

RESEARCH ARTICLE

High-risk morphological features are less prevalent among small (<5mm) papillary thyroid microcarcinomas compared to larger (≥5mm) tumors: a study of 206 cases

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Introduction: Papillary thyroid microcarcinoma (PTMC) is defined as a PTC measuring 1 cm or less, incidentally discovered. The aim of this study was to determine whether small (<5mm) tumors by contrast with large (≥5mm) ones are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness. **Materials and methods:** All consecutive PTMC cases registered at the Department of Pathology, Târgu-Mureș Emergency County Hospital between 2003-2014 were reviewed. The following have been assessed: tumor size, subcapsular versus nonsubcapsular location, extrathyroidal extension/invasion into the perithyroidal adipose tissue, multifocality, resection margins, lymph node involvement, histological variant, tumor border, stromal reaction (fibrosis/desmoplasia/sclerosis), presence of plump pink cells, nuclear features of the tumor cells, intratumoral lymphocytic infiltrate, multinucleated giant cells, psammoma bodies and stromal calcification. The cases were split in two categories: small (< 5mm) and large (≥ 5mm) PTMCs and the pathological features were evaluated in comparison. **Results:** Our study included 206 cases, 91 large and 115 small PTMCs, respectively. Large PTMCs were significantly associated with the presence of plump pink cells ($p=0.002$), well developed PTC nuclear features ($p=0.003$), stromal reaction (fibrosis/desmoplasia/sclerosis) ($p<0.001$), infiltrative tumor border ($p=0.011$), subcapsular location ($p<0.001$), positive resection margins ($p=0.022$), stromal calcifications ($p<0.001$) and intratumoral multinucleated giant cells ($p<0.001$). Small PTMCs were generally well circumscribed and nonsubcapsular. **Conclusions:** Our results have shown that small (<5mm) PTMCs are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness compared with large (≥5mm) tumors and could thus be considered as low-risk cancers.

Keywords: papillary, microcarcinoma, thyroid, tumor size, plump cells

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Introduction

Worldwide, the incidence of thyroid cancer has significantly increased over the past decades [1, 2]. This is mainly related to the rapid increase in the incidence of small, incidentally discovered, subcentimetric papillary thyroid carcinomas (PTC), namely microcarcinomas (PTMC) [3, 4]. This increase might be explained by the widespread use of imaging techniques and fine needle aspiration (FNA) biopsy of small thyroid nodules, allowing the identification of a large number of clinically silent PTMCs [5]. Moreover, many PTMCs have lately been detected following advances in the sampling technique and a more watchful and careful examination of the thyroid specimens resected for benign diseases [6]. All this together, resulted in an increased detection of PTMCs, considered as a global phenomenon called epidemic of overdiagnosis [1, 7, 8].

Despite this, many current guidelines and recommendations regarding the optimal treatment strategy for PTMC remain controversial [9]. The management of PTMC ranges from observation alone to total thyroidectomy +/- central lymph node dissection [10]. This reflects our in-

ability to accurately predict the aggressiveness of PTMCs before surgery [9, 11]. The prognosis of PTMC is excellent in the great majority of cases [3, 12], although some PTMCs might behave more aggressively, but no definite biological or clinical parameters currently exist to distinguish indolent PTMCs from potentially aggressive PTMCs [13].

PTMCs that have poorer prognosis are usually multifocal, incompletely resected, have extrathyroidal extension or lymph node involvement [14, 15]. Some microscopic morphological features have also been shown to predict potential aggressiveness in PTC cases. These include: the histological variant (eg. conventional and tall cell versus follicular variant), infiltrative tumor borders, well developed nuclear features of PTC, stromal reaction (including fibrosis, desmoplasia and/or sclerosis), focal polygonal eosinophilic (plump pink) cells, presence of psammoma bodies [16, 17]. The problem is that all these features are available only after surgery.

Tumor size, by contrast, is the most available preoperative parameter, as it can easily be assessed by ultrasonography.

In this study, we analyzed and assessed the morphological features of PTMCs in a large series of cases, including <5mm and ≥5mm tumors. Our aim was to determine whether small (<5mm) tumors by contrast with large

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(≥ 5 mm) ones are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness and could thus be regarded as low-risk cancers.

Material and Methods

Selection of the cases

After obtaining the approval of the Ethics Committee of "George Emil Palade" University of Medicine, Pharmacy, Sciences and Technology of Târgu-Mureș, we conducted a retrospective study on a series of PTMCs. The cases included in the study were registered in the database of the Pathology Department, Târgu-Mureș Emergency County Hospital from January 2003 to December 2014. The cases were included in the study if (1) the histopathological diagnosis was PTMC and (2) the corresponding hematoxylin/eosin (HE)-stained slides were available for review.

Pathological data

For all the cases included in the study, the corresponding slides (HE-stained) were reviewed by three pathologists interested in endocrine pathology (EAS, ANB and AB). All controversial features were analyzed and discussed together at the triple-headed microscope. The following morphological features have been assessed: the size of the tumor, the tumor location (subcapsular versus nonsubcapsular), the extrathyroidal extension/invasion into the perithyroidal adipose tissue, the multifocality, the resection margins, the lymph node involvement, the histologic variant (conventional, follicular, tall cell, Warthin-like, oncocytic), the tumor margins (well circumscribed (not encapsulated/ encapsulated) versus infiltrative), the stromal reaction (fibrosis/desmoplasia/sclerosis versus none of these changes), the presence of plump pink cells, intratumoral lymphocytic infiltrate, intratumoral multinucleated giant cells, psammoma bodies, stromal calcification and the nuclear features.

The diagnosis of PTMC, as well as the histological variant of the tumor (conventional PTC versus variants of PTC: follicular, tall cell, oncocytic, Warthin-like) were all set in accordance to the 2017 WHO (World Health Organization) Classification of Tumors of Endocrine Organs [18].

Subcapsular PTMCs were defined as tumors located under the thyroid capsule, with 0-0.1mm distance between the edge of the tumor and the thyroid capsule; nonsubcapsular PTMCs were defined by a >0.1 mm distance between the edge of the tumor and the thyroid capsule (Fig. 1 A, B). Extrathyroidal extension (ETE) was defined as limited tumor extension either into adipose perithyroidal soft tissues (Fig. 1 C) or into the strap muscles (sternohyoid, sternothyroid or omohyoid muscles) according to the 2009 AJCC [19] or only strap muscles invasion, according to the 2017 AJCC [20]. As it is a retrospective study, all cases were assessed according to 2009 AJCC classification system and were reassessed based on current 2017 AJCC classification system. Multifocality was defined as the presence of two or more isolated/non-contiguous tumor foci

in one or both thyroid lobes. Lymph node involvement (pN1) was defined as metastasis into at least one regional lymph node (Fig. 1 D).

Tumor associated stromal reaction was also documented. Fibrosis was defined as the presence of fibroblasts in a collagenous (non-mixoid) stroma (Fig. 2 A), desmoplasia as the presence of proliferating fibroblasts in a myxoid stroma, and sclerosis as the presence of paucicellular, eosinophilic, dense bundles of collagen (Fig. 2 B) [16]. The degree of tumoral fibrosis was also evaluated and scored, as follows: fibrosis 1+ (mild fibrosis with the presence of few inconspicuous, delicate fibrous areas within or at the periphery of the tumor nodule) and fibrosis 2+ (moderate/extensive fibrosis that was clearly recognizable, with multiple fibrotic bands within and at the periphery of the tumor nodule) [21]. The presence of psammoma bodies and stromal calcification was also noted (Fig. 2 C, D).

Multinucleated giant cells, as well as plump pink cells (large polygonal tumor cells with nuclear features of PTC and moderate to abundant homogenous, eosinophilic cytoplasm, that were not "tall enough" to be like the cells in the tall-cell PTC variant) were carefully evaluated if present [16, 22] (Fig. 3 A, B).

Further on, the tumor cell nuclei were assessed for seven nuclear features: nuclear enlargement, overlapping, grooves, irregular nuclear membrane, chromatin clearing, pseudo-inclusions (Fig 3 C) and "sickle" nuclei (smaller, eccentrically located nuclei, with a particular sickle shape) [23] (Fig 3 D). Well-developed PTC nuclear features were considered if ≥ 5 nuclear features were present and poorly developed if fewer (≤ 4) nuclear features were present.

The tumor size was measured in millimeters, under the microscope (Olympus BX46, Olympus Life Science, Waltham, Massachusetts, USA) at low magnification (40x). Based on this parameter, the cases were divided in two categories: small (< 5 mm) and large (≥ 5 mm) PTMCs. All the pathological features were assessed in comparison between these two groups.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 20, Chicago, IL, USA). Data were labeled as nominal or quantitative variables. Nominal variables were characterized by means of frequencies. Quantitative variables were tested for normality distribution using Kolmogorov-Smirnov test and were described by mean \pm standard deviation or median and percentiles (25; 75%), whenever appropriate. The frequencies of nominal variables were compared with a chi-square test. Differences in the mean or median between groups were analyzed using the t test. The level of statistical significance was set at $p < 0.05$.

Results

A total of 221 patients with PTMC were registered at the Department of Pathology, Târgu-Mureș Emergency Coun-

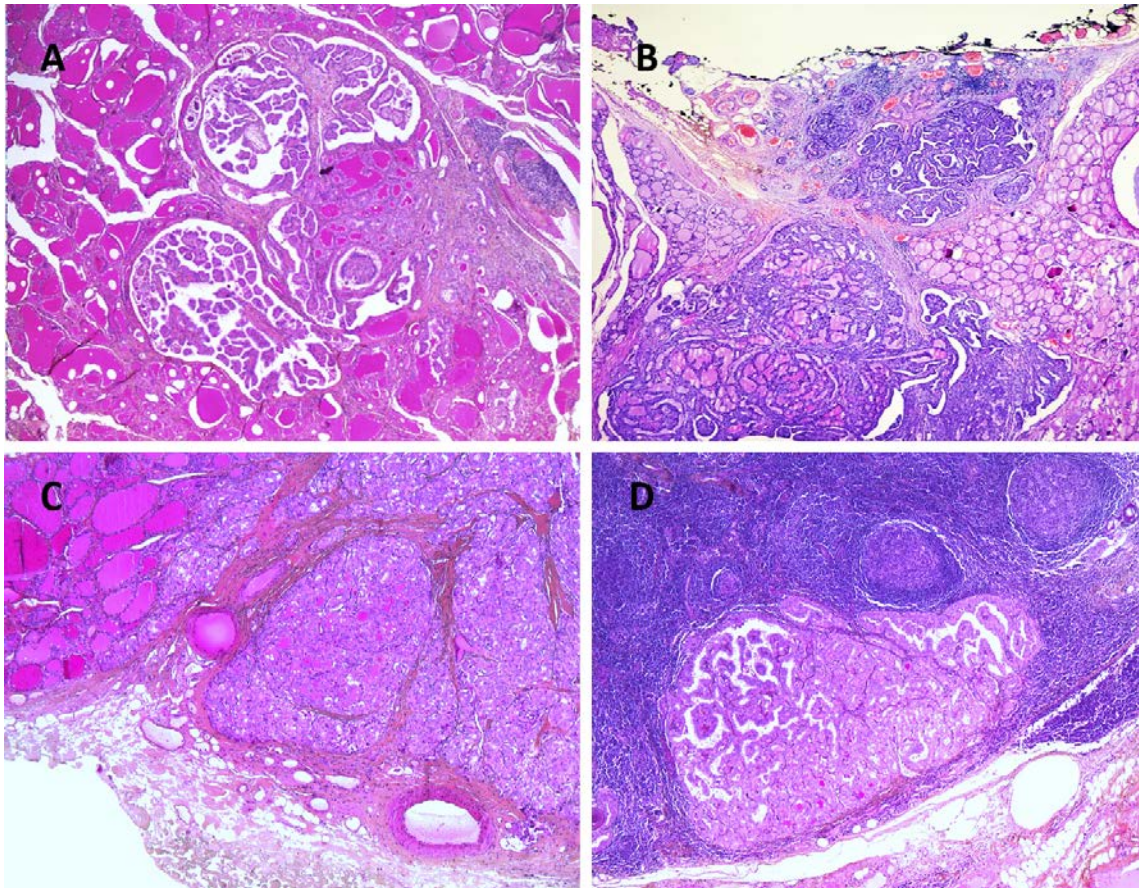


Fig. 1. Papillary thyroid microcarcinomas, morphological features (hematoxylin/eosin). Nonsubcapsular, conventional papillary thyroid microcarcinoma (A, x 2.5); Subcapsular conventional papillary thyroid microcarcinoma (B, x 2.5); Subcapsular papillary thyroid microcarcinoma that extends into the perithyroidal soft tissue (C, x 5); Lymph node involvement of papillary thyroid microcarcinoma (D, x 5)

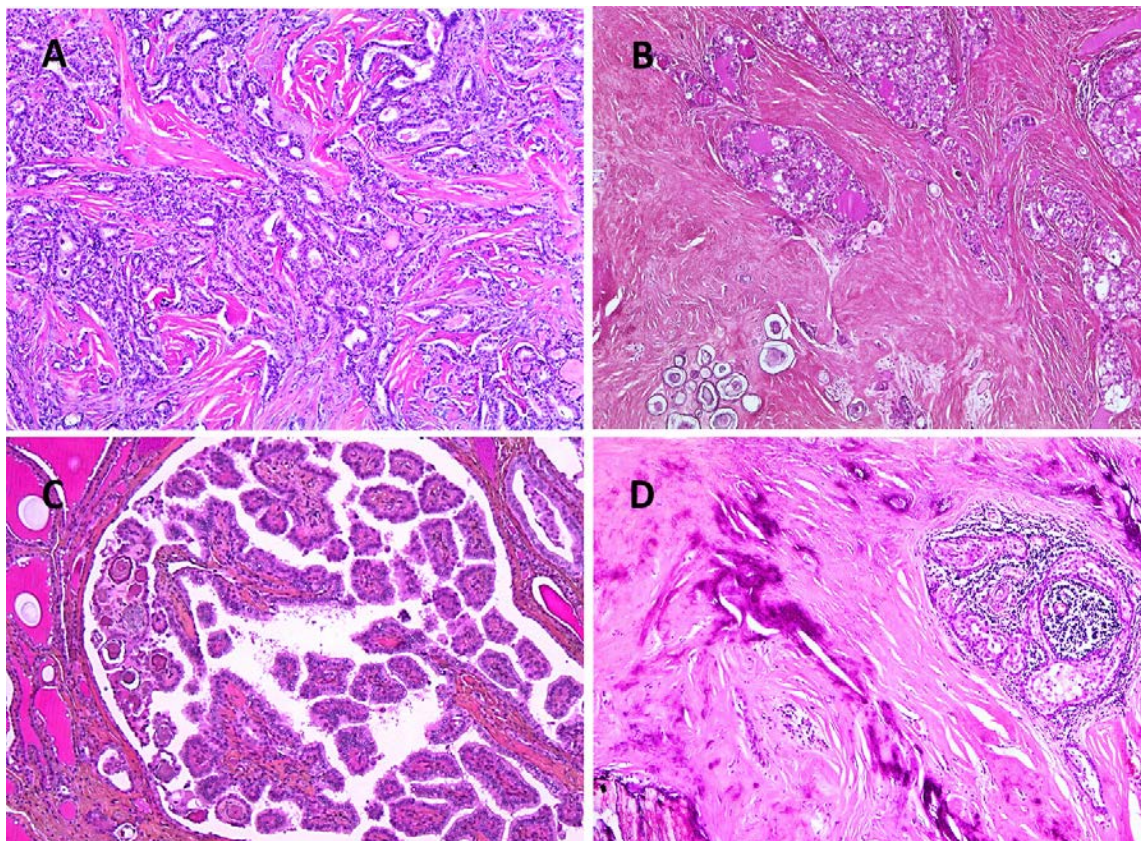


Fig. 2. Stromal reaction in papillary thyroid microcarcinomas (hematoxylin/eosin). A papillary thyroid microcarcinoma case showing fibrosis with multiple fibrotic bands within the tumor (A, x 10); A papillary thyroid microcarcinoma case showing sclerosis with the presence of paucicellular, eosinophilic, dense bundles of collagen and psammoma bodies (B, x 10); Psammoma bodies in a papillary thyroid microcarcinoma case (C, x 10); Stromal calcification in a papillary thyroid microcarcinoma case (D, x 10)

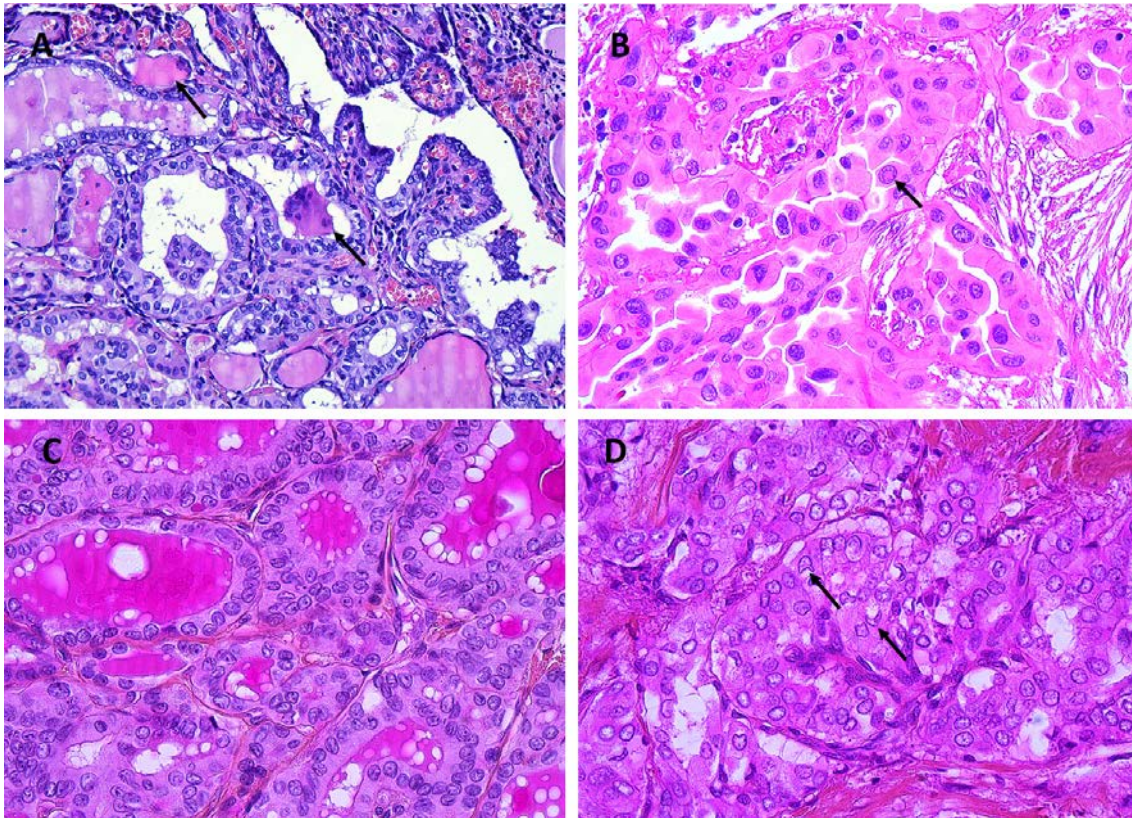


Fig. 3. Cellular and nuclear characteristics in papillary thyroid microcarcinomas (hematoxylin/eosin). Presence of intratumoral multinucleated giant cells (arrows) (A, x 10); Presence of plump pink cells (large polygonal cells, with eosinophilic cytoplasm, height less than twice the width and nuclear features of papillary thyroid microcarcinomas, including nuclear enlargement, irregular nuclear membranes and pseudoinclusions [arrow]) (B, x 10); Tumor cells with well-developed nuclear features of papillary thyroid microcarcinomas (C, x 40); Tumor cells with “sickle” nuclei (smaller, eccentrically located nuclei, with a particular sickle shape [arrows]) (D, x 40)

ty Hospital during the study period. Out of these, fifteen cases were excluded from our analysis because: (1) the tumors did not meet all the diagnostic criteria for PTMC (n=9 cases) or (2) the histological slides were not available for evaluation (n=6 cases). The remaining 206 PTMC cases were further included in the study; 91 were large (≥ 5 mm) and 115 were small (< 5 mm) PTMCs.

Table I shows the demographic and morphological characteristics of the study cases. No differences in terms of sex and age between small and large PTMCs were observed. The majority of cases occurred in women, both in small (n=104, 89.6%) and large (n=91, 93.4%) PTMCs (p=0.550). The mean age at diagnosis was 53.1 ± 10.16 and 51.09 ± 10.48 years-old for small and large PTMCs, respectively (p=0.130).

Approximately half of the cases were consistent with a diagnosis of conventional PTMCs in small PTMCs (51.3%). Other PTC variants (tall cell, oncocytic, Warthin-like) accounted for only few cases (n=19, 9.2% in total) and, although not reaching statistically significant values (p=0.161), appeared to be rather more numerous among large PTMCs.

Large PTMCs were found to be significantly associated with subcapsular location (p=0.0001) and infiltrative tumor border (p=0.011), compared to small PTMCs. Unlike large PTMCs, small PTMCs were nonsubcapsular in the great majority of cases (n=97/115, 84.3%). More than

half had either well circumscribed tumor border (36.5%) or were encapsulated tumors (21.7%). Seven cases of large and only one case of small PTMC had positive resection margins (p=0.022) and were all located in the subcapsular area.

None of the 206 PTMC cases showed extension into the strap muscles, defined as extrathyroidal extension by the 8th/2017 AJCC. If the 7th/2009 AJCC definition of extrathyroidal extension was applied, 18 cases were extrathyroidal, revealing tumor invasion into the perithyroidal adipose tissue; the differences were statistically significant when comparing small to large PTMCs (p=0.002). Multifocality was documented in 45.2% small PTMCs, compared to 33% large PTMCs (p=0.086). Lymph node dissection was performed in only 11 cases (5.3%). Of these, three cases displayed lymph node involvement and they were all subcapsular, large PTMCs, with infiltrative tumor borders.

Stromal reaction (fibrosis, desmoplasia or sclerosis) was significantly more prevalent among large versus small PTMCs (p=0.0001). Also, when scoring fibrosis, both fibrosis 1+ (45.1% versus 28.7%) and 2+ (26.4% versus 20%) were significantly more prevalent among large versus small PTMCs. Intratumoral multinucleated giant cells were documented in 31 (15%) PTMCs, and they were more frequently present among large PTMCs (27.5% versus 5.2%, p<0.001). Ten cases of large PTMCs showed stromal calci-

Table I. Demographic and morphological differences between large ($\geq 5\text{mm}$) versus small ($< 5\text{mm}$) papillary thyroid microcarcinomas in our study.

Demographic and morphological features	Size		p
	Tumor $< 5\text{ mm}$ n=115 PTMC (%)	Tumor $\geq 5\text{ mm}$ n=91 PTMC (%)	
Age at diagnosis (mean \pm SD, years)	53.1 \pm 10.16	51.09 \pm 10.48	0.130
Female sex	104 (89.6)	83 (93.4)	0.550
Location			<0.001
Subcapsular	17 (14.8)	59 (64.8)	
Nonsubcapsular	97 (84.3)	33 (36.3)	
Extrathyroidal extension			0.002
8 th TNM	0 (0.0)	0 (0.0)	
7 th TNM	8 (6.9)	10 (11.0)	
Multifocality	52 (45.2)	30 (33.0)	0.086
Positive resection margin	1 (0.9)	7 (7.7)	0.022
Lymph node involvement ^a	0/0 (0.0)	3/11	0.085
Histological variant			0.161
Conventional	59 (51.3)	43 (47.2)	
Follicular	50 (43.5)	35 (38.5)	
Tall cell	0 (0.0)	1 (1.1)	
Oncocytic	4 (3.5)	6 (6.6)	
Warthin-like	2 (1.7)	6 (6.6)	
Tumor border			0.011
Well-circumscribed, non-encapsulated	42 (36.5)	23 (25.3)	
Encapsulated	25 (21.7)	11 (12.1)	
Infiltrative	48 (41.7)	57 (62.6)	
PTC nuclear features			
Nuclear enlargement	115 (100.0)	91 (100.0)	
Overlapping	113 (98.3)	87 (95.6)	0.409
Irregular nuclear membrane	85 (73.9)	87 (95.6)	<0.001
Grooves	112 (97.4)	91 (100.0)	0.257
Chromatin clearing	113 (98.3)	87 (95.6)	0.409
Pseudoinclusions	37 (32.2)	56 (61.5)	<0.001
Sickle shaped	21 (18.3)	23 (25.3)	0.065
Well-developed PTC nuclei	86 (74.8)	82 (90.1)	0.003
Poorly developed PTC nuclei	29 (25.2)	9 (9.9)	
Tumor associated stromal reaction			<0.001
None	52 (45.2)	28 (30.8)	
Fibrosis	46 (40.0)	24 (26.4)	
Desmoplasia	10 (8.7)	13 (14.3)	
Sclerosis	7 (6.1)	26 (28.6)	
Tumor fibrosis			0.004
None	59 (51.3)	26 (28.6)	
Fibrosis 1+(mild)	33(28.7)	41 (45.1)	
Fibrosis 2+(moderate/extensive)	23 (20.0)	24 (26.4)	
Plump, pink cells	17 (14.8)	31 (34.1)	0.002
Intratumoral lymphocytic infiltrate	28 (24.6)	18 (19.8)	0.501
Intratumoral multinucleated giant cells	6 (5.2)	25 (27.5)	<0.001
Psammoma bodies	10 (8.7)	14 (15.4)	0.189
Stromal calcification	0 (0.0)	10 (11.0%)	<0.001

PTMC: papillary thyroid microcarcinoma; PTC: papillary thyroid carcinoma; ^a Data regarding only cases with lymph node dissection (no. of cases with lymph node involvement/no. of cases with lymph node dissection). The level of statistical significance was set at $p < 0.05$ and the differences are shown in bold.

fication versus none small PTMC ($p < 0.001$). Psammoma bodies were slightly more prevalent among large PTMCs (15.4% versus 8.7%, $p = 0.189$), whereas the presence of lymphocytes was more prevalent among small PTMCs (24.6% versus 19.8%, $p = 0.501$).

Plump pink tumor cells were documented in 48 (23.3%) PTMCs, mainly among large PTMCs compared to small PTMCs (34.1% versus 14.8%, $p = 0.002$). Large PTMCs were significantly associated with nuclear features such as irregular nuclear membranes ($p < 0.001$) and pseudoinclusions ($p < 0.001$). "Sickle"-shaped nuclei were identified with almost equal distribution among large PTMCs ($n = 23$, 25.3%) and small PTMCs ($n = 21$, 18.3%) cases ($p = 0.065$). Well-developed nuclear features were present almost in all large PTMCs (90.1%, $p = 0.003$).

Discussion

Papillary thyroid microcarcinoma becomes a more and more frequent diagnosis in many countries around the world [14, 3]. It is accepted that these small papillary thyroid cancers are common and rarely behave as aggressive cancers, with extrathyroidal extension and lymph node and distant metastasis [24]. Therefore, the biological characteristics of PTMC have gradually attracted more attention from researchers [25]. The main questions for the clinician remain (1) how to distinguish between harmless and harmful PTMCs and (2) which PTMCs can adequately and safely be managed by active surveillance as an alternative to immediate surgery [26]. The current guidelines also recognized active surveillance as the best alternative for the patients with low-risk PTMCs [10, 27].

Tumor size is considered to be an essential prognostic factor in patients with PTMC [28]. A close relationship between larger tumor size and worse outcome, both in terms of recurrence and survival is documented in the literature, but with controversies regarding the optimal cut-off value for defining small and large PTMCs [9]. Lim et al indicated that this cut-off value could be 7 mm [29], Zhang et al. that it could be 6 mm [30] and Chang et al suggested 5 mm as the cut-off value [31]. Lombardi et al. also demonstrated that tumor size >5 mm was significantly associated with invasion into the perithyroidal adipose tissue [32]. Other groups have found no relationship between PTMC size and the presence of high-risk features [33, 34].

Previous studies demonstrated that PTMC with a larger tumor size may behave more similar to PTC. Gong et al. suggested 8.5 mm as the adequate tumor size to distinguish PTMC from PTC [11]. Song et al demonstrated that tumor size larger than 6.5 mm represent a risk factors for cervical lymph node metastases [34].

The size of the tumor is widely used to predict the aggressiveness of PTMC because it is the easiest parameter to determine using ultrasound images. In this study, we analyzed and assessed the morphological features of PTMCs in a large series of cases, including <5mm and ≥5mm tumors. Our aim was to determine whether small (<5mm) tumors by contrast with large (≥5mm) ones are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness and could thus be regarded as low-risk cancers.

Our results have highlighted important morphological differences between the two PTMC groups (≥5mm versus <5 mm). High-risk morphological features were significantly more prevalent among large PTMCs compared with small PTMCs. Large PTMCs were located mostly in the subcapsular area and had infiltrative borders. By contrast, small PTMCs were nonsubcapsular in the great majority of cases and had well circumscribed tumor border or were encapsulated. Recently Tallini et al. have demonstrated that tumor's location (subcapsular versus nonsubcapsular) and tumor size (<5mm versus ≥5 mm) represent valuable morphological tools in the proper selection of patients for active surveillance [35]. The subcapsular location of the tumor, immediately adjacent to the perithyroidal adipose tissue has been recognized as an adverse prognostic factor [24]. This is not unexpected, because subcapsular tumors have an easy access to the extrathyroidal soft tissues. In our study only eighteen PTMCs showed invasion into the perithyroidal adipose tissue, that was seen significantly more often among large, subcapsular PTMCs.

We have also shown that large PTMCs were more frequently associated with other high-risk morphological features, like stromal reactions (fibrosis/desmoplasia/sclerosis) ($p<0.001$), intratumoral multinucleated giant cells ($p<0.001$), calcifications ($p<0.001$) and polygonal plump pink cells ($p=0.002$). Small PTMCs revealed a completely different morphological profile. Unlike large PTMCs,

small tumors were characterized by a scarcity of tumor-associated stromal reactions ($p<0.001$), plump pink cells ($p=0.002$), and multinucleated giant cells ($p<0.001$).

Only few studies in the literature have investigated the importance of multinucleated giant cells in PTCs. Probably these cells are a response to abnormal colloid productions in PTC [36]. Although multinucleated giant cells have been described most commonly in inflammatory conditions of the thyroid, some studies have demonstrated that the presence of multinucleated giant cells were associated with lymph node metastasis and advanced stage of PTC [37]. The results of our study demonstrated their presence mainly in larger tumors and this should prompt a careful evaluation of large PTMCs.

The plump cell morphology has yield importance as a morphological feature predictive for poor prognosis in PTCs back in 2013 with the study of Virk RK et al. [16]. In line with this, our results revealed a high prevalence of plump pink cells among large PTMCs and a scarcity of these cells among small PTMCs.

Large PTMCs revealed well developed nuclear features of PTC in most of the cases, whereas subtle nuclear features of PTC were more frequently present among small PTMCs.

In the present study, lymph node dissection was performed in 11 cases. Of these, three cases showed lymph node involvement, all large PTMCs. Several authors have demonstrated that PTMCs with >5 mm in diameter are significantly more frequently associated with central lymph node metastasis compared to <5 mm PTMCs [38]. Clinical ultrasound studies have also shown that ≥5 mm, subcapsular tumors are more likely to be associated with lymph node metastases, compared to smaller tumors [39, 40]. In our study, no small, <5mm PTMC case was associated with lymph node metastasis, but no definite conclusion regarding tumor size and lymph node involvement can be drawn due to the limited number of PTMCs with lymph node dissection.

The current study has some limitations. It is a retrospective analysis from a single institution and results may not be generalizable to all populations. Further on, an important morphological parameter, lymph node involvement could not be evaluated with optimal accuracy due to the limited number of PTMC cases in which lymph node dissection was performed. This is mainly related to the diagnosis of cancer being established after surgery for the majority of cases in our study.

Conclusions

We have shown that small (<5mm) PTMCs are less frequently associated with high-risk morphological features, predictive of tumor aggressiveness compared with large (≥5mm) tumors. It is uncertain and still a matter of debate whether these high-risk morphological features are less frequently present in small compared to large PTMCs because of their different biological phenotype or because

they did not have time to develop. However, based on our results, small, <5mm PTMCs could be considered as low-risk cancers and, thus possible candidates for active surveillance instead of immediate surgery. Further broader studies, with long-term follow-up data are however needed to confirm these results.

Authors' contribution

EAS - Data collection, conceptualization, histological examination of the cases, writing original draft

ANB - Histological examination of the cases, writing and editing

AZ - Data collection, statistical analysis

AB - Conceptualization, editing, supervision

Conflict of interest

None to declare.

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