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Multicentricity Is More Common in Thyroid Papillary Microcancer with a Preoperative Diagnosis Compared to Incidental Microcancer

Yalin Iscan Ismail Cem Sormaz Fatih Tunca Yasemin Giles Senyurek

Department of General Surgery, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

Keywords
Multicentricity · Thyroid cancer diagnosis · Thyroid papillary microcancer

Abstract
Objective: Although multicentricity is a common feature of thyroid papillary microcancer, it might be difficult to predict this histopathological feature preoperatively. ***Methods:*** The records of 306 papillary microcancer patients who underwent thyroidectomy were evaluated. Papillary microcancer was diagnosed as an incidental histopathological finding in 242 (group 1), and by preoperative fine-needle aspiration biopsy in 64 (group 2). Demographic data and histopathological features were compared between the two groups. ***Results:*** Age (44 ± 11.4 vs. 43 ± 14 years) and male/female ratio (44/193 vs. 12/52) showed no significant difference between groups 1 and 2 (p > 0.05). Mean tumor size was significantly larger in group 2 (5.2 ± 2.8 mm) compared to group 1 (3.7 ± 2.4 mm) ($p = 0.004$). The frequency of thyroid capsule invasion (44 vs. 19%, $p = 0.0001$), microscopic extrathyroidal invasion (25 vs. 10%, $p = 0.004$) and multicentricity (44 vs. 29%, $p = 0.04$), and bilateral lobar involvement (22 vs. 10%, $p = 0.0001$) was significantly higher in group 2 compared to group 1. ***Conclusion:*** Multicentricity with bilateral lobar involvement and aggressive histopathological features are more frequent in papillary microcancer patients diagnosed with preoperative fine-needle aspiration biopsy compared to papillary microcancer diagnosed as postoperative incidental histopathological finding.

Introduction

Papillary carcinoma is the most common histopathologic type of malignancy of the thyroid [1]. Papillary microcarcinoma (PMC) is defined as a thyroid cancer measuring ≤1 cm in greatest diameter by the World Health Organization [2]. Most of these tumors are nonpalpable and clinically inapparent and diagnosed incidentally during the pathological examination of a thyroid specimen after surgery. However, over the last few decades, the technical improvement in thyroid ultrasonography (US) and the widespread use of fine-needle aspiration biopsy (FNAB) provided to identify PMC preoperatively [1, 3].

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E-Mail karger@karger.com
www.karger.com/etj

Yalin Iscan
Department of General Surgery, Istanbul Faculty of Medicine
Istanbul University, Turgut Özal Cad.
TR–34390 Fatih/Istanbul (Turkey)
E-Mail yaliniscan@gmail.com

In autopsy studies, the pathological detection rate of clinically occult papillary carcinoma has been in the range of 5.6 to 35.6% [4, 5] but such tumors were definitely occult and not life threatening for these patients. The incidence of PMC has increased in recent years due to thinner histopathologic slices, advances in US and FNAB, iodine deficiency, ionized radiation, and hormonal, dietary, and environmental factors [6]. The prognosis of PMC is generally excellent, but the disease may have an aggressive behavior in a group of patients with local or distant metastasis, recurrence after surgery, and eventually death of the patients in 0.6% of the cases [7–11]. The management of PMC in the literature may vary from active surveillance without surgery in selected patients to a total thyroidectomy with or without radioactive iodine treatment [12]. Lobectomy alone was suggested to be a sufficient treatment for unifocal, intrathyroidal PMC in patients without prior head and neck irradiation or any evidence of lymph node involvement or distant metastasis [10]. Total thyroidectomy has been recommended for multifocal PMC [13]. However, in PMC diagnosed by preoperative FNAB of a subcentimeter nodule, it is difficult to predict histopathological features of the tumor, including multifocality, preoperatively. In such PMC cases with a preoperative diagnosis but no evidence of regional or distant metastasis, it is a challenge to decide on the extent of surgery. Some authors discovered that multifocality, extrathyroidal extension of the tumor, lymph node metastasis, and distant metastasis were more frequent in nonincidental than in incidental PMC [14, 15]. However, others observed no significant clinicopathological differences between incidental and nonincidental PMC patients [16]. In papillary thyroid carcinoma (PTC) patients, multifocality in one thyroid lobe was found to be a significant risk factor for contralateral disease, independent of tumor size [17]. In studies including large numbers of PMC patients, the rate of multifocality ranges from 9.2 to 32% and that of bilateral disease from 8.1 to 25.6% [7, 12, 14, 16–20]. Most, but not all, studies of PMC have observed increased cancer recurrence when multifocal as opposed to unifocal disease is present [7, 15, 21]. Multicentricity was also reported to be a risk factor for lymph node metastasis [21, 22].

The aim of this study was to evaluate the rate of multicentricity and bilobar involvement in patients with incidental and nonincidental PMC.

Materials and Methods

The medical records of 306 papillary microcancer patients who underwent thyroidectomy between January 1998 and February 2012 in the Department of General Surgery, Istanbul Faculty of Medicine, were evaluated retrospectively. Papillary microcancer was diagnosed as an incidental histopathological finding in 242 (group 1) and by preoperative FNAB in 64 (group 2) patients.

Ultrasonography was performed in all patients before surgery. FNAB was performed in patients who were found to have nodules or lymph nodes suspicious for malignancy. Of the 242 patients in group 1, 133 (54%) underwent total and 109 (46%) underwent near-total thyroidectomy for presumed benign nodular goiter. In group 2, 49 (76.5%) patients with no preoperative or intraoperative evidence of lymph node metastasis underwent total thyroidectomy and ipsilateral prophylactic central neck dissection (CND) which included prelaryngeal, pretracheal, and ipsilateral paratracheal regions. The remaining 15 (23.5%) patients had enlarged lateral cervical lymph nodes which proved to be metastatic by FNAB cytology.

Total thyroidectomy with unilateral ($n = 14$) or bilateral ($n = 1$) modified radical neck dissection and bilateral therapeutic CND was performed in these 15 patients. Demographic data (age and gender) and histopathological features (mean tumor size, thyroid capsule invasion, microscopic extrathyroidal invasion, multicentricity, and bilateral lobar involvement) were compared between the two groups with incidental and nonincidental PMC. The histopathological features were also re-evaluated after the stratification of PMC according to the tumor size (≤5 mm vs. > 5 mm).

Statistical Analysis

Results are expressed as mean ± standard deviation. SPSS 16.0 (SPPS Inc., Chicago, IL, USA) was used for the statistical analysis. The Pearson χ^2 test, Fisher exact test, and *t* test were used to perform the analysis. A p value <0.05 was considered to be statistically significant.

Results

The mean age in groups 1 and 2 were 44 ± 11.4 versus 43 ± 14 years, respectively ($p = 0.8$). The female/male ratios in group 1 (47/195) and group 2 (12/52) were not statistically different ($p = 0.9$).

The mean tumor size was 4.0 ± 2.6 mm. The most common histopathological subgroup was classical variant PMC (n = 227, 74%). Follicular variant PMC was found in 74 (24%), tall cell variant in 4 (1%) patients, and diffuse sclerosing subtype in 1 (0.3%) patient. Of these 306 patients, 99 (32%) had multicentric tumors. Bilateral multicentric tumors were observed in 38 (12.4%) patients.

The histopathological features of PMC in groups 1 and 2 are summarized in Table 1. Mean tumor size was significantly larger in group 2 (5.2 ± 2.8 mm) compared to group 1 (3.7 ± 2.4 mm) ($p = 0.004$). The rate of micro-

Table 1. Histopathological features in group 1 and group 2

	Group 1 (n = 242)	Group 2 (n = 64)	p
Tumor diameter, mm	3.7±2.4	5.2±2.8	0.004
Extrathyroidal invasion	24 (9.9)	16 (25)	0.004
Thyroid capsule invasion	47 (19.4)	28 (43.8)	<0.0001
Multicentricity	71 (29.3)	28 (43.8)	0.04
Vascular invasion	6 (2.5)	3 (4.7)	0.4
Bilateral lobar involvement	24 (10)	14 (22)	0.0001
Lymph node metastasis	5 (2)	19 (29.6)	0.0001

Data are presented as mean ± SD or n (%), as appropriate.

Table 2. Histopathological features after re-grouping according to tumor diameter (≥5 mm and <5 mm)

	≥5 mm (n= 132)	<5 mm (n= 174)	p
Extrathyroidal invasion	24 (18.2)	16 (9.2)	<0.001
Thyroid capsule invasion	52 (39.4)	32 (18.4)	<0.0001
Multicentricity	59 (44.7)	40 (23)	<0.001
Bilateral lobar involvement	29 (22)	9 (5)	0.0001
Lymph node metastasis	17 (15)	7 (4.8)	0.005

Data are presented as n (%).

scopic extrathyroidal invasion was 10 and 25% in groups 1 and 2, respectively (p = 0.004). Thyroid capsule invasion was observed in 47 (19.4%) patients in group1 and in 28 (43.8%) in group 2 (p = 0.0001). The rates of multicentric tumors in group 1 and 2 were 29.3 and 43.8%, respectively (p = 0.04). Bilateral lobar involvement was found in 24 (10%) patients in group 1 and in 14 (22%) patients in group 2 (p = 0.0001). The rate of vascular invasion showed no statistical significance between the two groups (p = 0.4) (Table 1).

A total of 24 patients had lymph node metastasis. Central lymph node metastasis was found incidentally in 5 (2%) patients in group 1 (adjacent to the thyroid specimen). In group 2, lymph node metastasis was found in 19 (29.6%) patients. Of these 19 patients, 15 had both central and lateral lymph node metastasis, while 4 had only central lymph node metastasis. The rate of lymph node metastasis was significantly higher in group 2 compared to group 1 (29.6 vs. 2%, respectively; p < 0.0001). The rate of lymph node metastasis in 99 PMC patients with multicentric tumors was 14% (n = 14), whereas it was 4.8% (n = 10) in 207 patients with unifocal PMC (p = 0.005).

The histopathological features were re-analyzed after the stratification of PMC according to the tumor size with a 5-mm threshold. Of 306 patients, 132 (43%) had PMC ≥5 mm while the tumor size was <5 mm in the remaining 174 (57%) patients. The rates of multicentricity, bilateral lobar involvement, microscopic extrathyroidal invasion, lymph node metastasis, and thyroid capsule invasion were significantly higher in tumors ≥5 mm compared to those <5 mm (Table 2). Of the patients with PMC ≥5 mm, 44.7% had multicentric tumors and 22% had bilateral multicentricity.

Only 1 (1.5%) patient in group 2 has central compartment recurrence. This patient had both central and lateral cervical lymph node metastasis at the time of initial diagnosis and underwent reoperation for excision of the recurrent lymph node 16 months after the first operation. There was no significant difference in recurrence rates between groups.

Discussion/Conclusion

Over the past decades, the incidence of papillary thyroid cancer increased significantly, and the rate of increase was most prominent in PMC [23]. Improved detection of PMC with wide use of neck imaging tests and FNAB, and application of increased number of histopathological slices per thyroidectomy specimen had significant impact on the increased incidence of PMC [13, 24, 25]. The prognosis of PMC is excellent with a 15-year survival rate of 99.3% [26]. Although PMC generally seems to have an indolent course, as many as 10.3% of the patients experience locoregional recurrence and 2.5% experience distant metastasis. Ito et al. [27] reported the results of active surveillance in 1,235 PMC patients during an average follow-up period of 60 months. Nodule size enlargement, development of lymph node metastasis, and progression of disease was observed in 4.6, 1.5, and 3.5% of the patients, respectively, during the period of surveillance. Of these patients, 191 (15.5%) underwent surgery for various reasons. None of the patients in this series developed distant metastasis or died due to PMC. The authors suggested that active surveillance might be an option in well-selected PMC patients.

PTC is the most common thyroid malignancy. Clinically occult thyroid cancer is diagnosed with greater frequency due to the advancement of US imaging and FNAB for incidentally detected nonpalpable thyroid nodules. In

some cases, clinical features still remain uncertain. There is controversy with respect to their clinical manifestation, molecular and biological behavior, prognosis, and surgical management [22–28]. Ito et al. [29] concluded that most microcarcinomas can be followed up without immediate surgical treatment but they also suggested that US-diagnosed lateral metastasis may have an aggressive character and a surgical procedure with nodal dissection should be performed. The decision on the extent of surgery in a setting of malignant cytology in a nodule ≤1 cm is a challenge for the surgeon. Lobectomy is recommended for unifocal and intrathyroidal PMC in patients with no previous head and neck irradiation, family history of thyroid cancer, and evidence of lymph node or distant metastasis [10]. These criteria solve the problem mainly in patients who underwent surgery for presumed benign goiter and where incidental PMC was detected during the pathological examination of the thyroidectomy specimen. In such cases, it is possible to evaluate the histopathological features of PMC and to consider completion thyroidectomy or RAI ablation treatment according to the individual risk factors of the patient. However, it is often not possible to predict multifocality as well as bilateral multifocal disease, extrathyroidal extension, or vascular invasion of the tumor when papillary carcinoma is diagnosed nonincidentally by FNAB of a subcentimeter nodule. Unilateral lobectomy in PMC patients without extrathyroidal extension and node negativity has been suggested by the American Thyroid Association [10]. In addition, Noguchi et al. [11], from an analysis of 867 patients affected by PMC, concluded that total thyroidectomy is not necessary. Because of the lack of randomized studies, temporal changes in diagnosis and surgical practice, and different reports on postoperative radioiodine treatment, surgeons focused on the histopathological behavior of aggressive subgroups in retrospective studies.

In the literature, the reported rates of extrathyroidal extension, bilateral multifocal disease, and multifocality have been as high as 62.1, 48, and 56.8%, respectively [30–32]. Molecular profiling of multifocal PMC demonstrated that more than 60% of such tumors were multiple synchronous tumors rather than intrathyroidal dissemination of a single primary tumor [33, 34]. Multifocality in one lobe has been found to be an independent predictive factor for bilateral disease in PMC [17, 19]. The rate of lymph node recurrence has increased 5.6-fold in PMC when multifocality was present at diagnosis [21]. Tumor size was observed to be a significant prognostic factor in PMC. In PMC ≥5 mm, the rates of bilateral disease, extrathyroidal extension, and lymph node metastasis were found to be higher compared to those of smaller-sized PMC [11, 19, 21, 35]. Noguchi et al. [11] documented that tumor size >5 mm and the presence of extrathyroidal extension significantly decreased the recurrence-free survival rate during a mean follow-up of 16.5 years. In our study, we observed higher rates of bilateral multifocal disease, extrathyroidal extension, thyroid capsule invasion, and lymph node metastasis in nonincidental PMC or PMC ≥5 mm as opposed to incidental PMC or PMC <5 mm. In our patients, the presence of multicentricity was significantly associated with increased rate of lymph node metastasis.

Several studies have analyzed the clinicopathological features and outcome of incidental and nonincidental PTC [14–16]. Pellegriti et al. [14] investigated the clinical behavior and outcome of 299 patients with PTC <1.5 cm in diameter. In their study, PMC patients constituted 62.5% of the cases, and lymph node metastasis at presentation, multifocality, and nonincidental diagnosis were significantly associated with persistent or recurrent disease. In the study by Roti et al. [16], clinicopathological features of PMC patients showed no significant difference according to the type of initial diagnosis, whereas tumor size >8 mm was associated with increased rate of distant metastasis at initial presentation.

The main goal of thyroid cancer surgery is to remove the tumor completely and to minimize the risk of recurrent disease. In multifocal PMC, rest tumor might be left in when lobectomy is performed. Therefore, total thyroidectomy is recommended for multifocal tumors. In our study, the rate of bilateral multifocal tumor was significantly higher in PMC patients who were diagnosed with thyroid FNAB compared to those with incidental PMC. Age and gender of our patients with a preoperative diagnosis had no predictive value for multifocal disease.

Hay et al. [18] observed 900 PMC patients who had initial surgical treatment at the Mayo Clinic for a mean period of 17.2 years. In this study the majority of patients underwent bilobar resection for PMC and 15% received unilateral lobectomy. The authors documented that multifocality and lymph node metastasis were significant risk factors for recurrence, but the extent of surgery and postoperative RAI ablation had no impact on the rate of recurrence. Contrary to the findings of Hay et al. [18], Pelizzo et al. [7] found that in PMC patients who underwent partial thyroidectomy, the probability of recurrence was 2-fold higher than in patients treated with total thyroidectomy and radioactive iodine, especially for PMC ≥5 mm. The difference in the outcome of PMC patients between these two studies is probably associated with postoperative management and criteria to define recurrence during follow-up. In

the study by Hay et al. [18], 17% of PMC patients received postoperative RAI ablation treatment, and structural recurrence was reported during follow-up. However, in the study by Pelizzo et al. [7] 64.5% of PMC patients received postoperative radioactive iodine treatment, and disease-free status was considered as serum triglyceride level <2 ng/dL, independent of the findings by imaging modalities.

In a study by Yu et al. [26], analysis of 18,445 PMC patients who were surgically treated revealed that African-American or minority race, male gender, age >45 years, extrathyroidal extension of tumor, lymph node metastasis, and distant metastasis were significant adverse prognostic factors in PMC patients. The authors documented that PMC patients with two or more of these risk factors had better prognosis if total thyroidectomy was performed compared to either near-total thyroidectomy or lobectomy. Cramer et al. [23] examined the trends of incidence and surgical treatment in PTC from 1973 to 2006. The authors documented that the incidence of papillary thyroid cancer increased 2.6-fold from 1973 to 2006, and PMC increased the most by 19.2% per year. Between 1987 and 2006, the percentage of total thyroidectomies was found to increase from 27 to 82.6%, whereas the percentage of partial thyroidectomies decreased from 20.5 to 13.5%. These data suggest that the surgical trend in PTC has changed towards total thyroidectomy in spite of the rising incidence of PMC, and most PMC patients have been treated with total thyroidectomy. RAI ablation is not recommended in multifocal PMC if the patient does not have prognostic risk factors such as vascular invasion, lymph node metastasis, distant metastasis, gross extrathyroidal extension, or aggressive subtype of PTC. In our study, PMC which was diagnosed by FNAB of a subcentimeter thyroid nodule was significantly associated with larger tumor size (≥5 mm) compared to incidental PMC; and PMC ≥5 mm was significantly associated with microscopic extrathyroidal extension, multicentricity with bilobar involvement, and lymph node metastasis. Although there is inadequate data about the impact of postoperative RAI ablation on the outcome in PMC patients with unfavorable histopathological features, individualized decision to selective use of RAI ablation was suggested to facilitate the follow-up in such patients. As TSH stimulation enhances RAI uptake of remnant thyroid tissue, TSH >30 mU/L is advocated for optimal ablation therapy. Therefore, for patients in whom postoperative RAI is considered, total or near-total thyroidectomy should be performed.

There are some limitations of the study. First, this was a retrospective study. We compared the histopathological features and recurrence rate in patients with incidental and nonincidental PMC. The patients who underwent surgery for presumed benign goiter and were found to have incidental PMC did not undergo prophylactic CND, while CND was routinely performed in patients with a preoperative diagnosis. Therefore, we could not compare the rate of subclinical central compartment metastasis in incidental and nonincidental PMC, nor could we analyze the histopathological factors influencing the rate of subclinical central metastasis.

In conclusion, in nonincidental PMC ≥5 mm, there might be an increased risk of bilateral multifocal disease, microscopic extrathyroidal extension, and lymph node metastasis. During the decision-making course about the management of a subcentimeter nodule with papillary cancer cytology, it should be kept in mind that tumor size ≥5 mm might be significantly associated with bilobar multicentric tumors, as well as other adverse histopathological features.

Statement of Ethics

Ethical approval was obtained from the local ethics committee of Istanbul Faculty of Medicine.

Disclosure Statement

The authors have no conflicts of interest to declare.

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