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Clinicopathological features of papillary thyroid microcarcinoma with a diameter less than or equal to 5 mm☆

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ABSTRACT

Purpose: This retrospective study was conducted to assess the epidemiological, clinical and histologic characteristics of incidentally identified and presurgically diagnosed papillary thyroid microcarcinomas less than or equal to 5 mm in size (small PTMC).

Materials and methods: Cases from October 2003 to February 2018 were retrieved from pathology databases, and their clinicopathological features were reviewed.

Results: There were a total of 182 cases of small PTMCs, 141 women and 41 men. The mean age at diagnosis was 53.5. Most of the small PTMCs were not detected on clinical examination and workup and were diagnosed incidentally during pathologic examination. 21.4% of small PTMCs showed multifocality, with 21 cases of unilateral multifocal lesions and 18 cases with bilateral multifocal tumors. Small PTMCs were most often follicular variant (51.9%) followed by classic type (47.5%). The average size of follicular variants appeared to be larger than that of the classic type PTMCs (2.84 ± 1.43 mm vs 2.26 ± 1.51 mm, $P = 0.01$). A total of 66 cases (36.3%) had regional lymph node sampling or selective neck dissection and 15 of these cases identified lymph node metastasis (22.7%). 46.7% of patients with node positive microcarcinomas were male compared with 16% male in group with negative lymph nodes ($P = 0.03$).

Conclusions: Small PTMCs (≤5 mm) are often multifocal and bilateral and histology is commonly both the classical and follicular variant of PTC. While often diagnosed incidentally small PTMC can lead to regional lymph node involvement in a significant portion of cases and evaluation of the regional lymph nodes should be considered in the clinical management of these patients.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most frequently diagnosed thyroid cancer worldwide; accounting for 85% of all thyroid tumors [1]. Its incidence in the U.S. has seen a significant increase over the past several decades [2]. Papillary thyroid carcinoma has several histological variants, including papillary thyroid microcarcinoma (PTMC) which is defined as a PTC which measures less than or equal to 1 cm in diameter [3]. It is often not detected on physical examinations and often incidentally in surgical specimens resected for benign thyroid diseases or during high-resolution ultrasound examination for other thyroid conditions.

There has been a rapid rise in the incidence of PTMCs worldwide in the past decade. This might be explained by the more prevalent use of ultrasound-guided fine needle aspiration on thyroid nodules and increased awareness of the incidental presence of this entity in thyroidectomy specimens for benign thyroid conditions [4,5]. Some studies showed that PTMCs accounted for nearly 50% of the newly diagnosed papillary thyroid carcinomas [6]. However, the American Thyroid Association guidelines for management of thyroid nodules only recommend fine-needle aspiration for nodules larger than 1.0 cm with suspicious ultrasound features [7]. Thus, fine-needle aspiration for thyroid nodules smaller than 5 mm is rarely performed unless lymph node metastasis is clinically suspected. As a result, small PTMCs (< 5 mm in diameter) are uncommonly diagnosed on thyroid FNA cytologic material and mostly identified as incidental findings in thyroidectomy or surgical lobectomy specimens. The clinical significance of PTMCs smaller than 5 mm and their optimal management have not reached consensus.

Traditionally, PTMC has been considered an indolent thyroid cancer

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that rarely causes direct tumor related death and patients usually have a > 90% progression-free survival [8,9]. PTMCs that have a poor prognosis are usually multifocal, have extrathyroidal extension and lymphovascular invasion or have lymph node metastases, especially if multiple nodes are involved or extra-nodal extension is present [10]. PTMC occasionally presents with neck lymph node involvement and has a reported potential for distant metastasis [11]. It has been shown that multifocal microcarcinoma and PTMC with lymph node involvement were associated with lower recurrence-free survival [12]. In this single-institution series of 182 patients with small papillary thyroid microcarcinoma (≤5 mm), we studied the clinical features of small PTMCs and investigated the potential risk factors, such as gender, age, multifocality, tumor size, histologic variants, background thyroid conditions leading to thyroidectomy and their association with PTMC lymph node metastasis at diagnosis.

2. Materials and methods

2.1. Study population

After obtaining Rush University Medical Center Institutional Review Board's approval, we conducted a retrospective study in patients with papillary thyroid microcarcinomas less than or equal to 5 mm in size. The patients included in the study were diagnosed between October 2003 and February 2018 at Rush University Medical Center in Chicago. A total of 182 patients were identified and studied for their clinicopathological features.

2.2. Study design

One hundred eighty-two cases of papillary thyroid microcarcinoma ≤5 mm were identified in our institutional electronic surgical pathology archives based on SNOMED (Systematized Nomenclature of Medicine-Clinical Terms) code search in CoPath Plus (Cerner Corporation). Clinical and pathologic materials were reviewed by two pathologists. All relevant clinical information including age, gender, past medical history, surgery records, histopathologic results and clinical follow-up results were retrieved from patients' electronic medical records in EPIC (Epic Systems Corporation).

2.3. Statistics

Frequencies and percentages were calculated for categorical variables. $\chi 2$ analysis was used to compare the association between categorical variables and outcomes. The continuous variables were compared with unpaired *t*-test. Comparison of dependent proportions was calculated with binomial test. A *P*-value < 0.05 was considered significant and all statistical analyses were conducted using GraphPad Prism 7 (GraphPad Software).

3. Results

The following are the overall patient characteristics: A total of 182 patients with papillary thyroid microcarcinoma with a diameter less than or equal to 5 mm were identified with a female to male ratio of 3.4:1.0. There were 141 females (77.5%) and 41 males (22.5%). The prevalence of small PTMCs (≤5 mm) appeared to be significantly higher in females ($P < 0.001$). The mean age at diagnosis was 53.5 (range 14 to 83) years. The average age was 54 years for females and 53 years for males ($P > 0.05$). About 76% of small PTMCs (139 of 182 cases) occurred in patients older than 45 years. The clinicopathologic features of small PTMCs are summarized in Table 1.

Most of small PTMCs were not detected at clinical examination and were diagnosed incidentally during pathologic examination of thyroid specimens resected for benign thyroid diseases (89%, 162 of 182 cases). Only 14 of 182 cases of PTMC were detected presurgically by ultrasound-guided thyroid FNA cytology (7.7%). The most common benign conditions that led to thyroidectomy or lobectomy were: Goiter (45.6%, 83 of 182 cases), Hashimoto's thyroiditis (19.2%, 35 of 182 cases), follicular adenomas (18.1%, 33 of 182 cases), parathyroid adenoma (4.4%, 8 of 182 cases) and Graves' disease (1.6%, 3 of 182 cases). 17 of 182 thyroidectomies were performed for thyroid malignancies (9.3%), including 14 cases of papillary thyroid carcinoma- all cases confirmed as PTMC on thyroidectomy specimen, 2 cases of follicular carcinoma and 1 case of medullary carcinoma. 3 of 182 thyroidectomies (1.6%) were performed for non-thyroid primary malignancies, including 1 case of metastatic lung adenocarcinoma to thyroid, 1 case of parathyroid carcinoma and 1 case of squamous carcinoma of larynx.

Table 1
Clinicopathologic features of papillary thyroid microcarcinoma ≤5 mm in size.

	Total of patients (n = 182)	Percentage
Age, years		
Mean	53.5	
Range	14 to 83	
Sex		
Male	41	22.5%
Female	141	77.5%
Reason for thyroidectomy		
Benign thyroid diseases	162	89%
Goiter	87	45.6%
Hashimoto's thyroiditis	35	19.2%
Follicular adenoma	33	18.1%
Parathyroid adenoma	4	4.4%
Graves's disease	3	1.6%
Thyroid malignancies	17	9.3%
Papillary thyroid carcinoma	14	7.7%
Follicular carcinoma	2	1.1%
Medullary carcinoma	1	0.5%
Location		
Right thyroid	94	51.6%
Left lobe	60	33.0%
Isthmus	8	4.4%
Pyramidal lobe	2	1.0%
Size of microcarcinoma		
Mean ± SD	2.59 ± 1.49 mm	
Multifocal tumors	39	21.4%
Bilateral involvement	18	10%
Histologic subtypes		
Follicular variant	94	51.9%
Classic type	87	47.5%
Sclerosing variant	1	0.5%
Lymph node sampling	66	36.3%
Lymph node metastasis	15	22.7% of 66 cases

More than half of the small PTMCs involved the right thyroid (51.6%, 94 of 182) with the rest of the cases residing in the left lobe (33.0%, 60 of 182), isthmus (4.4%, 8 of 182) and pyramidal lobe (1.0%, 2 cases). 10% of the cases involved both lobes. 39 of the 182 tumors (21.4%) showed multifocality, including 21 cases of unilateral lesions (11.5%, 13 cases in the right thyroid and 8 cases in the left thyroid) and 18 cases of bilateral multifocal lesions. The average diameter of small PTMCs was 2.59 mm (2.59 ± 1.49 mm, $n = 182$). In some patients tumors as small as 0.2 mm were diagnosed. Small PTMCs were most often follicular variant accounting for 51.9% of the cases, including 4 cases of noninvasive encapsulated follicular variant (2%), with an average size of 2.84 mm (Fig. 1). The classic type papillary microcarcinoma was observed in 47.5% of cases with an average size of 2.26 mm. The sclerosing type was observed in only one thyroid microcarcinoma with a diameter of 2.5 mm. No tall cell variant or columnar cell variant was observed in our study. The average size of follicular variant PTMC appeared to be larger than that of the classic type (2.84 ± 1.43 mm vs. 2.26 ± 1.51 mm, $P = 0.01$).

Thyroid capsule invasion was very infrequently observed in papillary thyroid microcarcinoma, 2 out of 182 cases including one case of

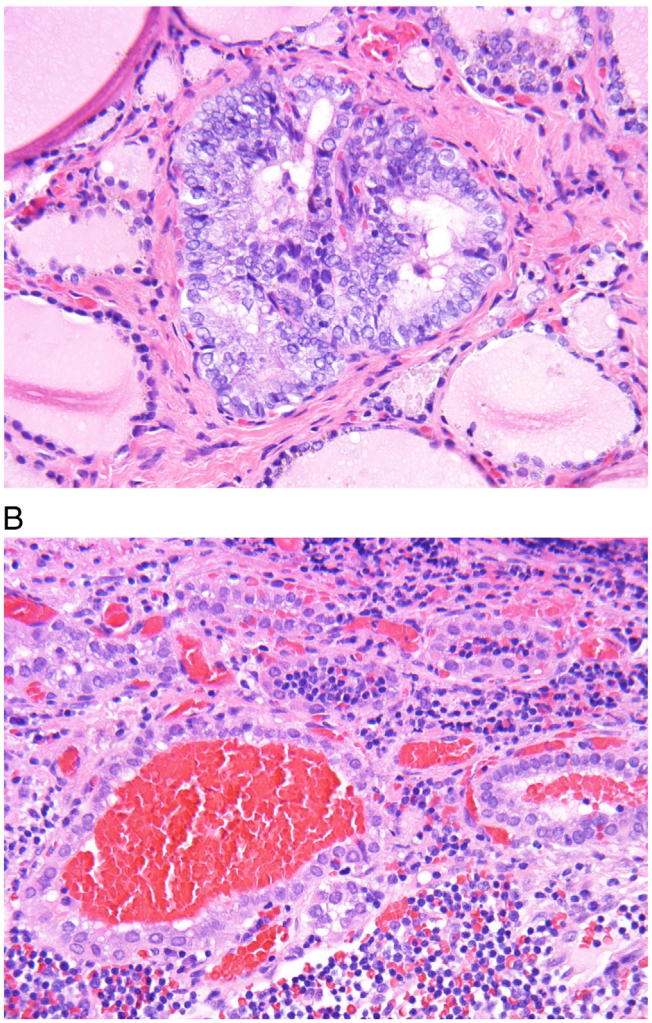

Fig. 1. (A) A 2 mm in size follicular variant of papillary thyroid microcarcinoma with prominent nuclear crowding, enlargement and clearing (40×). (B) A lymph node of the case shows paracortical metastasis with large and irregular nuclei and multiple nuclear pseudoinclusions (40×).

follicular variant and one case of classic type PTMC. No lymphovascular invasion or extrathyroid extension was identified. Twenty-seven thyroidectomies had lymph node tissue identified incidentally on thyroidectomy specimen. In addition, lymph node biopsy was done on 8 cases to identified parathyroid gland due to patients' hyperparathyroidism. Additional 18 cases of thyroidectomy had lymph node biopsies done due to intraoperative findings of enlarged lymph nodes. Furthermore, 13 of 17 cases of presurgically diagnosed thyroid malignancies received selective neck dissection. The average number of lymph nodes examined was 5 (range 1 to 36 lymph nodes). 15 of 66 cases with lymph node samples were found to have nodal metastasis (22.7%). The average size of primary microcarcinoma with lymph node metastasis was 3.2 mm (range 0.5 to 5.0 mm). The average size of node negative small PTMCs was 2.9 mm (range 0.5 to 5.0 mm). No association was found between primary tumor size and lymph node metastasis ($P = 0.42$). 4 of 15 node-positive cases showed primary tumor multifocality compared with that of 11 cases in 51 node negative PTMCs. No difference in rate of lymph node metastasis was found between multifocal and solitary microcarcinomas ($P > 0.05$). Sixty percent of the node positive microcarcinomas were classic type (9 of 15 cases) and 40% were follicular variant (6 of 15 cases). The node negative small PTMCs were 39.2% classic types and 60.8% follicular variant (20 and 31 respectively in 51 cases). No association of histologic types with lymph node metastasis was observed ($P = 0.24$). The mean age of patients with node positive microcarcinoma was 48.5 ± 11.3 years and was not significantly different from that of the node negative microcarcinomas (52.7 ± 14.7, $P = 0.31$). Interestingly, the male to female ratio in the node positive microcarcinomas were significantly higher than that of the node negative patients (1,1.1 vs 1,5.4). In this study 46.7% (7 of 15) of patients with node positive microcarcinomas were male compared with 16% (8 of 51) male in node negative patients ($P = 0.03$). The demographic and clinicopathological characteristics of patients with positive and negative lymph nodes are summarized in Table 2.

Table 2
Demographic and clinicopathological characteristics of patients with nodal metastasis vs. negative lymph nodes.

Parameter	Node positive	Node negative	Significance
Age, years			
Mean ± SD	48.5 ± 11.3	52.7 ± 14.7	P = 0.31
Gender, n (%)			
Male	7 (46.7%)	8 (15.7%)	
Female	8 (53.3%)	43 (84.3%)	P = 0.03
Primary tumor size			
Mean ± SD, mm	3.2 ± 1.8	2.9 ± 1.4	P = 0.42
Histologic subtypes			
Classic type	9 (60.0%)	20 (39.2%)	
Follicular variant	6 (40.0%)	31 (60.8%)	P = 0.23
Multifocal lesions			
Multifocal	4 (26.7%)	11 (21.6)	
Solitary	11 (73.3%)	40 (78.4%)	P = 0.73

The majority of patients were surveillanced without further treatment after thyroidectomy (79.1%). Six patients received completion thyroidectomy and 2 of them showed microcarcinoma in the completion specimen (33.3%). In addition, a total of 32 patients received radioactive iodine ablation (I-131) therapy (17.6%).

4. Discussion

Small PTMCs have been traditionally considered indolent tumors with an excellent prognosis. However, PTMCs have been found to have diverse disease courses and sometimes are capable of spreading to lymph nodes [13]. Our study showed that small PTMCs (≤5 mm) had a regional lymph node metastasis rate of 22.7%, confirming small PTMCs' metastatic potential despite its minute size. Some series have reported a similar rate of lymph node metastasis in about 26% cases of PTMC (< 1.0 cm) with distant metastasis reported in 3% of PTMC patients [14]. In a study of 487 small PTMC patients who received thyroidectomy and lymph node dissection, nodal metastasis was found in 34.9% of cases [15]. Our findings suggest that small PTMC is a malignancy with metastatic potential to lymph nodes and certain cases have regional lymph node involvement despite the small primary tumors.

The most commonly occurring papillary thyroid cancer in the United States is now PTMC in patients older than 45 years [16]. They are found to account for almost 25% of newly diagnosed papillary thyroid carcinomas [16]. 76% thyroid microcarcinomas in our study occurred in patients older than 45 years. In reported series of PTMC (< 5 mm), the age of patients ranged from 22 to 80 years, with an average of 46 years [15]. Interestingly, we observed an even higher average age of patients, 54 for females and 53 for males. The difference might be explained by different patient demographics. Studies have shown a female gender predominance in small PTMC patients (77.4%), similar to the female ratio of 77.5% in our study [15]. Similar findings have been observed for PTMCs < 1.0 cm as well with reported female patient percentage of 82% [17]. The higher prevalence of thyroid microcarcinoma in women might be associated with overall higher

incidence of other thyroid diseases in women which result in more screening procedures and more thyroidectomy that lead to the identification of PTMCs.

Despite higher disease prevalence, female patients with small PTMC were less likely to develop lymph node metastasis, 15.7% vs. 46.7% for males in our study. In a study of the prognostic significance of male gender for papillary thyroid carcinoma and microcarcinoma, male patients were more frequently found to have advanced stage tumor, lymph node metastasis, distant metastasis, extrathyroidal extension and multifocal tumors [18]. In addition, a recent meta-analysis also demonstrated that male gender was a strong prognostic factor with increased risk of PTC recurrence [19]. A study by Guo et al. showed that the incidence of thyroid cancer was more than three times higher in women than man [20]. However, the estimated death rate of women from thyroid cancer was only 1.3 times higher than that in men [21]. Furthermore, in a study of 61,523 adult patients with thyroid cancer from the Surveillance, Epidemiology and End Results (SEER) database of the national cancer institute, male patients were found to have more poorly differentiated and undifferentiated thyroid cancers than their female counterparts [22]. The above findings suggest that male patients have a worse prognosis for papillary thyroid carcinoma may represent more aggressive behavior of PTMC in men, even at a small size, for some currently unknown mechanisms.

Small PTMCs were often multifocal and sometimes involved both thyroid lobes. The mean rate of tumor multifocality in our study was 21.4% and it was 10% for bilateral tumors, similar to other published findings of 22.9% multifocality and 15.7% bilaterality [15]. Currently a lobectomy is the treatment of choice for papillary microcarcinoma, unless there are clear indications to remove the contralateral lobe, such as bilateral tumor involvement, previous history of head and neck radiation, strong family history of thyroid cancer or patient reasons that will make follow up difficult. Our findings that PTMCs are frequently bilateral emphasize the need of close clinical and imaging surveillance on the residual thyroid lobe if lobectomy is performed. Incidentally identified thyroid cancers usually fall in the category of microcarcinomas. An autopsy study of incidental thyroid carcinomas found that the tumor diameter varied from 0.15 mm to 14.0 mm, with 67% of tumors smaller than 1.0 mm [23]. In the current study, we found that follicular variant of PTMC had a higher incidence than classic type microcarcinomas (51.9% vs. 47.5%) and appeared to be larger in size (2.84 mm vs. 2.26 mm). However, no difference in nodal metastasis rate was observed between the two common histologic subtypes. The clinical implications of the larger sizes of follicular variants still need to be determined.

Our findings suggest that certain small PTMCs behave as malignancies with the ability to metastasize to regional lymph nodes. We identified a lymph node metastasis rate of 35% at diagnosis [15]. A study followed a group of 259 patients with PTMC, all of whom underwent lymph node dissection at the time of thyroidectomy [24]. They found that nodal metastasis was higher in patients with palpable lymph nodes at initial presentation. In their follow-up study, prophylactic node dissection in patients without enlarged nodes did not change the overall nodal recurrence rate [24]. The high nodal metastasis rate suggests that patients with small PTMC should be closely monitored for lymph node status presurgically and after thyroidectomy to prevent nodal recurrence.

Small PTMCs are often multifocal and bilateral and histology is commonly both the classical and follicular variant of PTC. While often diagnosed incidentally small PTMC can lead to regional lymph node involvement in a significant portion of cases, and evaluation with diagnostic testing of the regional lymph nodes should be considered in the clinical management of these patients.

Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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