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Original Article

Relationships between clinicopathological prognostic factors in papillary thyroid microcarcinoma: a refined analysis based on 428 cases

Delia Ciobanu Apostol[1,2], Simona Eliza Giuşcă[1], Irina-Draga Căruntu[1], Ludmila Lozneanu[1,2], Elena Corina Andriescu[1,2], Mihaela Moscalu[3]

[1]Department of Morphofunctional Sciences I-Histology, Pathology, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy, Romania; [2]Department of Pathology, "Sf. Spiridon" County Clinical Emergency Hospital, Iassy, Romania; [3]Department of Preventive Medicine and Interdisciplinarity-Medical Informatics and Biostatistics, "Grigore T. Popa" University of Medicine and Pharmacy, Iassy, Romania

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Abstract: A clear definition of the prognostic factors for papillary thyroid microcarcinoma (PTMC) is still debatable, as the tumor characteristics which indicate a high risk of metastasis are little known. We investigated the clinicopathological profile of a large group of PTMC, aiming to ascertain possible relationships between a set of clinicopathological characteristics and four parameters expressing tumor extension and aggressiveness (namely lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension and lymph node metastasis). For 428 patients, the following data were retrospectively documented: sex, age, tumor size, histological variant, associated thyroid pathology, location (subcapsular, intraparenchymal), unilateral or bilateral involvement, number of foci, lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension and lymph node metastasis. Data were analyzed using univariate and multivariate logistic regression analysis. Multivariate analysis confirmed that the tumor size is a negative prognostic factor for lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension and lymph node metastasis. We also demonstrated a strong relationship between the subcapsular location and lympho-vascular and capsule invasion, and extrathyroidal extension. The multifocality was correlated only with thyroid capsule invasion and extrathyroidal extension. Regarding the histological variants, the only validated correlation was between the oncocytic variant and extrathyroidal extension. Our work contributes to the validation of PTMC prognostic factors, useful in stratification of PTMC in high or low risk classes, and able to explain the behavioral differences in the tumor development.

Keywords: Papillary thyroid microcarcinoma, lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension, lymph node metastasis

Introduction

Thyroid carcinomas are the most frequent malignant tumors in the head and neck area; they account for 1% of all malignant diagnostics in the entire population and represent the 9th most common malignity (2.7%) identified in females [1].

Papillary thyroid carcinoma (PTC) represents 80-85% of all malignant thyroid tumors, with a largely favorable prognostic, a 10-year survival rate of over 90% and a 15-year survival rate of 87% [2, 3]. PTC incidence has risen worldwide as diagnosis methods have become more reliable by the large implementation of high-resolution medical imaging or fine needle aspiration biopsy (FNAB), as well as by the refinement of histopathological and immunohistochemical methods [4, 5].

The 2004 WHO classification of thyroid tumors defines papillary thyroid microcarcinoma (PTMC) as a tumor with a diameter of or less than 1 centimeter [6]. The introduction of the term of PTMC came to replace and make uniform a variety of labels and definitions mostly descriptive which confused and rendered the diagnosis more difficult, such as small papillary carcinoma with a diameter of less than 1.5 cm,

occult papillary carcinoma and incidentaloma. The latter designated the incidentally discovered tumors in total thyroidectomies for other thyroid pathology [7] or in the event of an autopsy [8]. PTMC represents up to 30% of PTC cases [9, 10]. The TNM staging system has undergone alterations, i.e. if thyroid tumors of less than 2 cm were initially classified as T1 stage, as of 2006 the T1a category was added, and it is the counterpart of PTMC [6, 11]. The lymph nodes in the head and neck area were divided into seven levels according to the standard classification proposed by the American Head and Neck Society (AHNS) and the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). The central lymph node compartment, corresponding to level VI, is the most frequent location for lymph node metastasis in PTC patients [10].

An impressive percentage of all PTMC has a favorable evolution [6], rarely reporting metastasis, and less than 1% mortality rate [12-15]. Despite the indolent behavior encountered in most PTMC cases, a small number has an aggressive clinical trajectory, similar to PTC. These cases are characterized by secondary involvement of lymph nodes [12, 16-18], a high rate of recurrence (up to 20%), distant metastasis and mortality [12, 14, 19-21].

The management of PTMC varies from monitoring without surgical therapy to total thyroidectomy, with or without radioactive iodine treatment. The routine dissection of central lymph nodes is yet another controversial theme, especially as the long-term lack of benefit has been demonstrated, and this has been supported by possible post-surgery complications such as transitory hypocalcaemia [19, 22, 23].

Contrary to the clear definition of prognostic factors for PTC [6] which includes age (with a threshold at 55 years old (yo) according to the last UICC TNM classification [24]), tumor size, capsule invasion, histologic variants (diffuse sclerosing, tall or columnar cell, micropapillary/hobnail) and differentiation degree, local or distant metastasis, and surgical resection of the lesion, the prognostic factors for PTMC are still contentious. The PTMC characteristics which indicate a high risk of metastasis are little known [25], some studies considering that metastasis of central lymph nodes is directly involved in tumor relapse, other data sustaining the prognostic role of histological variants with aggressive behavior (oncocytic, sclerosing or tall cell) or of associated lesional background [15, 26].

Within this context, we analyzed the clinicopathological profile of a large group of PTMC (428 cases). Our analysis means possible relationships between a set of clinicopathological characteristics and four parameters expressing tumor extension and aggressiveness (namely lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension and lymph node metastasis). Thus, supplementary data may be considered as supporting the refinement and accuracy of PTMC prognostic factors, by a broader perspective on tumor behavior.

Material and methods

Subjects

The study group comprised 428 patients diagnosed with PTMC between January 2010 and July 2016 at the “Sf. Spiridon” County Clinical Emergency Hospital. Within the study group, 168 patients underwent thyroidectomy with cervical lymph node dissection for PTMC, whereas for 260 cases PTMC was incidentally found, after surgery for non-tumor thyroid pathology.

Medical files and histopathological reports were retrospectively reviewed in order to document the main clinicopathological characteristics in each patient. No familial cases were registered. Our database included information regarding sex, age (<55 and respectively ≥55 yo), tumor size, histological variant (papillary, follicular, oncocytic), location (subcapsular, intraparenchymal), unilateral or bilateral involvement, number of foci (two or more foci for multifocality, taking into account the diameter of largest foci for tumor size), lympho-vascular invasion, thyroid capsule invasion (defined as microscopic presence of tumor cells into the thyroid capsule), extrathyroidal extension (defined as microscopic presence of tumor cells into perithyroidal soft tissues: adipose tissue, skeletal muscle, sizable vessels and nerves), and lymph node metastasis (including the number of positive lymph nodes). On the histological evaluation we also noted the associated thyroid pathology.

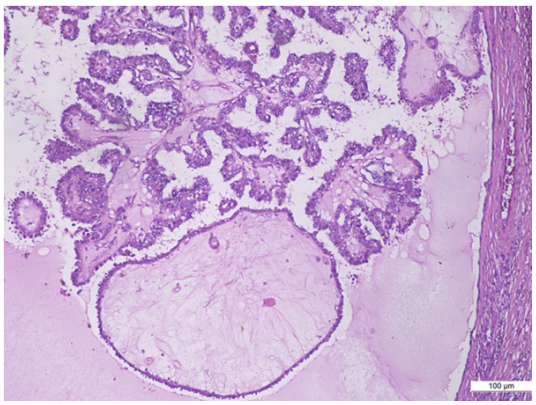

Figure 1. Papillary variant of PTMC, with edematous stromal cores (HE×10).

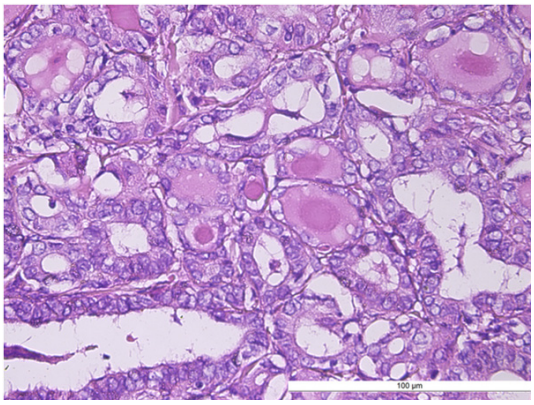

Figure 2. Follicular variant of PTMC, nuclei with ground glass appearance, grooves and irregular contour (HE×40).

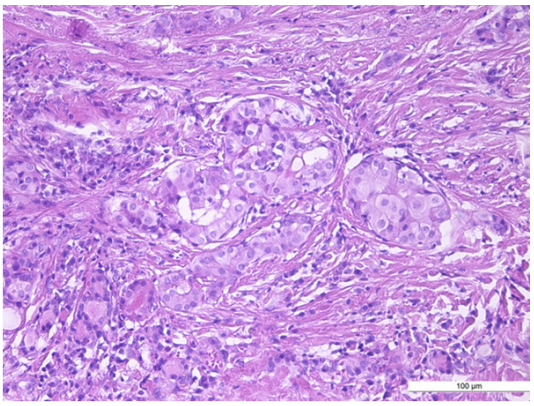

Figure 3. Oncocytic variant of PTMC - oxyphilic cells with abundant eosinophilic granular cytoplasm and typical papillary carcinoma nuclei (HE×40).

The follow-up revealed 3 recurrences and 7 deaths not related to the disease. The three patients with recurrence in the lymph node compartments corresponding to level VI and VII were female, aged over 55 yo, with the following characteristics of the primary tumor: tumor size of 5, 7 and 9 mm, subcapsular location, papillary (2 cases) and oncocytic (1 case) histology, lympho-vascular invasion and extrathyroidal extension; all have been treated by thyroidectomy without cervical lymph node dissection.

The study was approved by the Ethics Committee of "Grigore T. Popa" University of Medicine and Pharmacy lassy based on the patients' informed consent on the usage of their biologic material leftover after diagnostic testing, in accordance with the ethical standards of Helsinki declaration.

Statistical analysis

Data were analyzed using the SPSS V.22-SPSS Inc., IBM Corporation, Chicago, IL, USA). The results of the univariate analysis were reported as mean ± standard deviation for continuous variables. Total count and percent were reported for categorical variables. Chi-square test (Maximum-Likelihood, Yates, Mantel-Haenszel) was performed for categorical variables and Kruskal-Wallis test for continuous variables. Correlations between predictor and outcome variables were determined using univariate analysis (Spearman Rank test, Gamma) and multiple logistic regression. The significance level (*p*-value), which represents the maximum error probability, was considered to be 0.05 (5%); a confidence interval of 95% shows that the decision is correct.

Results

Clinicopathological profile of the studied group

Among the 428 patients in the study, 364 (85.04%) were female and 64 (14.96%) male, with a mean age of 54.64 ± 11.12 years. 245 patients (57.25%) were over 55 yo at the time of the diagnosis, whereas 183 were under 55 yo (42.75%). The mean diameter of the tumor was 3.76 mm ± 2.50 mm with a median value of 3 mm and a range between 0.1 and 10 mm.

The histopathological exam identified three histologic variants of PTMC, namely papillary (155 cases-36.22%) (**Figure 1**), follicular (244

Table 1. Clinicopathological characteristics according to lympho-vascular invasion

Clinicopathological characteristics	Lympho-vascular invasion		Univariate analysis	OR (95% CI)
	Absent (n=410)	Present (n=18)		
Age at diagnosis	54.7 ± 11.03	53.6±13.41	P=0.845	
<55 years old	174 (95.1%)	9 (4.9%)	P=0.695	1.36 (0.48-3.81)
≥55 years old	236 (96.3%)	9 (3.7%)		
Tumor size (mm)	3.68 ± 2.46	5.85 ± 2.60	P=0.009*	
Location				
Subcapsular	157 (91.8%)	14 (8.19%)	P=0.0019*	5.64 (1.7-20.68)
Intraparenchymal	253 (98.4%)	4 (1.6%)		
Histopathologic type				
Papillary	142 (91.6%)	13 (8.4%)	P=0.0027*	4.91 (1.59-16.12)
Follicular	240 (98.4%)	4 (1.6%)	P=0.00506*	0.20 (0.06-0.67)
Oncocytic	28 (96.5%)	1 (3.5%)	P=0.7881	0.80 (0.12-6.94)
Focality of the tumor				
Unifocal	286 (96%)	12 (4%)	P=0.782	0.87 (0.29-2.66)
Multifocal	124 (95.4%)	6 (4.6%)		
Multifocality-number of tumor foci			P=0.652	
2	82 (96.5%)	3 (3.5%)	P=0.913	0.87 (0.19-3.42)
3	31 (91.2%)	3 (8.8%)	P=0.4008	2.31 (0.49-9.48)
≥4	11 (100%)	0 (0%)	P=0.996	2.17 (0.39-12.64)
Unilateral or bilateral involvement				
Unilateral	64 (96%)	2 (3%)	P=0.647	2.13 (0.32-17.49)
Bilateral	60 (93.7%)	4 (6.3%)		
Coexisting thyroid pathology				
Thyroid adenoma	7 (100%)	0 (0%)	P=0.7711	3.36 (0.14-23.57)
Graves' disease	17 (100%)	0 (0%)	P=0.7706	1.35 (0.06-8.25)
Colloid goiter	104 (93.7%)	7 (6.3%)	P=0.2006	1.86 (0.66-4.97)
Nodular goiter	217 (96.4%)	8 (3.6%)	P=0.4810	0.71 (0.26-1.87)
Hashimoto's thyroiditis	65 (95.6%)	3 (4.4%)	P=0.9265	1.06 (0.23-3.50)

OR: odd ratio; CI: confidence interval; *P-value <0.05 was considered to be statistically significant.

cases-57%) (**Figure 2**), and oncocytic (29 cases-6.78%) (**Figure 3**). Other histological variants were excluded, because specific features that could define such variants appeared in less than 10% of tumor areas (meaning tall cells in 8 cases, clear cells in 4 cases). Accompanying thyroid pathology included nodular goiter-225 cases (52.57%), colloid goiter-111 cases (25.93%), Hashimoto thyroiditis-68 cases (15.89%), Basedow disease-17 cases (3.97%), and thyroid adenoma-7 cases (1.63%).

Most of the tumors had intraparenchymal location (257 cases-60.04%) as opposed to subcapsular (171 cases-39.96%). Multifocality was found in 130 cases (30.37%) of PTMC, almost half of them (64 cases-49.23%) with bilateral involvement of the thyroid. The number of foci varied between 2 and 5, and were distributed as follows: 85 patients (65.39%) had 2 tumor foci, 34 cases (26.15%)-3 foci, 9 (6.92%)-4 foci and 2 patients (1.54%)-5 foci.

Histopathological exam also showed lympho-vascular invasion in 18 cases (4.20%), perineural invasion in 7 cases (1.63%), thyroid capsule invasion in 93 cases (21.73%), and extrathyroidal extension in 74 cases (17.29%).

Lymph node dissection was performed only for 168 patients, and lymph node metastases were identified in 23 of these patients-13.69% (18 cases N1a and 5 cases N1b). The number of positive lymph nodes varied between one and ten, as follows: 14 cases with one node, 2 cases with three nodes, 2 cases with four nodes, whereas the remaining 5 cases present-

Table 2. Clinicopathological characteristics according to thyroid capsule invasion

Clinicopathological characteristics	Thyroid capsule invasion		Univariate analysis	OR (95% CI)
	Absent (n=335)	Present (n=93)		
Age at diagnosis	54.6 ± 11.13	54.8 ± 11.17	P=0.559	
<55 years old	147 (80.3%)	36 (19.7%)	P=0.372	0.81 (0.49-1.33)
≥55 years old	188 (76.7%)	57 (23.3%)		
Tumor size (mm)	3.16 ± 2.23	5.96 ± 2.17	P<<0.001*	
Location				
Subcapsular	94 (55%)	77 (45%)	P<<0.001*	12.34 (6.62-23.27)
Intraparenchymal	241 (93.8%)	16 (6.2%)		
Histopathologic type				
Papillary	113 (72.9%)	42 (27.1%)	P=0.0427*	1.62 (1.09-2.65)
Follicular	205 (84%)	39 (16%)	P=0.00091*	0.46 (0.28-0.75)
Oncocytic	17 (58.6%)	12 (41.4%)	P=0.0079*	2.77 (1.19-6.42)
Focality of the tumor				
Unifocal	246 (82.6%)	52 (17.4%)	P=0.00149*	2.18 (1.32-3.60)
Multifocal	89 (68.5%)	41 (31.5%)		
Multifocality-number of tumor foci				
2	63 (74.1%)	22 (25.9%)	P=0.0827	1.65 (0.90-3.03)
3	22 (64.7%)	12 (35.3%)	P=0.0125*	2.58 (1.12-5.88)
≥4	4 (36.4%)	7 (63.6%)	P=0.00058*	8.28 (2.08-15.13)
Unilateral or bilateral involvement				
Unilateral	53 (80.3%)	13 (19.7%)	P=0.00328*	3.17 (1.36-7.49)
Bilateral	36 (56.3%)	28 (43.7%)		
Coexisting thyroid pathology				
Thyroid adenoma	6 (85.7%)	1 (14.3%)	P=0.984	0.59 (0.02-4.10)
Graves' disease	16 (94.1%)	1 (5.9%)	P=0.1879	0.21 (0.01-1.23)
Colloid goiter	84 (75.7%)	27 (24.3%)	P=0.4415	1.22 (0.72-2.02)
Nodular goiter	180 (80%)	45 (20%)	P=0.3617	0.80 (0.50-1.28)
Hashimoto's thyroiditis	49 (72.1%)	19 (27.9%)	P=1.1761	1.40 (0.81-2.68)

OR: odd ratio; CI: confidence interval; *P-value <0.05 was considered to be statistically significant; for P<0.00000001 we have noted P<<0.001.

ed two, six, seven, eight, and ten nodes, respectively. For these 23 cases the location of the primary tumor was variable: multifocal and bilateral (10 cases), or limited to a thyroid lobe in upper third (5 cases), middle third (3 cases) and lower third (5 cases).

Relationships between clinicopathological prognostic factors-univariate analyses

The association between the clinicopathological characteristics and the four parameters expressing tumor extension and aggressiveness are summarized in **Tables 1**-**4**.

Age and parameters of tumor extension/aggressiveness: Our results indicate no statistically significant association between the patients' age (related to the threshold of 55 yo) and lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension or lymph node metastasis (including the number of the positive lymph nodes).

Tumor size and parameters of tumor extension/aggressiveness: The tumor size was significantly larger in the patients with lympho-vascular invasion (P=0.009), thyroid capsule invasion (P<<0.001), extrathyroidal extension (P<<0.001), presence of lymph node metastasis (P=0.00006) and number of metastatic lymph nodes (P=0.020).

Location particularities and parameters of tumor extension/aggressiveness: The subcapsular location was significantly associated with

Table 3. Clinicopathological characteristics according to extrathyroidal extension

Clinicopathological characteristics	Extrathyroidal extension		Univariate analysis	OR (95% CI)
	Absent (n=354)	Present (n=74)		
Age at diagnosis	54.7±11.12	54.3±11.2	P=0.994	
<55 years old	151 (82.5%)	32 (17.5%)	P=0.925	1.02 (0.60-1.75)
≥55 years old	203 (82.9%)	42 (17.1%)		
Tumor size (mm)	3.34±2.33	5.85±2.26	P<<0.001*	
Location				
Ssubcapsular	111 (64.9%)	60 (35.1%)	P<<0.001*	9.38 (4.85-18.41)
Intraparenchymal	243 (94.5%)	14 (5.5%)		
Histopathologic type				
Papillary	118 (76.1%)	37 (23.9%)	P=0.00673*	2.00 (1.17-3.42)
Follicular	218 (89.3%)	26 (10.7%)	P=0.00002*	0.34 (0.19-0.59)
Oncocytic	18 (62.1%)	11 (37.9%)	P=0.0023*	3.26 (1.36-7.7)
Focality of the tumor				
Unifocal (foci)	258 (86.6%)	40 (13.4%)	P=0.00184*	2.28 (1.32-3.94)
Multifocal (foci)	96 (73.9%)	34 (26.1%)		
Multifocality-number of tumor foci				
2	67 (78.8%)	18 (21.2%)	P=0.7896	1.73 (0.89-3.35)
3	24 (70.6%)	10 (29.4%)	P=0.0136*	2.69 (1.11-6.44)
≥4	5 (45.5%	6 (54.5%)	P=0.00017*	7.74 (1.97-13.99
Unilateral or bilateral involvement				
Unilateral	55 (83.3%)	11 (16.7%)	P=0.0127*	2.80 (1.15-6.96)
Bilateral	41 (64.1%)	23 (35.9%)		
Coexisting thyroid pathology				
Thyroid adenoma	6 (85.7%)	1 (14.3%)	P=0.8323	0.79 (0.03-5.48)
Graves' disease	17 (100%)	0 (0%)	P=0.3045	0.27 (0.01-1.53)
Colloid goiter	86 (77.5%)	25 (22.5%)	P=0.0393*	6.62 (1.13-14.42)
Nodular goiter	192 (85.3%)	33 (14.7%)	P=0.1312	0.67 (0.40-1.12)
Hashimoto's thyroiditis	53 (77.9%)	15 (22.1%)	P=0.0384*	6.41 (1.04-14.01)

OR: odd ratio; CI: confidence interval; **P*-value <0.05 was considered to be statistically significant; for P<0.00000001 we have noted P<<0.001.

lympho-vascular invasion (P=0.0019, OR= 5.64), thyroid capsule invasion (P<<0.001, OR=12.3), extrathyroidal extension (P<<0.001, OR=9.38) and lymph node metastasis (P= 0.0065, OR=3.53).

Histologic type and parameters of tumor extension/aggressiveness: Statistical analysis performed for each histological variant in comparison with the others showed a significant association between the papillary type and presence of lympho-vascular invasion (P= 0.0027, OR=4.91). All three histological subtypes significantly associated with thyroid capsule invasion and extrathyroidal extension, the highest risk being registered for the oncocytic variant (P=0.0079, OR=2.77, and P=0.0023, OR=3.26, respectively). Concurrently, the subunitary values of OR indicated that the follicular variant displayed the lowest risk for lympho-vascular (OR=0.2) and thyroid capsule invasion (OR=0.46), as well as extrathyroidal extension (OR=0.34). We demonstrated a significant association (P<0.001, OR=4.39) with lymph node metastasis only for oncocytic variant.

Focality and bilaterality and parameters of tumor extension/aggressiveness: Multifocality and bilaterality were significantly associated with thyroid capsule invasion (P=0.0014, OR=2.18, and P=0.0032, OR=3.17, respectively) and extrathyroidal extension (P=0.0018, OR=2.28, and P=0.012, OR=2.80, respectively). In parallel, we noticed that thyroid capsule invasion and extrathyroidal extension are directly influenced by the number of tumor foci.

Table 4. Clinicopathological characteristics according to lymph node metastasis

Clinicopathological characteristics	Lymph node metastasis		Univariate analysis	OR (95% CI)
	Absent (n=145)	Present (n=23)		
Age at diagnosis	53.1±11.97	52.6±11.93	P=0.915	
<55 years old	67 (83.7%)	13 (16.3%)	P=0.357	1.51 (0.58-4.01)
≥55 years old	78 (88.6%)	10 (11.4%)		
Tumor size (mm)	3.51±2.39	5.85±2.41	P=0.00006*	
Location				
Subcapsular	57 (78.1%)	16 (21.9%)	P=0.0065*	3.53 (1.26-10.17)
Intraparenchymal	88 (92.6%)	7 (7.4%)		
Histopathologic type				
Papillary	56 (82.4%)	12 (17.6)%	P=0.219	1.73 (0.66-4.57)
Follicular	82 (91.1%)	8 (8.9%)	P=0.052	0.41 (0.15-1.11)
Oncocytic	7 (70%)	3 (30%)	P<<0.001*	4.39 (1.73-7.11)
Focality of the tumor				
Unifocal (foci)	99 (88.4%)	13 (11.6%)	P=0.274	1.66 (0.62-4.41)
Multifocal (foci)	46 (82.1%)	10 (17.9%)		
Multifocality-number of tumor foci				
2	25 (83.3%)	5 (16.7%)	P=0.601	1.33 (0.39-4.31)
3	13 (76.5%)	4 (23.5%)	P=0.214	2.14 (0.52-8.11)
≥4	8 (88.9%)	1 (11.1%)	P=0.789	0.8 (0.12-5.31)
Unilateral or bilateral involvement				
Unilateral	21 (84%)	4 (16%)	P=0.980	1.26 (0.26-6.27)
Bilateral	25 (80.7%)	6 (19.3%)		
Coexisting thyroid pathology				
Thyroid adenoma	2 (100%)	0 (0%)	P=0.9017	3.11 (0.27-35.68)
Graves' disease	6 (75%)	2 (25%)	P=0.6696	2.20 (0.41-11.66)
Colloid goiter	29 (82.9%)	6 (17.1%)	P=0.6954	1.41 (0.51-3.89)
Nodular goiter	70 (89.7%)	8 (10.3%)	P=0.3268	0.57 (0.22-1.43)
Hashimoto's thyroiditis	38 (84.4%)	7 (15.6%)	P=0.8634	1.23 (0.47-3.22)

OR: odd ratio; CI: confidence interval; **P*-value <0.05 was considered to be statistically significant; for P<0.00000001 we have noted P<<0.001.

Thus, for the capsule invasion, the presence of 3 foci causes an OR of 2.58, which grows exponentially for a number of more than 4 foci to 8.28. Similarly, for extrathyroidal extension the presence of 3 foci causes an OR of 2.69, which grows significantly for a number of more than 4 foci to 7.74. We found no significant association between multifocality (regardless of the number of foci) and lympho-vascular invasion or lymph node metastasis; similarly for bilaterality. However, statistical analysis showed a significant correlation between unifocality and the number of metastatic lymph nodes (P=0.0264).

Associated endocrine pathological background and parameters of tumor extension/aggressiveness: By considering all accompanying thyroid lesions, colloid goiter and Hashimoto thyroiditis were significantly associated with extrathyroidal extension (P=0.0393, and P=0.0384, respectively).

Relationships between clinicopathological prognostic factors-multivariate analyses

The multivariate analysis was based on the prognostic clinicopathological factors which showed a significant association within the univariate analysis.

For lympho-vascular invasion, only tumor size (P=0.016, OR=1.28) and subcapsular location (P=0.041, OR=3.44) had predictive value.

For thyroid capsule invasion, 3 from 6 factors presented predictive value, namely: tumor size (P=0.015, OR=1.28), subcapsular location (P=

0.036, OR=3.54), and multifocality (P=0.024, OR=2.63).

For extrathyroidal extension, the negative predictive factors included: tumor size (P=0.018, OR=1.28), subcapsular location (P=0.037, OR=3.20), oncocytic histological variant (P= 0.041, OR=1.95), and multifocality (P=0.021, OR=1.97). The presence of follicular variant (P=0.037, OR=0.49) significantly decreased the risk for extrathyroidal extension.

For lymph node metastasis, out of the four factors which showed significant associations in the univariate analysis only one maintained a predictive potential. We found that tumor size (P=0.003, OR=1.37) is a negative prognostic factor, which increases the risk of metastasis.

Discussion

The dual behavior of PTMC, predominantly favorable and rather rarely aggressive [27], is currently a stirring topic in thyroid pathology, especially because PTMC incidence has been rising after its definition as a distinct diagnostic entity-undoubtedly due to the imaging techniques progress [28]. The major issue consists in the identification of those clinicomorphological characteristics which can distinguish between the two behavioral types. This focus is absolutely necessary since the percentage of cases with a central lymph node metastasis is also rising, varying from under 10% [26] up to 61% [10, 29-33]. A recent point of view contends that PTMC is essentially an early stage in the development of PTC [14, 21, 34] and not a different entity. Consequently, a paradigm shift in the PTMC treatment is recorded in relation to risk stratification [27]. A certain trend recommends an initial rather aggressive treatment similar to PTC [27, 28] motivated by the high percentage of central lymph node metastasis revealed through prophylactic central lymph node dissection [31]. Nonetheless, such a treatment must be regarded as a bold decision, since criteria to anticipate further evolution are not really available, and the prognostic value of this therapy failed to be demonstrated even by randomized clinical trials [14, 35].

The most studied potential prognostic factors are age, gender, finding modality (incidental versus non-incidental), tumor size, histological type, extension, multifocality, lymph node or distant metastasis upon diagnosis, type of surgical treatment, and ablative radioiodine therapy [15, 36, 37]. Unfortunately, the identification of those prognostic factors meant to ensure the stratification of PTMC in two large classes, with high or low risk of recurrence, is far from being completed. The results until now are unconvincing.

The four parameters associated with tumor aggressiveness

In the entire study group, lympho-vascular invasion was rather rare (4.20%), and thyroid capsule invasion was identified in approximately one fifth of our cases (21.73%). To the best of our knowledge, these two parameters are less studied as prognostic factors in PTMC in comparison with PTC.

The extrathyroidal extension, present in less than one fifth of our cases (17.29%), is reported in a percentage which varies, largely, between 2 and 52% of PTMC [10, 12, 20, 27, 34, 38]. Nevertheless, its role of prognostic factor is a contradictory issue, with evidences in support [25, 27, 39, 40] or against it [12, 20, 32, 41].

The lymph node involvement was recorded for 13.69% of cases, lower than the percentages reported in the literature (i.e. 24.3-64%) [42]. Only in 5 of the 23 cases with lymph node metastasis, the primary tumor was located in the upper third of the thyroid lobe, so that the association between the lateral neck lymph node involvement and this location [43, 44] cannot be confirmed. Recent studies argue that lymph node metastasis represents a negative prognostic factor-as independent predictor of disease recurrence [12, 13, 21, 45] or as risk factor for distant metastasis rarely present at the diagnosis time [15]. However, there are differences regarding the location of the involved lymph nodes; the prognostic value for metastasis in lateral neck lymph nodes is already ascertained [35], whereas for central lymph nodes is still under discussion [9, 10].

The prognostic value of the clinicopathological characteristics

Age: The prognostic value of age has been intensively studied using a cutoff of 45 yo [15], with contradictory results [30, 32, 44, 46]. For most studies, age is not a prognostic factor for lymph node metastasis, disease recurrence or survival [10, 12, 35]. On the other hand, age

over 45 yo is more frequently correlated with the thyroid capsule invasion [37], central lymph node metastasis [22, 35, 47, 48] and nodal recurrence [27]. These controversial results allow to a major change in the 8th Edition of the TNM Classification of Malignant Tumours, applicable from January 2017, where the age for a poor prognosis in well-differentiated thyroid carcinoma has changed from 45 to 55 years of age [24]. The implementation of the new cutoff of 55 yo in the AJCC/UICC staging system aims to prevent the low-risk category of patients from overstaging and consequently from overtreatment [24]. To the best of our knowledge, there are no data regarding the risk stratification of PTMC and the age of 55 yo. Unfortunately, our results cannot confirm a relationship between this age cutoff and the four considered parameters of aggressiveness. Therefore we consider that the prognostic value of the age is still debatable.

Tumor size: Tumor size may have potential as independent predictive factor, although there are also contrary opinions [26]. The cutoff is very variable [12, 29-31, 37, 44, 46, 49], most of the studies using a threshold of 5 mm [25, 26, 35]. Our study demonstrated the association between tumor size larger than 5 mm and the aggressiveness parameters. The role of independent predictive factor was confirmed by multivariate analysis. These results agree with reported data, which certify that the tumor size is associated with multifocality [42], bilateral location [31, 37], lympho-vascular invasion and extrathyroidal extension [12, 20, 34, 37, 38, 42], lymph node metastasis [27, 35, 37, 42, 48], disease persistence [28] and distant metastasis during diagnosis [15].

Tumor location: To the best of our knowledge, there is little information on the prognostic value of the tumoral, subcapsular or intraparenchymal situs [50]. We formulated the hypothesis according to which the location of the tumor microfocus may influence the subsequent evolution in a negative way. The data obtained showed, beyond any doubt, that subcapsular PTMC has a high potential of lympho-vascular and thyroid capsule invasion, extrathyroidal extension and lymph node metastasis. The multivariate analysis emphasized the role as independent predictive factor for the subcapsular location in relation to the first three parameters of aggressiveness considered, but not for lymph node metastasis. We consider this a valuable result since PTMC can be identified by high-resolution medical imaging, and the location (subcapsular or intraparenchymal) may guide the therapeutic conduct towards either conservative or aggressive approaches.

Histologic type: Relatively few studies are focused on the prognostic value of the histological configuration of PTMC. According to literature, the papillary variant represents 65-99% of the total cases, the follicular variant being reported in 0.3-31% of the cases, sclerosing variant in 5-11.7% of cases, whereas oncocytic and tall cell variants in 0.8% [15, 20]. The follicular variant is associated with distant metastasis at diagnosis [15], and the oncocytic or tall cells variants are considered more aggressive [20]. The structure of the study group was largely different from already reported percentages. Thus, we recorded higher percentages for the follicular (57%) and for the oncocytic variant (6.78%) than those reported (31% and 0.8%, respectively), while for the papillary variant, the percentage we noted, namely 36.22%, was below to the 65% found in the literature. These histologic findings could express regional features. At national level, the research on thyroid pathology is focused mainly on epidemiologic and clinical elements. An increase in the thyroid cancer incidence by 10 times in the last decades (mostly on young population) and a high frequency for follicular variant of PTC have been documented, possibly related to the Chernobyl nuclear accident [51, 52], or to the iodine salt administrated as a food supplement [53]. These features should be confirmed by extensive histological studies, as Romanian data about the histological variants of PTC and PTMC are currently very limited [54, 55]. Although we noticed discrepancies in the frequency of histological variants, the obtained results partially overlap the state of the art. Thus, the oncocytic variant, considered to be the most aggressive [20], had the highest risk of associating with thyroid capsule invasion, extrathyroidal extension and lymph node metastasis. We also noted a significant correlation between the papillary variant and lympho-vascular invasion. Furthermore, the follicular variant had the lowest risk of lympho-vascular, thyroid capsule invasion, and extrathyroidal extension. While very few studies

target the potentially prognostic value of the histologic type, we consider the multivariate analysis result to be important, and accordingly the oncocytic variant is an independent predictive factor for extrathyroidal extension.

Focality and bilaterality: The hypothesis of multifocal PTC arising from independent clonal origins of distinct tumor foci [56, 57] is not confirmed for PTMC. Several articles target the analysis of multifocality as a prognostic factor in PTMC, with contradictory results. Multifocality could be an independent predictor or risk factor for lymph node metastasis (central or not) [4, 10, 15, 17, 28, 31, 32, 46, 48, 56], irrespective of age [32], and relapse [12, 13, 16, 17, 32, 36, 58]. Likewise, multifocality is associated with extrathyroidal extension [21], thyroid capsule invasion and a significant risk of a contralateral tumor [10, 29]. In contrast, complementary data show that there is no correlation between multifocality and prognosis, assessed through lymph node metastasis [59] and recurrence rate [60]. Our study confirms the association of multifocality and bilaterality with thyroid capsule invasion and extrathyroidal extension. According to the multivariate analysis, multifocality is an independent predictive factor. For example, from 3 foci to over 4, the OR value increases exponentially, and this observation could represent a major decisional event in the assessment of prognosis. On the other hand, our study corroborates the report series [48, 59, 60] which dispute the role of multifocality and bilaterality as prognostic factors for lymph node metastasis. These results may be explained either through the timing of PTMC diagnosis (made in more or less incipient stages), or through the behavioral differences of this tumor (indolent versus aggressive type).

Associated thyroid pathology: Endocrine pathology in the thyroidal tissue observed concurrently with PTC is more frequently studied than in PTMC. Some data indicates a positive correlation of Hashimoto disease with disease free survival and overall survival [61]. The potential prognostic role of Hashimoto thyroiditis [26], Graves' disease [62], nodular goiter, and adenoma for PTC is controversial. In the case of PTMC, only Hashimoto thyroiditis is constantly identified [62, 63], although the relation with the central lymph node metastasis [26, 48] or the persistence of disease [27] is not confirmed. Our study group was characterized by a great variety of associated lesions. There was no correlation between thyroid pathology associated with PTMC and the considered parameters of aggressiveness, except for colloid goiter and Hashimoto thyroiditis versus extrathyroidal extension. It is difficult to explain why these associated endocrine diseases are correlated only with extrathyroidal extension and not with lympho-vascular invasion, thyroid capsule invasion or lymph node metastasis. Possibly this result reflects the peculiarity of the analyzed group, which had extrathyroidal extension and high frequency of colloid goiter (25 out of 111 cases, 22.5%) and Hashimoto thyroiditis (15 out of 86 cases, 22.1%). Consequently, we cannot recommend the associated thyroid pathology as a prognostic factor for PTMC. The future challenge is to demonstrate whether the preexistent pathological background leads to the development of PTMC or not.

Conclusion

The present study confirmed that the tumor size is a negative prognostic factor for lympho-vascular invasion, thyroid capsule invasion, extrathyroidal extension and lymph node metastasis. We also demonstrated the strong relationship between the subcapsular location and lympho-vascular and thyroid capsule invasion, and extrathyroidal extension. The multifocality was correlated only with capsule invasion and extrathyroidal extension. Regarding the histological variants, the only validated correlation was between the oncocytic variant and extrathyroidal extension. This work contributes to the validation of PTMC prognostic factors, useful in stratification of PTMC in high or low risk classes, and able to explain the behavioral differences in the tumor development.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Simona Eliza Giuşcă, Department of Morphofunctional Sciences I-Pathology, "Grigore T. Popa" University of Medicine and Pharmacy, 16 University Street, 700115 Iassy,

Romania. Tel: 0040-758383773; E-mail: simonaelizagiusca@gmail.com

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