressive clinical behavior[19–21]. However, accurately identifying these aggressive subtypes preoperatively through fine-needle aspiration biopsy (FNAB) remains challenging, thus limiting their utility in guiding clinical management prior to surgery[22,23].

While the ATA guidelines suggest active surveillance as an option for PTC owing to its generally indolent nature, and many institutions have adopted this approach for PTMC[8,15,16], a growing trend exists to extend this management strategy to PTUMC. This shift may lead to less aggressive FNA, and potentially result in the loss of regular follow-ups in some cases. Although only 3% of the patients with PTUMC in our study had lateral neck metastasis requiring surgery, a risk exists that some patients with progressive thyroid cancer may be misclassified as having localized disease, potentially delaying appropriate treatment.

Our findings suggest that for PTUMCs located in the upper pole or near the thyroid capsule (indicating microscopic ETE), a thorough preoperative ultrasound examination of the lateral neck LN is warranted. If LN enlargement or suspicious nodes are detected, additional imaging, such as neck CT scans should be considered for a more comprehensive analysis of lateral neck LN metastasis[24,25].

While active surveillance is increasingly accepted as a safe management option for early stage thyroid cancer, applying the risk factors identified in this study for patients with PTUMC with lateral neck metastasis could help in more accurately selecting suitable candidates for this approach. Furthermore, patients with risk factors identified in univariate analysis, such as male sex, multiplicity, or bilaterality, should be thoroughly evaluated and counseled before opting for active surveillance.

Understanding these risk factors for lateral neck metastasis in patients with PTUMC can not only aid in selecting appropriate candidates for active surveillance, but also in determining the optimal surgical extent for small thyroid cancers.

Although not analyzed in the current study, emerging molecular tests are increasingly being utilized to predict the prognosis of thyroid nodules[22,26,27]. For patients with small tumors at risk of lateral neck LN metastasis, molecular profiling of high-risk genetic alterations, such as BRAF V600E, TERT promoter mutations, and RET/PTC rearrangements may aid in risk stratification[28,29]. While cost-effectiveness remains debated, recently commercialized multi-gene panels, such as ThyroSeq v3 and Afirma Gene Sequencing Classifier enable prognostic assessment using FNA samples[30,31]. Although not universally applicable, these tests may serve as viable adjuncts in selecting patients with PTUMC suitable for active surveillance, potentially reducing unnecessary interventions.

This study had some limitations. Despite analyzing a substantial dataset, the study was retrospective in nature and compared a small number of patients with lateral neck LN metastasis to a larger cohort without metastasis. Additionally, as lateral neck LN dissection was not performed in all patients, there is a potential for error in assessing the LN metastasis status. Future studies employing more accurate methods to evaluate lateral neck LN metastasis or prospective designs incorporating lateral neck LN dissection could help overcome these limitations.

In conclusion, microscopic ETE, upper pole location, psammomatous calcification, and central neck node metastasis are significant independent risk factors for lateral neck metastasis in patients with PTUMC. The presence of these risk factors in patients with PTUMC warrants careful consideration when deciding between active surveillance and surgical intervention. Active surveillance protocols for PTUMC should be applied judiciously, considering the identified risk factors to avoid undertreatment of potentially aggressive diseases. The risk stratification model developed in this study may aid in selecting appropriate candidates for active surveillance and in optimizing the extent of surgery in patients with PTUMC.

Materials and methods

The study included patients treated at the Department of Surgery of Gangnam Severance Hospital between January 2009 and June 2013. Overall, 3,004 patients with PTUMC were analyzed.

Inclusion and exclusion criteria

Patients with a tumor size < 0.5 cm based on final pathological results, complete medical records, diagnosis of PTC confirmed by final pathological examination, history of thyroidectomy and LNs dissection (including the central and lateral neck), and no evidence of distant metastasis, were included in this study. Patients with PTC with a tumor size exceeding 0.5 cm based on the final histopathological examination results, those with missing medical record, those with pathological findings indicating malignancies other than PTC, and those who did not undergo LNs dissection during thyroid surgery, were excluded.

Preoperative evaluation

All patients were diagnosed with PTC, classified as Bethesda category ≥ 5 through preoperative neck ultrasonography and FNA biopsy. Additionally, neck CT scan was performed as part of the preoperative evaluation.

Surgical procedure

Five endocrine surgeons performed all the surgeries, including thyroidectomy and central neck dissection, using standardized techniques. Prophylactic central neck dissection was performed on the ipsilateral side of the tumor in cases in which imaging studies showed no evidence of central LN metastasis. Lateral neck LNs dissection was performed when lateral LN metastases were diagnosed based on imaging studies and biopsy results, with the extent of dissection covering levels II–Vb.

Data collection

Patient demographic information, such as sex and age, was anonymized by assigning encrypted individual identifiers. Data from preoperative imaging studies, surgical records, and final pathological reports were collected to summarize variables, including operation type, tumor size, tumor location, multiplicity, thyroiditis, microscopic ETE, and nodal status.

Statistical analysis

Data were organized using Microsoft Excel, and statistical analyses were conducted using SPSS (version 21.0; IBM Corp., Armonk, NY, USA). Univariate analyses were performed using χ^2 tests, t-tests, and Fisher's exact tests. Multivariate analysis of factors associated with lateral neck LN metastasis in patients with PTC was conducted using unconditional logistic regression for variables with a p-value < 0.05.

Data availability

All data generated or analysed during this study are included in this published article [supplementary information files].

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Author contributions
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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
This study adhered to the ethical principles outlined in the Declaration of Helsinki for medical research involving human participants. This study was approved by the Institutional Review Board of Yonsei University (approval number: 3-2025-0072). Informed consent was waived from IRB due to the retrospective design.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-16519-y.

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