

# Clinical characteristics of papillary thyroid microcarcinoma less than or equal to 5 mm on ultrasonography

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**Abstract** Management of papillary thyroid microcarcinoma sized  $\leq 5$  mm identified on ultrasonography is controversial. In this study, we evaluated the clinical characteristics of papillary thyroid microcarcinoma sized  $\leq 5$  mm on ultrasonography in comparison to those  $> 5$  mm and sought to present rationales for optimal management in papillary thyroid microcarcinoma  $\leq 5$  mm. The medical records of 396 patients who underwent surgery for papillary thyroid carcinoma between 2009 and 2011 were retrospectively analyzed. The patients were grouped into A ( $\leq 5$  mm,  $n = 132$ ) or B ( $> 5$  mm,  $n = 264$ ) and the clinicopathologic characteristics of the patients were reviewed and compared between the two groups. Tumor capsular invasion (45.5 vs. 59.8 %,  $p = 0.007$ ) and cervical lymph node metastasis (18.2 vs. 29.2 %,  $p = 0.018$ ) were more frequent in group B. Nonetheless, group A presented lymph node metastasis in 42.3 % of multifocal cases showing no difference to that of group B (41.5 %,  $p = 0.946$ ) and also included five cases (3.8 %) of lateral neck metastasis. Multifocality was the only predictive factor for lymph node metastasis in group A ( $p < 0.001$ ). Over half (55.3 %) of

the patients of group A were diagnosed with papillary carcinoma in private clinics; however, only 5.5 % of these patients underwent assessment of lateral neck lymph nodes initially. In conclusion, higher risk of cervical lymph node metastasis should be considered in evaluation and surgical decision of papillary thyroid microcarcinoma  $\leq 5$  mm identified on ultrasonography with multifocality. Evaluation of the cervical lymph nodes including the lateral neck should not be overlooked when suspicious thyroid nodule suggesting malignancy sized  $\leq 5$  mm shows multifocal lesions.

**Keywords** Papillary thyroid microcarcinoma · Papillary thyroid carcinoma · Ultrasonography · Fine-needle aspiration biopsy

## Introduction

A papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid carcinoma (PTC) that is  $\leq 10$  mm in size, which in most cases shows favorable prognosis. Recently, the diagnosis of PTMC measuring  $\leq 5$  mm (i.e.,  $\leq 5$  mm) has increased with the development of diagnostic technology using high-resolution ultrasonography and skillful fine-needle aspiration biopsy (FNAB). However, the guidelines of the American Thyroid Association (ATA) [1] primarily recommend FNAB for patients with a nodule  $> 5$  mm in size when the patient falls within the high-risk category or if ultrasonographic examination shows manifestations that suggests malignancy. Thus, FNAB for suspicious nodule  $\leq 5$  mm is generally not recommended unless metastatic cervical lymphadenopathy is accompanied. However, we have experienced that a considerable number of patients with PTMC  $\leq 5$  mm who were referred

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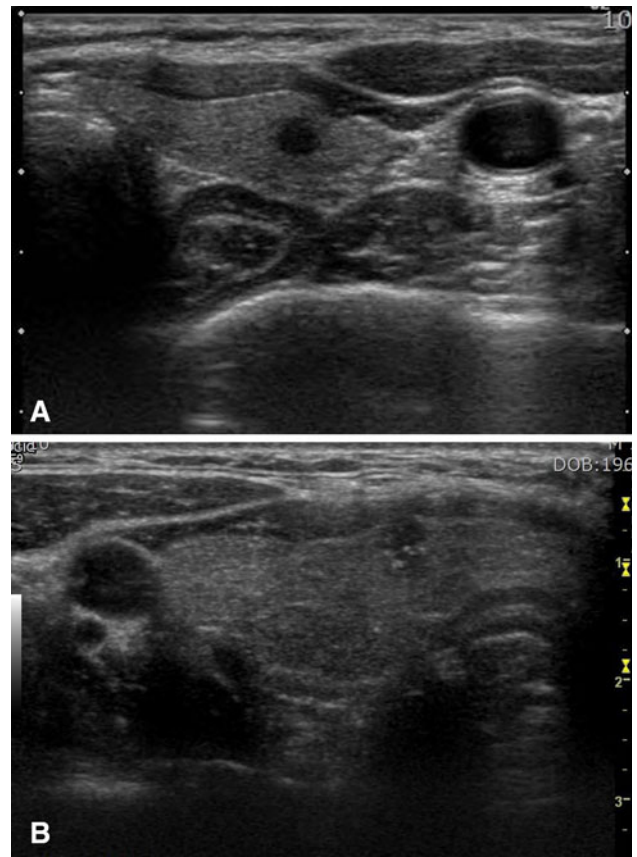
from local clinics or hospitals visit our center without any evaluation for cervical lymph node metastasis. We assumed that following the guidelines of ATA with the size criteria only, while omitting evaluations for central and lateral neck may overlook cases of PTMC  $\leq 5$  mm showing aggressive behavior such as multiple lymph node metastases.

To address this problem, we classified patients with PTMC into  $>5$  mm and  $\leq 5$  mm groups based on preoperative ultrasonographic measurements, and the clinicopathologic factors of the two groups were analyzed and compared. We speculated that such an analysis may provide some rationales for determining the optimal management including the necessity of performing FNAB on suspicious PTMC  $\leq 5$  mm and decisions on surgical management. In addition, considering the widespread use of thyroid ultrasonography and FNAB in South Korea regardless of the capacity of the medical institute, we investigated the patterns of the diagnosing process for PTMC according to the size of the institute where the patient was first diagnosed.

## Materials and methods

We retrospectively reviewed the medical records of 684 patients who underwent surgery for papillary thyroid cancer at the Department of Otolaryngology–Head and Neck Surgery of Kosin University Gospel Hospital and Dong-A University Medical Center from January 2009 to May 2011. Among them, we focused on 396 patients whose ultrasonography measurements of preoperative thyroid nodules were  $\leq 10$  mm (i.e., PTMC). These patients were classified into ‘group A’ consisting of 132 patients with tumor size  $\leq 5$  mm (Fig. 1) and ‘group B’ consisting of 264 patients with tumor size of  $\leq 10$  mm but  $>5$  mm. When a patient had multiple nodules, the largest one was used for classification. Unilateral lobectomy was conducted for patients with a single, intraglandular tumor with no suspicious cervical lymph node metastasis and total thyroidectomy was performed for those with multifocality, suspicious capsular invasion or lymph node metastasis and tumor at the isthmus. All patients underwent unilateral or bilateral central compartment neck dissection. Therapeutic lateral neck dissection including level IIa, III, IV and Vb was performed when lateral neck lymph node metastasis was identified.

Clinicopathologic factors including gender, age, size of the tumor, extent of operation, tumor capsular invasion, multifocality and lymph node metastasis were compared between the two groups. The medical institutes where the patients underwent the initial ultrasonography and FNAB were classified as private clinics, non-training hospitals or



**Fig. 1** **a** A 4 mm-sized nodule with marked hypoechoogenicity and spiculated margin without microcalcification. **b** A 4 mm-sized hypoechoic nodule with microcalcification and suspicious extrathyroidal extension

training hospitals, and the frequency of ultrasonography examination of lateral neck was investigated. Patients who had no evaluation of the lateral neck at the initial clinic underwent neck ultrasonography before the surgery to evaluate the status of cervical lymph node metastasis. Statistical analysis was performed using PASW 18 software program (SPSS Inc., Chicago, IL, USA) with the  $\chi^2$  test and independent *t* test used as appropriate and statistical significance was determined as  $p < 0.05$ .

## Results

The clinicopathologic factors of the patients are summarized in Table 1. There were no significant differences in age or male–female ratio between the two groups; however, the size of the tumor showed a significant difference between the two groups. The incidence rates of tumor capsular invasion (45.5 vs. 59.8 %) and cervical lymph node metastasis (18.2 vs. 29.1 %) were higher in group B. Invasion of the thyroid capsule was more frequent in group B ( $p = 0.007$ ) and invasion of the recurrent laryngeal

**Table 1** Comparison of clinicopathologic factors between the two groups

Characteristics	Group A (n = 132)	Group B (n = 264)	p value
Age (years)			
Mean age	47.2 ± 10.8	48.8 ± 10.1	0.149
<45	50 (37.9 %)	82 (31.1 %)	0.175
≥45	82 (62.1 %)	182 (68.9 %)	0.137
Gender			
Male	15 (11.4 %)	45 (17.0 %)	
Female	117 (88.6 %)	219 (83.0 %)	
Size of tumor, mean ± SD (mm)			
Preoperative ultrasonography	4.6 ± 0.1	7.8 ± 0.1	<0.001
Postoperative pathology report	4.3 ± 0.1	7.5 ± 0.2	<0.001
pT			
pT1a	72 (54.5 %)	106 (40.2 %)	0.024
pT3	58 (43.9 %)	154 (58.3 %)	
T4a	2 (1.5 %)	4 (1.5 %)	
pN			
pN0	108 (81.8 %)	187 (70.8 %)	0.053
pN1a	19 (14.4 %)	65 (24.6 %)	
pN1b	5 (3.8 %)	12 (4.5 %)	
AJCC stage			
Stage I	89 (67.4 %)	142 (53.8 %)	0.031
Stage III	38 (28.8 %)	111 (42.0 %)	
Stage IV	5 (3.8 %)	11 (4.2 %)	
LN metastasis			
Yes	24 (18.2 %)	77 (29.2 %)	0.018
No	108 (81.8 %)	187 (70.8 %)	
Tumor capsular invasion			
Yes	60 (45.5 %)	158 (59.8 %)	0.007
No	72 (54.5 %)	106 (40.2 %)	
Multifocality			
Single tumor	106 (80.3 %)	199 (75.4 %)	0.272
Multiple tumor	26 (19.7 %)	65 (24.6 %)	
Thyroidectomy			
Total thyroidectomy	96 (72.7 %)	215 (81.4 %)	0.047
Lobectomy	36 (27.3 %)	49 (18.6 %)	

SD standard deviation, AJCC American Joint Committee on Cancer, LN lymph node

nerve or trachea (pT4) was detected in two patients (1.5 %) of group A and four patients (1.6 %) of group B. Lateral neck metastasis was identified in 5 patients (3.8 %) and 12 patients (4.5 %) in group A and B, respectively, which showed no significant difference ( $p = 0.726$ ). The two groups showed no significant difference in multifocality of the tumor, while total thyroidectomy was more frequently performed in group B ( $p = 0.047$ ). Among the patients

who underwent total thyroidectomy, the incidence of multifocality between the two groups still showed no difference (24 vs. 24.7 %,  $p = 0.896$ ).

Multifocality ( $p < 0.001$ ) was the only factor related to cervical lymph node metastasis in group A (Table 2), while tumor capsular invasion ( $p < 0.001$ ) and multifocality ( $p = 0.011$ ) were both related to lymph node metastasis in group B (Table 3). While cervical lymph node metastasis was more frequent in group B, there was no difference between the two groups in multifocal cases (42.3 vs. 41.5 %,  $p = 0.946$ ). When the patients who underwent unilateral lobectomy ( $n = 85$ ) were excluded thereby including only those who underwent total thyroidectomy, multifocality still showed significant correlation to lymph node metastasis in group A (13.7 vs. 43.5 %,  $p = 0.006$ ), while it showed borderline significance in group B (28.4 vs. 41.5 %,  $p = 0.075$ ). The correlation between multifocality and lateral neck metastasis showed borderline significance ( $p = 0.052$ ) in group A. The incidence of lateral neck metastasis in group A was 11.5 % (3/23) in multifocal lesions and 1.9 % (2/104) in solitary lesions. However, no significant correlation was identified between multifocality and lateral neck metastasis in group B.

The frequency of ultrasonography of the lateral neck lymph nodes at the pre-referral institutes was significantly lower at private clinics and non-training hospitals compared to that of training hospitals in both groups (Table 4). Over half (55.3 %) of the patients with PTMC ≤5 mm were diagnosed in private clinics, but only 5.5 % of these patients underwent lateral neck assessment.

## Discussion

Our study revealed that the clinical features of PTMC ≤5 mm were less aggressive compared to those >5 mm. PTMC >5 mm has been shown to be a predictive factor for central lymph node metastasis, extracapsular invasion and multifocality [2–6]. Thus, some authors consider sizes >5 mm to be an aggressive risk factor of PTMC [7]. In our series, PTMC >5 mm showed a significant correlation with cervical lymph node metastasis and tumor capsular invasion. In fact, the systemic autopsy study of Harach et al. [8] suggested that an incidentally found PTMC <5 mm should be classified as an occult papillary tumor instead of a carcinoma and should not be treated. Ito et al. [9] suggested that continuous observation only is necessary because most cases of PTMC change little in size during long-term follow-up and occurrence of metastasis is not frequent. These results may coincide with the rationales for the recommendation of the ATA guidelines [1] which consider 5 mm to be the threshold size for FNAB for nodule with suspicious sonographic features.

**Table 2** Clinicopathologic factors related to lymph node metastasis in group A

Characteristics	No. of patients ( <i>n</i> = 132)	LN metastasis ( <i>n</i> = 24)	<i>p</i> value
Age (years)			
<45	50	12 (24.0 %)	0.176
≥45	82	12 (14.6 %)	
Gender			
Male	15	4 (26.7 %)	0.474
Female	117	20 (17.1 %)	
Tumor capsular invasion			
Yes	60	11 (18.3 %)	0.967
No	72	13 (18.1 %)	
Multifocality			
Single tumor	106	13 (12.3 %)	<0.001
Multiple tumor	26	11 (42.3 %)	

No. number, LN lymph node

**Table 3** Clinicopathologic factors related to lymph node metastasis in group B

Characteristics	No. of patients ( <i>n</i> = 264)	LN metastasis ( <i>n</i> = 77)	<i>p</i> value
Age (years)			
<45	82	24 (29.3 %)	0.981
≥45	182	53 (29.1 %)	
Gender			
Male	45	13 (28.9 %)	0.964
Female	219	64 (29.2 %)	
Tumor capsular invasion			
Yes	158	60 (38.0 %)	<0.001
No	106	17 (16.0 %)	
Multifocality			
Single tumor	199	50 (25.1 %)	0.011
Multiple tumor	65	27 (41.5 %)	

No. number, LN lymph node

However, others have demonstrated that PTMC size showed no significant impact on lymph node metastasis [10–12]. Since cervical lymph node metastasis is related to higher incidence of recurrence, it is considered to be an aggressive clinical feature of PTMC [13, 14]. In fact, several authors [12, 15–17] have shown no significant difference in recurrence between PTMC ≤5 mm and PTMC >5 mm. Thus, the significance of lymph node metastasis in PTMC ≤5 mm should not be overlooked.

We found that while the well-known predictive factors for cervical lymph node metastasis, tumor capsular invasion and multifocality, were identified as independent predictive factors of cervical lymph node metastasis in

**Table 4** Frequency of lateral neck assessment with ultrasonography according to the medical institute of initial diagnosis

	Group A		Group B	
	<i>N</i> = 132	Lateral neck assessment (%)	<i>N</i> = 264	Lateral neck assessment (%)
Private clinics	73	4 (5.5)	127	14 (11.1)
Community hospital*	32	20 (62.5)	88	31 (35.2)
Private clinics + Community hospital	105	24 (22.9)	215	45 (20.9)
Training hospital	27	27 (100)	49	49 (100)
<i>p</i> value		<0.001**		<0.001**

\* Non-training hospital

\*\* Fisher's exact test to compare frequency of lateral neck assessment between patients referred from training hospitals and others

PTMC >5 mm, tumor capsular invasion in PTMC ≤5 mm showed no significant impact on lymph node metastasis. Despite the noted negative impact of tumor capsule invasion on oncologic outcomes of PTC [6, 7], relatively high incidence rates (45.5 %) of tumor capsule invasion in PTMC ≤5 mm in our series may not justify aggressive treatment in these cases. In fact, others [14, 15] have reported that a minimal extra thyroidal extension to the perithyroid soft tissue or sternothyroid muscle has no impact on recurrence in patients with PTMC.

We focused on the finding that there was no significant difference in multifocality between the two groups and that multifocality was identified as a single predictive factor for lymph node metastasis in PTMC ≤5 mm. The incidence of lymph node metastasis was relatively high (42.3 %) in PTMC ≤5 mm when the tumor was multifocal showing no significant difference to that of multifocal PTMC >5 mm. The impact of multifocality on lymph node metastasis in PTMC ≤5 mm was also verified by analyzing the data of patients who underwent total thyroidectomy. Since node-positive cases of PTMC may lead to increased recurrence [13, 14], we suspected that omitting FNAB and surgery in these cases could have impeded the correct diagnosis and decision for additional treatments such as completion thyroidectomy or radioiodine ablation.

Moreover, multifocality has been demonstrated to be a significant risk factor for recurrence in PTMC when surgery less than near-total thyroidectomy was conducted [13], and others [18] have reported that multifocality is the only independent risk factor for recurrence in patients with incidental PTMC (average tumor size, 0.44 cm). Chow et al. [12] showed no difference in lymph node metastasis, multifocality and recurrence between PTMC ≤5 mm and >5 mm and demonstrated that multifocality was an independent factor for recurrence. Therefore, FNAB may be required for suspicious thyroid lesions suggesting

malignancy on ultrasonography with size  $\leq 5$  mm when lesions are multifocal, and thorough evaluation of the cervical lymph nodes should be conducted.

The necessity of assessing the lateral and central neck lymph nodes with ultrasonography is well described in the ATA guidelines 2009, even when a sub-centimeter nodule with a suspicious appearance is identified [1]. Our results suggest that lateral neck metastasis does occur in PTMC  $\leq 5$  mm, although at a low incidence (3.8 %) and that the lateral neck should be thoroughly evaluated as the guideline recommends. However, our review on the frequency of lateral neck assessment at the medical institute of initial diagnosis showed the pattern of PTMC evaluation in South Korea. The significantly lower frequency of lateral neck assessment in institutes other than training hospitals reflects the risk of PTMC misdiagnosis with possibly aggressive clinical features by omitting FNAB of the suspicious thyroid lesions, when the 5 mm size criteria is strictly followed. Thus, ultrasonography of the lateral neck to assess the cervical lymph nodes should be conducted by an experienced radiologist before any thyroidectomy for PTMC. As it has been suggested from our study, increased tendency of lateral neck metastasis in PTMC  $\leq 5$  mm with multifocal lesions should also be considered. We believe that such policy may prevent residual disease or possible recurrence, which may not necessarily threaten the life of patients, but remains a burden for both the patient and the surgeon as additional surgery. Ito et al. [19], who suggested observation without treatment for PTMC not associated with unfavorable features, still showed that lateral node metastasis was an independent prognostic factor for recurrence. They pointed out the necessity of therapeutic neck dissection at first surgery of N1b PTMC, even though the primary tumor might be small. The impact of lymph node metastasis to the lateral neck in comparison to that of the central neck has been demonstrated by several authors showing a higher risk of recurrence and a shorter disease-free survival [20, 21]. Moreover, others have shown an increased risk of distant metastasis [22] or death from PTC [23, 24] in patients with lateral neck metastasis.

This study is not without limitations. We performed a retrospective review without evaluating the oncologic outcomes. Therefore, oncologic outcomes in relation to the clinicopathologic factors including cervical lymph node metastasis should be analyzed in future prospective studies with long-term follow-up. We are planning to review the metastatic lymph nodes of PTMC based on size, number and extranodal extension, which have been suggested as prognostic factors of nodal metastasis [25]. Such studies may be required to stratify the clinical significance of the identified lymph node metastasis in PTMC and may lead to more specific rationales for the management of PTMC.

## Conclusion

Our study showed that the clinical behavior of PTMC  $\leq 5$  mm had a less aggressive nature compared to PTMC  $> 5$  mm, which may support the recommendation of ATA guideline 2009 for FNAB. Nonetheless, higher risk of cervical lymph node metastasis should be considered in evaluation and surgical decision of PTMC  $\leq 5$  mm identified on ultrasonography with multifocality. Evaluation of the cervical lymph nodes including the lateral neck should not be overlooked when suspicious thyroid nodule suggesting malignancy, sized  $\leq 5$  mm, shows multifocal lesions.

**Conflict of interest** We have no financial relationship with any organizations regarding this study.

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