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Clinicopathological Characteristics of Incidental Papillary Thyroid Microcarcinoma in an Endemic Goiter Area

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Abstract: Papillary thyroid microcarcinoma (PTMC) is a common malignant disease of the endocrine system, which has rapidly increased in incidence and prevalence in recent decades. The aim of our paper was to identify correlations between pathological and clinical features of cases of PTMC. A total of 612 patients of both genders, who were operated on for benign thyroid diseases in the 3rd Surgical Unit of St. Spiridon University Hospital of Iasi, were monitored for a period of 2 years. According to pathological reports, PTMC was diagnosed in 144 cases. Of those cases, 81.2% were female and 18.8% were male, with an overall mean age of 54.77 ± 11.9 years. The mean diameter of tumors was 3.04 ± 2.2 mm (75.7% were under 5 mm), and 35.4% were multifocal tumors. Of all tumors studied, 76.4% were the follicular variant, 13.2% were conventional, and 10.4% of cases included tall cell, hobnail, or columnar variants. The underlying diseases were multinodular goiters (73.6%), adenomas (25%), Hashimoto thyroiditis (17.4%), Basedow's disease, and other types of hyperthyroidism (4.9%), primarily hyperparathyroidism (7.6%), with a small percentage presenting a combination thereof. Extracapsular invasion was present in 14.6% while 5.6% presented perineural invasion and 0.7% of cases had vascular invasion. Lymphatic emboli were found in 9% of cases and lymph node metastasis in 5.6% of cases. PTMC is not as innocent as believed, and further studies, performed on larger batches, would be necessary in order to identify high oncological risk cases and to determine when a more aggressive surgical approach is indicated.

Keywords: thyroid; papillary; microcarcinoma; incidental

1. Introduction

Papillary thyroid microcarcinoma (PTMC) is defined as papillary thyroid carcinoma (PTC) measuring less than 1 cm at its largest diameter [1]. In most cases PTMC has a steady state or is very slow growing with a low rate of metastasis, and based on those characteristics it is considered to have a very good prognosis [2]. However, we should not neglect the fact that it is still a carcinoma and a small percentage of patients do not have such good prognoses, due to development of lymph nodes or distant metastases. Given the morbidity associated with thyroidectomy, which cannot be decreased under 1–3%, even in specialized centers [3], extensive surgical treatment for all cases of diagnosed

PTMC is not justified; nowadays, even if it is still under debate and only used for selected cases, active surveillance gains an important place in the management of PTMC [2–5].

The guidelines of the American Thyroid Association (ATA) advise a risk-directed approach in the management of thyroid cancer; lobectomy, or an active surveillance protocol based on repetitive imaging studies and thyroglobulin measurements, is now suggested for PTMC without known preoperative risk factors [6].

The prevalence of incidental PTMC in both malignant and benign thyroid diseases is reported to be between 7.1% and 16.3% [7,8]. It may be incidentally found in up to 22% of cases operated on for exclusively benign diseases of the thyroid, and also in 0.5% to 5.2% of autopsy studies of patients with non-thyroidal diseases [9,10]. As can be seen, the true prevalence of incidental PTMC is not really known, as the literature up to now gives variable data related to geographic region, base disease (benign or malignant), and type of study (live patient or postmortem diagnosis). The continuously increasing prevalence of PTMC in living people, despite an unchanged mortality rate, appears to be related to the development of diagnosis methods and screening programs for thyroid diseases [11].

As evidenced by histopathological examination, a non-negligible percentage of PTMC may be aggressive [12]. The aggressiveness of PTMC is expressed by metastasis in both lymph nodes (LNs) and distant areas and by an increased recurrence rate, which can be similar to papillary cancer as a percentage [13–15].

The purpose of the study was to evaluate the clinicopathological characteristics of the incidentally identified PTMC in a group of patients operated on for previously diagnosed benign thyroid pathology in an endocrine surgery center serving a large endemic goiter area. We also aimed to identify the cases of PTMC which had increased oncological risk.

2. Materials and Methods

The retrospective study was performed on a cohort of 612 patients operated on for benign thyroid diseases in the 3rd Surgical Unit of the St. Spiridon Hospital of Iasi between January 2016 and December 2018. The inclusion criterion was the presence of PTMC in the final pathological report for patients with an initial diagnosis of benign thyroid disease, whereas patients in whom other types of thyroid carcinoma were concomitantly discovered were excluded.

All patients included in the study signed informed consent for participation. The study was approved by the Ethics Commission of St. Spiridon Emergency Hospital of Iasi, Romania (approval no. 11 of 2016 in compliance with ethical and deontological rules for medical and research practices). The study was conducted in accordance with the Helsinki Declaration and with several published principles.

Regarding surgical procedures, total thyroidectomy was performed in 125 cases (86.8%), because of either the surgical indication or the expressed preference of the patient (in cases where only lobectomy was indicated). Thyroid lobectomy was performed in 14 cases (9.7%) and diagnosed with a single nodule with benign clinical, ultrasound, and FNAC features (fine-needle aspiration cytology). A later completion thyroidectomy was done in 5 cases (3.4%), due to unfavorable pathological reports (extra capsular invasion, vascular invasion, lymphatic emboli, or perineural invasion). Central compartment lymphadenectomies were also performed in these cases, concomitant with the completion of a thyroidectomy. In another 5 cases, lymphadenectomy was performed, following an interval of 11 to 23 months after thyroidectomy, for lymphatic recurrence (3 cases in the central compartment and 2 cases in both the central and homolateral compartments). Overall, a total of 8 cases (5.6%) were pathologically proven with lymph node metastases. No distant metastases were found in our group of patients.

The main clinicopathological characteristics analyzed were age, sex, underlying thyroid disease, number and size of the PTMC (we noted the largest and total diameter for multicentric tumors), histopathological variance of the tumors, extracapsular invasion, vascular and perineural invasion of the tumors, presence of lymphatic emboli, and lymph node status.

We used SPSS V.19.0 (SPSS Inc., Chicago, IL, USA) to analyze the obtained data. The continuous variables were expressed as mean ± standard deviation; total count and percent were reported for categorical variables. The assessment of predictable factors for a specific variable was analyzed by univariate and multivariate logistic regression. Risk factors associated with positive lymph nodes were analyzed with univariate analysis.

3. Results

Of all 612 patients operated on for benign thyroid diseases, the pathological examination after paraffin embedding diagnosed PTMC in 144 cases (23.52%); 117 (81.2%) patients were female and 27 (18.8%) were male. With an overall mean age of 54.77 ± 11.9 years, 79 patients (54.9%) were older than 55 years (mean age 63.65 years) and 65 (45.1%) were less than 55 years old, ranging from 25 to 54 years with a mean age of 43.67 years.

The overall mean diameter of tumors was 3.04 ± 2.2 mm, and 109 patients (75.7%) had small tumors (less than 5 mm at their largest diameter). Fifty-one patients (35.4%) were diagnosed with multifocal tumors. Regarding pathological type, 110 tumors (76.4%) were the follicular variant, 19 (13.2%) were conventional, and 15 patients (10.4%) were diagnosed with other variants of PTMC, as follows: 10 cases of tall cell variant (6.94%), 3 cases of hobnail PTMC (2.08%), and 2 cases of columnar PTMC (1.38%). The underlying diseases for which the patients were referred to surgical treatment were: multinodular goiter in 106 (73.6%) cases, adenoma in 36 (25%) cases, 25 cases of Hashimoto thyroiditis (17.4%), Basedow's disease and other types of hyperthyroidism in 7 cases (4.9%), and primary hyperparathyroidism in 11 cases (7.6%), with a small percentage presenting a combination thereof. When assessing the histopathologic factors of aggressiveness, the final reports showed that 14.6% of PTMC had extracapsular invasion (21 cases), 5.6% (8 cases) presented perineural invasion, and only 1 case (0.7%) had vascular invasion. Lymphatic emboli were found in 13 patients (9%) and lymph node metastasis in 8 patients (5.6%). The main characteristics of the patients with PTMC in our study are shown in Table 1.

The mortality rate after surgical treatment was zero; one permanent unilateral paresis (0.69%) and four (2.7%) transitory pareses of the recurrent laryngeal nerve were recorded. One (0.69%) case of permanent hypocalcemia and six (4.1%) cases of transitory hypocalcemia were noted. Considering the ATA risk stratification, most of the patients (112 cases, 77.7%) were included in the low risk category, whereas 32 patients (22.2%) had intermediate risk and no patient met the criteria for the high risk category.

We used the Pearson coefficient to find the correlations between positive lymph nodes, as the dependent variable, and other histopathological markers of aggressiveness. No relation with the patients' age and sex was found, but the presence of metastatic lymph nodes was positively correlated with extracapsular invasion (moderate to strong correlation, $r = 0.587$, $p < 0.001$), lymphatic emboli (moderate to strong correlation, $r = 0.558$, $p < 0.001$), and perineural invasion (strong correlation, $r = 0.603$, $p < 0.001$). Moreover, extracapsular invasion was positively correlated with the presence of lymphatic emboli (moderate correlation, $r = 0.488$, $p < 0.001$), perineural invasion (moderate correlation, $r = 0.501$, $p < 0.001$), and vascular invasion (weak correlation, $r = 0.2$, $p = 0.01$). It was also positively correlated (moderate correlation, $r = 0.45$, $p < 0.001$) with tumors larger than 5 mm and with total diameter when the tumors were multicentric (weak correlation, $r = 0.33$, $p < 0.001$). The presence of lymphatic emboli was also positively correlated with large tumors (moderate correlation, $r = 0.453$, $p < 0.001$) and with total diameter in cases of multicentric tumors ($r = 0.406$, $p < 0.001$) and negatively with small tumors (moderate correlation, $r = -0.443$, $p < 0.001$) (Table 2).

Table 1. Clinical and pathological characteristics of the patients.

Characteristics		*n (%)*
Age	< 55 years	65 (45.1%)
	≥ 55 years	79 (54.9%)
Sex	Male	27 (18.8%)
	Female	117 (81.2%)
Diameter	Small (<5mm)	109 (75.7%)
	Large (≥5mm)	35 (24.3%)
Multifocality	No	93 (64.6%)
	Yes	51 (35.4%)
Variants	Follicular	110 (76.4%)
	Conventional	19 (13.2%)
	Tall cell/hobnail/columnar	15 (10.4%)
Local invasion	Extracapsular	21 (14.6%)
	Vascular	1 (0.7%)
	Perineural	8 (5.6%)
	Lymphatic emboli	13 (9.0%)
Positive lymph nodes	Yes	8 (5.6%)
Base disease (including multiple lesions on same patient)	Multinodular goiter	106 (73.6%)
	Hashimoto Thyroiditis	25 (17.4%)
	Adenoma	36 (25.0%)
	Basedow disease/hyperthyroidism	7 (4.9%)
	Concomitant primary hyperparathyroidism	11 (7.6%)

Table 2. Assessment of correlations between different markers of tumoral aggressiveness.

Correlations		Positive Lymph Nodes	Extracapsular Invasion	Lymphatic Emboli	Perineural Invasion	Vascular Invasion	Age	Male	Female
Positive lymph nodes	Pearson Correl	1.00	0.587 **	0.558 **	0.603 **	−0.020	−0.023	−0.039	0.039
	Sig. (2-tailed)		0.000	0.000	0.000	0.809	0.781	0.644	0.644
Extracapsular invasion	Pearson Correl	0.587 **	1	0.488 **	0.501 **	0.202 *	0.061	0.104	−0.104
	Sig. (2-tailed)	0.000		0.000	0.000	0.015	0.467	0.215	0.215
Lymphatic emboli	Pearson Correl	0.558 **	0.488 **	1	0.347 **	0.265 **	−0.023	0.035	−0.035
	Sig. (2-tailed)	0.000	0.000		0.000	0.001	0.789	0.678	0.678
Perineural invasion	Pearson Correl	0.603 **	0.501 **	0.347 **	1	−0.020	0.000	0.039	−0.039
	Sig. (2-tailed)	0.000	0.000	0.000		0.809	0.996	0.644	0.644
Vascular invasion	Pearson Correl	−0.020	0.202 *	0.265 **	−0.020	1	−0.041	0.174 *	−0.174 *
	Sig. (2-tailed)	0.809	0.015	0.001	0.809		0.628	0.037	0.037
Age	Pearson Correl	−0.023	0.061	−0.023	0.000	−0.041	1	0.110	−0.110
	Sig. (2-tailed)	0.781	0.467	0.789	0.996	0.628		0.191	0.191
Male	Pearson Correl.	−0.039	0.104	0.035	0.039	0.174 *	0.110	1	0.590 **
	Sig. (2-tailed)	0.644	0.215	0.678	0.644	0.037	0.191		0.000
Female	Pearson Correl.	0.039	−0.104	−0.035	−0.039	−0.174 *	−0.110	0.590 **	1
	Sig. (2-tailed)	0.644	0.215	0.678	0.644	0.037	0.191	0.000	

**. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2-tailed).

Positive lymph nodes correlated positively with large tumors (weak to moderate correlation, $r = 0.365$, $p < 0.01$), but not with the type of disease for which the patient was initially operated on

(Table 3). No correlations were found between the histological variant and any of the markers of aggressiveness (extracapsular invasion, vascular invasion, lymphatic emboli, or neural invasion).

Table 3. Assessment of positive lymph nodes in relation with general histopathological data.

Correlations		Positive Lymph Nodes	Hashimoto	Adenoma	Multinodular Goiter	Basedow's Disease	Primary Hyperparathyroidism	Small	Large
Positive lymph nodes	Pearson Correl	1.00	0.049	0.070	0.076	−0.055	−0.070	−0.357 **	0.365 **
	Sig. (2-tailed)		0.560	0.404	0.363	0.514	0.406	0/000	0.000
Hashimoto	Pearson Correl	0.049	1	−0.138	−0.682 **	−0.104	0.075	−0.039	0.047
	Sig. (2-tailed)	0.560		0.100	0.000	0.217	0.370	0.639	0.573
Adenoma	Pearson Correl	0.070	−0.138	1	−0.055	−0.131	0.075	−0.084	0.094
	Sig. (2-tailed)	0.404	0.100		0.516	0.119	0.369	0.316	0.260
Multinodular goiter	Pearson Correl	0.076	−0.682 **	−0.055	1	−0.378 **	−0.006	−0.009	−0.001
	Sig. (2-tailed)	0.363	0.000	0.516		0.000	0.945	0.918	0.990
Basedow disease	Pearson Correl	−0.055	−0.104	−0.131	−0.378 **	1	0.057	−0.022	0.026
	Sig. (2-tailed)	0.514	0.217	0.119	0.000		0.501	0.789	0.753
Primary hyperparathyroidism	Pearson Correl	−0.070	0.075	0.075	−0.006	0.057	1	0.102	−0.098
	Sig. (2-tailed)	0.406	0.370	0.369	0.945	0.501		0.224	0.241
Small	Pearson Correl	−0.357 **	−0.039	−0.084	−0.009	−0.022	0.102	1	−0.981 **
	Sig. (2-tailed)	0.000	0.639	0.316	0.918	0.789	0.224		0.000
Large	Pearson Correl	0.365 **	0.047	0.094	−0.001	0.026	−0.098	−0.981 **	1
	Sig. (2-tailed)	0.000	0.573	0.260	0.990	0.753	0.241	0.000	

**. Correlation is significant at the 0.01 level (2-tailed).

Also, the presence of lymph node metastasis was not correlated with the histological variant of PTMC (seven cases of follicular and one tall cell variant).

Logistic regression analysis (Table 4) identified the most influential variables associated with positive lymph nodes. On multivariate analysis, large tumors (Odds Ratio/OR 28.25; $p < 0.05$), perineural invasion (OR 73.88; $p < 0.05$), and the presence of lymphatic emboli (OR 55.28; $p < 0.05$) were independent predictors of lymph node metastasis located in the central compartment.

Table 4. Multivariate analysis—risk factors for positive lymph nodes in the central compartment.

Parameters	Odds Ratio	95% Confidence Interval		*p*
		Lower	Upper	
Large tumors (≥ 5mm)	28.25	3.33	239.52	0.000
Lymphatic emboli	55.28	9.39	325.18	0.000
Extracapsular invasion	0.09	0.05	0.16	0.000
Perineural invasion	73.88	11.82	461.77	0.000
Vascular invasion	0.99	0.97	1.00	0.9

4. Discussion

The variability of the reported data concerning the incidence of PTMC is large. A recent study on a large cohort of 1793 patients operated on for benign diseases discovered a 4.62% incidence of incidental PTMC [16]. As the percentage of incidental PTMC in our cohort was higher, our results agree with two other studies that reported that PTMC in histological specimens after thyroid surgery for benign diseases was found in 22% and 27.4% of cases, respectively [15,17].

Age has long been debated as a prognostic factor for differentiated thyroid carcinoma. The data are still controversial, as there are studies that support age as a factor correlated to an increased risk for lymph node metastases and lymphatic recurrence [18] and other studies that argue that age is not a prognostic factor for lymph node metastases and local recurrence [19]. Almost half of our patients (45.1%) were less than 55 years old, the raised age cutoff considered by the 8th edition of The American Joint Committee on Cancer AJCC/TNM staging [20]. Even if the previous cutoff age (45 years), used until 2016, were to be used, more than a quarter of our patients (25.9%) would have been under the threshold, young age being a risk factor for disease progression [21]. However, our data cannot support

any of the ideas from the age-related controversy because we did not find any correlations between age and aggressiveness factors.

In a study on a large cohort of patients operated on for PTMC, the authors found that 35% of the cases had multicentric tumors, the same percent as in our study group [21]. The same study found 8% of tumors with capsular invasion, while extracapsular invasion was present in a higher percentage (30%), and the authors demonstrated that capsular invasion and extrathyroidal tumor extension are independent risk factors for recurrence and distant metastasis on a mean follow-up of 5.3 years. Our results showed that large diameter (≥ 5 mm), multifocality, and extracapsular invasion were correlated with an increased risk of positive lymph nodes, which is another important factor of aggressiveness. Other markers of aggressiveness, such as lymphatic emboli, vascular invasion, and perineural invasion, were also present in 9.0%, 0.7%, and 5.6% of our cases, comparable with the results of previous studies [22].

Positive lymph nodes in the central compartment were found in 5.6% of cases, which is far lower than in other studies in which central compartment lymphadenectomy was routinely performed (in the absence of macroscopic lymph nodes), showing the high frequency of subclinical central lymph node metastasis in PTMC [23,24]. Although the necessity of prophylactic central compartment lymphadenectomy is still not widely accepted for papillary thyroid carcinoma (not only PTMC) [25], a recent meta-analysis shows that, in addition to thyroidectomy, it reduces the risk of local recurrence without increasing the incidence of recurrent laryngeal nerve (RLN) injury (temporary or permanent) or the incidence of permanent hypocalcemia [26]. As we endorse elective central compartment neck dissection, it was performed in 6.9% of our patients and revealed positive lymph nodes in 80% of them.

In our PTMC population, positive lymph nodes correlated with perineural invasion, extracapsular invasion, and lymphatic emboli; moreover, our data show that the correlations between extracapsular invasion and perineural invasion, vascular invasion, and lymphatic emboli are statistically significant. The fact that lymphatic emboli, perineural invasion, and large tumor diameter (≥5 mm) increase the risk of lymph node metastases is demonstrated in our study by multivariate analysis. The literature in the field speaks about these factors that correlate with each other and give, along with positive lymph nodes, an increased risk of local recurrence for PTMC [21,23,27].

Limitations of the Study

Although the size of the cohort (144 cases) is consistent, a total of eight cases diagnosed with lymph nodes metastases is small for a correlation study, which is a limitation. A single surgical team, thus the uniformity of the surgical technique and unbiased results, performed the operations. Another limitation is the relatively short follow-up period of 2 years, which, if it had been extended, may have slightly raised the number of cases with LNs metastases.

5. Conclusions

Papillary microcarcinoma of the thyroid affects a significant percentage of patients considered to have benign thyroid diseases. Histopathological examination after surgical resection can precisely determine the risk classification of PTMC.

PTMC is not as innocent as believed, and further studies, performed on larger batches, would be necessary in order to identify high oncological risk cases and to determine when a more aggressive surgical approach is indicated.

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