

The Characteristic Clinical and Pathological Features of Incidental and Non-Incidental Papillary Microcarcinoma of the Thyroid

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Abstract- The incidence of papillary microcarcinoma (PMC) keeps raising due to fine needle aspiration (FNA) biopsies and the pathologic evaluation of thyroid specimens of cases operated for benign thyroid disorders. The files of 78 patients who underwent surgery between January 2006 and May 2013 in our department and were diagnosed with PMC were analyzed, retrospectively. Cases were grouped as incidental and non-incidental depending on the preoperative diagnosis. The diameter of the nodules in the preoperative ultrasonographic examination, pathological parameters such as tumor size, bilaterality, multifocality, and capsular invasion were found significantly high in non-incidental group ($P < 0.05$). No significant difference was detected between the two groups' age, sex, and vascular invasion. Preoperative radiologic examination by experienced radiologists and FNA performed for suspicious nodules may increase the rate of early and correct diagnosis. In our opinion, determining the most useful criteria for malignancy will help to detect incidental PMC in cases followed up for multinodular goiter.

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Introduction

The evaluation of patients and determination of the surgical procedures in surgery of thyroid cancer are still being argued depending on the high-resolution ultrasonography and revisions of classification systems in fine needle aspiration (FNA) biopsies. About 85% of thyroid cancers are papillary carcinomas, and 30-50% of them are microcarcinomas (1). Papillary microcarcinoma (PMC), first described by the World Health Organization (WHO) in the late 1980s, is defined as papillary thyroid carcinoma with a size of < 1 cm (2).

In autopsy series of endocrine unrelated deaths, PMC was diagnosed with a rate of 36% (3). In surgical series, PMC was detected in 24% of thyroidectomies performed due to benign thyroid disorders.

Most of the PMCs are unpalpable and detected incidentally in radiologic examinations or during the evaluation of thyroidectomies of benign conditions. However, FNAs from clinically suspicious thyroid masses or the presence of metastatic cervical lymph nodes help the preoperative diagnosis of PMC.

Prognostic factors such as lymph node metastasis,

multifocality and capsular invasion of the thyroid are the major differences of PMCs between suspicious nodules and undoubtful cases. In this article, we aimed to discuss the prognostic factors and diagnostic approaches that could be helpful in the preoperative diagnosis of PMC.

Materials and Methods

In this retrospective study, 78 PMC patients underwent surgical treatment at İzmir Katip Çelebi University Atatürk Training and Research Hospital, Department of Surgery. The patients were divided into 2 groups; patients in group 1 incidental ($n=25$), and those in group 2 had non-incidental PMC ($n=53$). Incidental PMC was defined as a postsurgical diagnosis of microcarcinoma with benign clinical course. Non-incidental PMC was defined by histopathology before the operation by fine-needle aspiration biopsy. Our database included age, sex, surgical procedure, clinical characteristics, and pathologic examination, including tumor size, multifocality, bilaterality, vascular and capsular invasion.

Our department has a routine treatment for the

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thyroid disease. We only operate patients with thyroid nodules more than 10 mm or whose fine-needle aspiration biopsy is positive. Patients diagnosed as PMC before the operation received a near total or total thyroidectomy with central cervical lymph node dissection.

We aimed to find the characteristic clinical and pathological features of incidental and non-incidental thyroid PMCs. SPSS version 15.0 (SPSS, Inc, Chicago, IL) was used for statistically significant. The statistical analysis is done. Chi-Square and Fisher's exact test was used for comparing groups of categorical data and Mann-Whitney U test for groups with continuous data. Univariate logistic regression analysis was used for testing the relationship between clinical risk factors and malignancy. $P < 0.05$ were considered statistically significant.

Consent from the Ethical Committee of İzmir Katip

Çelebi University Atatürk Training and Research Hospital.

Results

Among 78 cases, 25 were incidental papillary microcarcinomas, whilst 53 were non-incidental. Fifteen (19.2%) were men, and 63 (80.8%) were women. In incidental and non-incidental group, 5 and 10 patients were men, respectively. No significant difference was detected for sex between the two groups ($P > 0.05$). In incidental group, the mean age was 48.76 ± 11.973 whilst, the mean age was 49.51 ± 9.47 in the non-incidental group, and the difference was not significant even when the patients were also sub-grouped as < 45 and ≥ 45 (Table 1).

Table 1. Presentations of PMC in 2 groups.

		Incidental Group (n=25)	Non-incidental Group (n=53)	Total (n=78)	P
		n (%)	n (%)	n (%)	
Sex	Male	5 (20)	10 (18,9)	15 (19,2)	>0,05
	Female	20 (80)	43 (81,1)	63 (80,8)	
	Mean (Range)	$48,76 \pm 11,973$ (29-70)	$49,51 \pm 9,47$ (26-66)	$49,27 \pm 10,27$ (26-70)	>0,05
Age	45 ≤	12 (48)	16 (30,2)	28 (35,9)	>0,05
	45 >	13 (52)	37 (69,8)	50 (64,1)	
Size of nodule	Mean (Range)	$0,59 \pm 0,09$ (0,2-0,8)	$0,82 \pm 0,05$ (0,3-0,8)	$0,72 \pm 0,99$ (0,2-0,8)	<0,05
Size of tumor	Mean (Range)	$0,52 \pm 0,22$ (0,2-0,8)	$0,61 \pm 0,22$ (0,2-0,8)	$0,55 \pm 0,22$ (0,2-0,8)	>0,05
	<5 mm	8 (32)	8 (16)	16 (21)	<0,05
	≥5 mm	17 (68)	45 (84)	62 (79)	
Bilaterality	Yes	5 (20)	19 (36)	24 (31)	<0,05
	No	20 (80)	34 (64)	54 (69)	
Multifocality	Yes	7 (28)	29 (54)	36 (46)	<0,05
	No	18 (72)	24 (46)	42 (54)	
Vascular invasion	Yes	3 (12)	1 (1,9)	4 (5,1)	>0,05
	No	22 (88)	52 (98,1)	74 (94,9)	
Capsular invasion	Yes	2 (8)	16 (30)	18 (23)	<0,05
	No	23 (92)	37 (70)	60 (77)	

The preoperative diameter of the patients' nodules was 1.42 ± 0.99 cm, and in the incidental and non-incidental group, the mean diameters of the nodules were measured as 0.59 ± 0.09 cm and 0.82 ± 0.05 cm, respectively. Statistically, significant relationship was found between the two groups for the diameter of the nodules. In the pathologic evaluation, for all cases, the

mean size of the tumor was measured as 0.55 ± 0.22 cm, in the incidental group as 0.52 ± 0.22 cm and in the non-incidental group as 0.61 ± 0.22 cm. When the size of the tumor was sub-grouped as < 0.5 cm and ≥ 0.5 cm, the difference was significant between incidental and non-incidental group (Table 1).

Bilaterality was found as a significant factor with 5

(20%) cases in the incidental group and 19 (36%) cases in non-incidental group ($P<0.05$). Seven cases (28%) in the incidental group had multifocal tumor whilst 29 (54%) patients in the non-incidental group had multifocal tumor with a significant difference ($P<0.05$). Vascular invasion was detected in 3 (12%) of incidental tumors and only 1 case (1.9%) in the non-incidental group, but the difference was not statistically significant. However, the capsular invasion was found in 2 (8%) of incidental tumors and 16 (30%) of non-incidental tumors with a significant difference between the groups ($P<0.05$) (Table).

Discussion

The wide spread use of neck ultrasound has allowed the detection of non-palpable thyroid nodules as small as 1-3 mm. When these nodules are included, the incidence of thyroid nodules may be as high as 70% in the general population (5).

Papillary thyroid carcinomas which form more than 90% of 44670 thyroid cancer cases of the USA in 2010 are the most common type of thyroid malignancies (5). The revised incidence of age was doubled in the last 25 years (6). Incidental papillary thyroid microcarcinomas were detected in 27, 4 % of thyroidectomies performed for benign thyroid disorders such as multinodular goiter and chronic thyroiditis (7). Papillary thyroid cancer has the most favorable outcome among all malignancies with a 10-year survival rate of 93% (8).

PMCs are defined by WHO as PMCs with a size of ≤ 1 cm. PMC was detected in 2, 3-5, 2% in autopsy series of cases died of extrathyroidal reasons (3,9). PMCs are reported as the most common histological type among thyroid cancers (4,10). Bramley *et al.*, (11) were found the incidence of PMC as 0, 8-10, 8% in thyroidectomies performed for goiter. Vasileiadis *et al.*, (12) also reported the rate of PMC as 12% in total thyroidectomies.

Roti *et al.*, (13) discussed the clinical and histological features of 243 PMCs grouped as 52 incidental cases and 191 non-incidental cases. The biological behavior of the tumors, age, and sex showed similar results between the groups. Bo-Yean Kim *et al.*, (14) reported male sex as a poor prognostic factor. However, Roh *et al.*, (15,16) declared as male sex was not a poor prognostic factor in addition to the non-significant relationship between male sex and central lymph node metastasis. Londero *et al.*, (17) suggested that non-incidental PMCs are more commonly seen in male patients. In our study, PMCs were detected more in

female patients, but no significant relationship was found between incidental and non-incidental groups.

Age was shown as a prognostic factor in papillary thyroid cancers, but there is not enough study in the literature discussing age as a prognostic factor in PMCs (12,15,18,19). Roh *et al.*, (20) reported that age is not a prognostic factor in the univariate or multivariate analysis of a prospective study of 142 cases according to prophylactic central lymph node dissection is performed or not. In the study of Lombardi *et al.*, (21) central lymph node metastasis was found to be higher in younger patients. In English literature, patients younger than 45 years were reported to have a higher incidence of PMC (17,22). In our study, PMC was detected in patients older than 45 years however this relationship was not statistically significant between incidental and non-incidental tumors.

The size of PMCs was reported as higher than 0, 5 cm in 26-79% of cases in the literature with a mean diameter of 0, 41-0,8 cm (4,23,24). Tumor size over 0, 5 cm was found to be relevant with non-incidental PMCs (12,17,22). Lymph node metastasis was higher in cases with a tumor size over 0.5 cm in a study of Kasai *et al.*, in which 78 PMCs were sub-grouped as $<0,5$ cm and $\geq 0,5$ cm (25).

In addition to this, tumor size was found to be relevant to bilaterality, multifocality, extrathyroidal invasion, and lymph node metastasis in the study of Pellegriti *et al.*, in which tumors <1 cm and 1, 1-1, 5 cm were compared (26). On the other hand, distant metastasis and vascular invasion were found to be relevant to the biological behavior of the tumor rather than the size (26). In our study, tumor size was measured by ultrasonography and the tumors over 0, 5 cm was statistically significant in the non-incidental group. This might be related to the rise of the identification of the tumors with larger sizes.

The rate of multifocality and bilaterality for PMCs were reported as 7, 1-56, 8% and 20-35% in the literature, respectively (4,12,27,28,29). In our study, we found the rate of multifocality as 46% similar to the literature. Multifocality can be limited to one lobe or can be found bilaterally. Lesions can be explained with intraglandular metastasis or can arise from different origin (30). Some studies showed that multifocality is not related to incidental PMCs, vice versa (13,27,28,31). Barnaro *et al.*, (23) evaluated incidental (n=12) and non-incidental (n=128) PMCs for prognostic factors such as multifocality, lymph node metastasis, and capsular invasion and found that multifocality was seen less in incidental PMCs (23). Londero *et al.*, (17) found the rate

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of multifocality higher in non-incident papillary microcarcinomas (PMCs). Vasileiadis *et al.*, (12) also stated that bilaterality is more common in non-incident papillary microcarcinomas. In our study, we found that multifocality and bilaterality were significantly higher in non-incident papillary microcarcinomas. This can be related to the rise of the risk for multifocality and bilaterality in larger tumors.

Capsular invasion of the thyroid was reported to be one of the poorest prognostic factors which increase the risk of recurrence (4,28). Vasileiadis *et al.*, (12) detected capsular invasion in 31% of non-incident papillary microcarcinomas and 2% of incident papillary microcarcinomas. Barbaro *et al.*, (23) stated that none of the incident tumors show lymph node metastasis and capsular invasion. We detected that capsular invasion is more common in non-incident tumors, but the effect of capsular invasion could not be clarified because of the short follow-up time of the cases.

Despite the excellent prognosis of PMC, the rate of mortality was reported as nearly 1% in the literature (4). All of our cases were alive at the time of the study.

The weak sides of this study can be counted as being a retrospective, single-center study investigating clinicopathological parameters but with no long term follow-up and including patients examined by different radiologists, operated by different surgeons and specimens and FNAs evaluated by different pathologists.

In conclusion, PMC is a type of cancer with excellent prognosis; however, the high rate of lymph node metastasis led to discussing on treatment options. Unfortunately, there is no such marker that can determine the risk of malignancy in <1 cm nodules. Many different predictive factors were stated for aggressive behavior in different studies, but no such study existed in the literature for PMCs.

In our study, the large size of the tumor, bilaterality, multifocality and capsular invasion is found statistically relevant for non-incident papillary microcarcinomas. But only one of these factors, tumor size, can be detected preoperatively and is not predictable for PMC diagnosis alone. We think that preoperative radiological examination with experienced radiologists for revealing suspicious nodules and performing FNA will increase the rate of non-incident PMC cases. In addition to this, many studies with randomized larger number of cases are needed to determine the predictive factors for PMCs.

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