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Papillary thyroid microcarcinoma: clinical and pathomorphological differences from larger cancers

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Abstract. Papillary thyroid carcinoma (PTC) is frequent thyroid malignant neoplasm, measuring 1 cm or less in the greatest diameter, and is classified as papillary thyroid microcarcinoma (PTMC). Up to 10% of PTMCs have a biologically aggressive course, manifested by invasive characteristics of the tumor (invasion of blood vessels, lymphatic vessels, perineural invasion, the appearance of mitotic figures, etc.), recurrence of carcinoma, which are parameters that are difficult to predict. **Aim.** To study and evaluate the clinical and histopathological features of PTMC in comparison with PTC. **Material and methods.** There were identified 91 patients with PTC, who underwent surgical treatment at the clinical bases of the Department of Surgery at the Institute of Biology and Medicine of Taras Shevchenko National University. In the studied cohort of 91 patients, 50 (85%) patients were diagnosed with PTMC, and 41 (15%) patients with PTC. **Results.** Lymphovascular invasion was significantly less often diagnosed in 15 (30%) patients in the PTMC group, compared to 24 (58%) patients in the PTC group ($p<0.005$). Also, not a single case of perineural invasion of carcinoma was diagnosed in the PTMC group, which is significantly lower compared to 4 (10%) patients in the PTC group ($p<0.005$). Further analysis of the pathomorphological data also showed a statistically significant difference between the data of macroscopic and microscopic carcinoma invasion patterns. Microscopic extrathyroidal extension of carcinoma was less often detected in patients in the PTMC group – 2 (4%) patients, as compared to 12 (29%) patients in the PTC group ($p<0.005$). It should also be noted that macroscopically, extrathyroidal extension was diagnosed significantly less often in patients in the PTMC group in 1 (2%) patients as compared to 9 (22%) patients in the PTC group ($p<0.005$). **Conslusions.** PTMC exhibits lower biologic aggressiveness than PTC, as evidenced by lower rates of microscopic and macroscopic invasion, perineural invasion, and lymphatic invasion. Microcarcinoma may be considered a more favorable prognostic factor for patients with PTC.

Keywords: thyroid, papillary carcinoma, papillary microcarcinoma, extrathyroidal extension, macroscopic invasion, microscopic invasion.

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Background

PTC is the most common follicular-cell derived malignancy of the thyroid, constituting over 80% out of all other histopathological subtypes of thyroid malignant tumors [1-3]. The incidence of PTC in Ukraine is 1.7-1.8% in the structure of other malignant tumors, which corresponds to global trends [1]. As shown in our previous studies, PTC is often diagnosed coexstiting with other benign thyroid pathology or defined as a single solid nodule. A PTC measuring 1 cm or less in the greatest diameter is classified as PTMC according to the World Health Organization [4].

Often, PTMC is detected incidentally during pathology analyses of the removed thyroid in operations for a benign thyroid neoplasm, and in this case it is classified as incidental PTMC [5, 6]. There were also demostrated subgroups of PTMC as a latent tumor in autopsy studies, or occult, when distant or locoregional metastases are determined in the absence of data on the presence of a primary tumor in the thyroid gland [7, 8]. Taking into account the possible biological aggressiveness of PTMC it is an important issue of thyroidology for early diagnosis and detection of PTMC.

Early diagnosis of PTMC might be challenged, since the size of the tumor does not allow to identify a suspicious nodule by palpation, and when using ultrasound of the thyroid gland not all nodes are considered as potential carcinoma. Typically, ultrasound-guided fine-needle aspiration biopsy can be performed for nodules as small as 3 mm. The clinical course and diagnosis of PTMC is also complicated by the presence of carcinoma coexisting with other benign thyroid pathology, which does not always allow for detecting or suspecting microcarcinomas using ultrasound. According to literature sources and our own studies, PTMC is often associated with a lower level of biological aggressiveness, compared to large thyroid cancers (more than 1 cm in the largest diameter), and taking into account such data, according to some studies, patients may even be under clinical observation [9-13]. However, up to 10% of PTMCs have a biologically aggressive course, manifested by invasive characteristics of the tumor (invasion of blood vessels, lymphatic vessels, perineural invasion, the appearance of mitotic figures, etc.), recurrence of carcinoma, which are parameters that are difficult to predict, since reliable prognostic markers for both PTMC and PTC tests, such as MIB-1 index, do not have high enough specificity and sensitivity [13, 14].

Aim of the study: to investigate and evaluate the clinical and histopathological features of PTMC in comparison with PTC.

Material and methods

The study was approved by the local ethical committee of Verum Expert Clinic.

In the study there were identified 91 patients with PTC, who underwent surgical treatment at the clinical bases of the Department of Surgery at the Institute of Biology and Medicine of Taras Shevchenko National University. Patients were divided into two groups according to the size of carcinoma. The group of PTMC included patients with a maximum tumor size up to 1 cm in the largest diameter, the group of PTC comprised patients with a cancer size of 1 cm or larger. Tumors up to 1 cm in size were considered microcarcinoma according as also showed in our previous studies [9-12].

Clinical and pathomorphological parameters of patients were obtained from medical records of inpatients, extracts from inpatients' charts, data of histopathology were also used for analysis. Preoperative examination of the patients included hormonal studies, clinical chemistry, biochemical blood tests and concentration of ionized calcium. Ultrasound examination of the thyroid gland was performed in all patients using the Thyroid image reporting and data system (TIRADS) scale. Fine-needle aspiration biopsy was performed in all patients with focal thyroid pathology, followed by cytological verification according to the The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC, categories 1-6).

Ionized calcium levels were measured preoperatively and 24 hours after surgery, and parathyroid hormone levels were determined 48 hours postoperatively. During all operative interventions, the capsule dissection technique was used. During surgery, all parathyroid glands were identified and mobilized, both recurrent laryngeal nerves were visualized [2]. Intraoperative frozen section was performed in the case of TBSRTC categories 3, 4, 5, as well as in the presence of a unilateral PTC lesion without reliable data on locoregional metastasis. The volume of surgery less than total thyroidectomy was performed in patients with favorable clinical characteristics:

the size of the carcinoma up to 1 cm, minimally invasive characteristics of the PTC, the absence of multifocal growth, bilateral growth of PTC to the contralateral lobe, and the absence of locoregional metastasis to the lymph nodes of the neck. Dissection of central compartment was performed in all patients with verified PTC and TBSRTC categories 3-6. Dissection of central compartment was not performed in the absence of suspicion of PTC at the preoperative stage (TBSRTC category 2), in the absence of macroscopic extension to the locoregional lymph nodes. ^{131}I ablation was prescribed after total thyroidectomy, suppressive thyroid stimulating hormone therapy was carried out in all cases. The volume of surgery and postoperative treatment was carried out taking into account the recommendations of the American Thyroid Association [15]. ^{131}I ablation was prescribed when performing thyroidectomy, presence of extrathyroid invasion, or metastases.

The diagnosis was verified histopathologically according to the World Health Organization classification of endocrine tumors [16]. During surgery, visual identification of the parathyroid glands was performed with the naked eye, followed by analysis of the operative field using one of the available imaging systems. Confirmation of visually identified parathyroid glands with determination of their autofluorescence in the near infrared region (NIR) and consideration in surgical decision-making. NIR autofluorescence of the parathyroid glands was performed using Fluobeam 800 or Fluobeam LX systems (Fluoptics, France) equipped with a laser NIR camera, a console for adjusting the NIR signal, and a touch screen monitor. NIR assessment was carried out in accordance with previously published protocols [17-19]. Non-parametric statistical methods were used for statistical data processing by applying Mann-Whitney test, Fisher's exact test (two-tailed). Possible associations between the studied characteristics were tested using multivariate logistic regression. The difference between the studied groups was considered significant with $p<0.05$.

Results

Out of the 91 patients, 50 (85%) patients were diagnosed with PTMC, and 41 (15%) patients – with PTC, comprising study groups. The main studied characteristics of the patients are presented in table.

Table. Analyses of the clinical and histopathological characteristics of the patients with PTMC and PTC

Показники Parameters	PTMC (n=50)	PTC (n=41)	P values
Females, n	44 (88%)	24 (58%)	0.0157
Males, n	6 (12%)	17 (42%)	0.0157
Mean age at diagnosis (range), years	43.9 (20-76)	45.3 (25-69)	NS
Mean size of carcinoma (range), cm	0.54 (0.15-0.9)	1.76 (1-4)	<0.001
PTC coexisting with benign thyroid pathology	33 (66%)	27 (66%)	NS
Invasion to blood vessels	1 (2%)	5 (12%)	NS
Invasion to lymphatic vessels	15 (30%)	24 (58%)	0.0191
Perineural invasion	0	4 (10%)	0.0379
Figures of mitoses per 10 high power fields (400x)	0	3 (7%)	NS
Microscopic extrathyroid extension	2 (4%)	12 (29%)	0.0388
Macroscopic extrathyroid extension	1 (2%)	9 (22%)	0.0045
Bilateral growth	11 (22%)	13 (32%)	NS
Multifocality	17 (34%)	14 (34%)	NS
Metastases to local lymphnodes	19 (38%)	16 (39%)	NS
Extranodal extension	1 (2%)	4 (10%)	NS
Psammoma bodies in lymphnodes	3 (6%)	1 (2%)	NS
Relapse of PTC	2 (4%)	5 (15%)	NS

Note: NS – non-significant at statistical analyses (p>0.05).

Females were diagnosed with PTMC more frequent (88%) as compared to 58% of those with PTC ($p<0.05$). The mean age of patients at the time of surgery did not differ statistically. Analysis of data between groups revealed neither significant statistical difference between TIRADS grades nor with TBSRTC categories. The following proportion of TIRADS classes was found in the PTMC group: TIRADS5 1 (2%), TIRADS4 28 (56%), TIRADS3 18 (36%), TIRADS2 – 1 (2%); in the PTC group: TIRADS5 3 (7%), TIRADS4 31 (76%), TIRADS3 7 (17%), TIRADS2 – 0.

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The following TBSRTC category distributions were found in the PTMC group: TBSRTC category 6 – 34 (68%), TBSRTC category 5 – 8 (16%), TBSRTC category 4 – 5 (10%), TBSRTC category 3 – 1 (2%), TBSRTC category 2 – 2 (4%); as compared to patients with PTC: TBSRTC category 6 – 33 (81%), TBSRTC category 5 – 5 (12%), TBSRTC category 4 – 2 (5%), TBSRTC category 3 – 1 (2%), TBSRTC category 2 – 0 (p>0,05).

Thyroidectomy was performed in the majority of patients in both studied groups, whereas hemithyroidectomy was performed in a smaller proportion of cases with significant difference. In the PTMC group, thyroidectomy was performed in 34 (68%) cases, hemithyroidectomy in 16 (32%) patients; in the PTC group, thyroidectomy was performed in 38 (93%) patients, hemithyroidectomy in 3 (7%) patients (p=0.0043). central compartment neck dissection was performed in 45 (90%) patients with PTMC and in 40 (98%) patients with PTC, which is statistically similar (p>0.05). Lateral neck dissection was performed in the PTMC group in 12 (24%) patients, and in the PTC group - in 14 (34%) patients (p>0.05). Frozen section pathology was performed in the PTMC group in 17 (24%) patients, and in the PTC group in 4 (10%) patients, which is not statistically different (p>0.05).

Analysis of pathomorphological characteristics showed significant differences between a several parameters (**table**). Lymphovascular invasion was significantly less often diagnosed in 15 (30%) patients in the PTMC group, compared to 24 (58%) patients in the PTC group (p<0.005). Also, not a single case of perineural invasion of carcinoma was diagnosed in the PTMC group, which is significantly lower as compared to 4 (10%) patients in the PTC group (p<0.005). Further analysis of the pathomorphological data also showed a statistically significant difference between the data of macroscopic and microscopic carcinoma invasion patterns. Microscopic extrathyroidal extension of carcinoma was less often detected in patients of the PTMC group – 2 (4%) patients, as compared to 12 (29%) patients in the PTC group (p<0.005). It should also be noted that macroscopically, extrathyroidal extension was diagnosed significantly less often in patients of the PTMC group in 1 (2%) patients as compared to 9 (22%) patients in the PTC group (p<0.005). Multivariate logistic regression did not show a significant difference between the parameters in the studied groups.

Discussion

This study showed distinct features from the PTMC as compared to PTC. The results of the analysis show no statistical difference in the Bethesda data (TBSRTC categories) suggesting a relatively equal detection rate for both PTMC and large carcinomas greater than 1 cm (PTC) (grade 6) or suspicious for malignancy (grade 5) nodules by fine-needle aspiration biopsy in patients of this cohort. When analyzing the data, a higher proportion of Bethesda grades 2 and 3 in the PTMC group compared to PTC is noteworthy, indicating the clinical significance of the size of the malignant nodule in the preoperative period.

We showed absence of statistical difference in TIRADS data analysis (statistically equal indicators) indicating a relatively equal frequency of detection of nodes suspicious for a malignant process by ultrasound at the preoperative stage both in PTMC and in large carcinomas larger than 1 cm (PTC). The TIRADS data are also consistent with the relatively equal frequency of fine-needle aspiration biopsy classes according to the Bethesda system (TBSRTC categories).

Results from this study demonstrated higher and significant proportion of total thyroidectomy in PTC group. Such a finding of surgical operation volume indicate higher risks of biological aggressiveness in larger carcinomas as compared to PTMC, which is in line with principles of clinical guidelines of professional associations such as American Thyroid Association and European Thyroid Association.

We also showed frequent invasion of lymphatic vessels and perineural invasion in patients with PTC. These results are consistent with our previous studies, as well as with other authors, showing a lower proportion of invasive features in PTMC compared with cancers larger than 1 cm in size (*i.e.* PTC). [10-12, 20-22]. We also showed higher frequency of both macroscopic and microscopic extrathyroidal extension in patients with PTC. These data are consistent with the results of studies reported by other authors. In particular, J. Yang et al. showed a number of pathomorphological characteristics affecting the prognosis of PTC; and although the author did not have reliable statistical power for microscopic extrathyroidal lesions, this indicator is also used in assessing the biological aggressiveness of the tumor [23]. It should also be noted that the study by Q. Qi et al. also proved

the importance of determining the extrathyroidal extension of the tumor for predicting patients with PTC [24].

Conclusion

PTMC exhibits lower biologic aggressiveness than PTC, as evidenced by lower rates of microscopic and macroscopic invasion, perineural invasion, and lymphatic invasion. Microcarcinoma may be considered a more favorable prognostic factor for patients with PTC.

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List of abbreviations

NIR – near infrared region
PTC – papillary thyroid carcinoma
PTMC – papillary thyroid microcarcinoma
TBSRTC – The Bethesda System for Reporting Thyroid Cytopathology
TIRADS – Thyroid image reporting and data system

Папілярна мікрокарцинома щитоподібної залози: клінічні та патоморфологічні відмінності від великих раків

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Резюме. Папілярна карцинома щитоподібної залози (ПКЩЗ) є частим злоякісним новоутворенням щитоподібної залози. ПКЩЗ розміром 1 см або менше в найбільшому діаметрі класифікується як мікрокарцинома (ПМКЩЗ). До 10% ПМКЩЗ мають біологічно агресивний перебіг, що проявляється інвазивними характеристиками пухлини (інвазія кровоносних судин, лімфатичних судин, периневральна інвазія, поява фігур мітозів), рецидивом карциноми, які є параметрами, які важко передбачити, але які суттєво впливають на прогноз перебігу хвороби. **Мета.** Дослідити та оцінити клінічні та гістопатологічні особливості ПМКЩЗ порівняно з ПКЩЗ. **Матеріал і методи.** Виявлено 91 хворого на ПКЩЗ, які проходили оперативне лікування на клінічних базах кафедри хірургії ННЦ «Інститут біології та медицини» Київського національного університету ім. Тараса Шевченка. У досліджуваній когорті з 91 пацієнта в 50 (85%) хворих діагностовано ПМКЩЗ, у 41 (15%) — ПКЩЗ. **Результати.** Інвазію в лімфатичні судини достовірно рідше діагностували в 15 (30%) пацієнтів у групі ПМКЩЗ порівняно з 24 (58%) пацієнтами в групі ПКЩЗ (p<0,005). Також у групі ПМКЩЗ не було діагностовано жодного випадку периневральної інвазії карциноми, що достовріно нижче порівняно з 4 (10%) пацієнтами в групі ПКЩЗ (p<0,005). Подальший аналіз патоморфологічних даних також показав статистично значущу різницю між даними макроскопічної та мікроскопічної інвазії карциноми. Мікроскопічна екстратиреоїдна інвазія карциноми рідше виявлялася в пацієнтів групи ПМКЩЗ – 2 (4%) хворих, порівняно з 12 (29%) пацієнтами у групі ПКЩЗ (p<0,005). Макроскопічна екстратиреоїдна інвазія діагностувалась значно рідше в пацієнтів групи ПМКЩЗ в 1 (2%) пацієнта, порівняно з 9 (22%) пацієнтами в групі ПКЩЗ (p<0,005). **Висновки.** ПМКЩЗ виявляє нижчу біологічну агресивність, ніж ПКЩЗ, про що свідчать нижча частота мікроскопічної та макроскопічної інвазії, периневральної інвазії та лімфатичної інвазії. Мікрокарциному можна вважати більш сприятливим прогностичним фактором для пацієнтів із ПКЩЗ.

Ключові слова: щитоподібна залоза, папілярна карцинома, папілярна мікрокарцинома, екстратиреоїдна інвазія, макроскопічна інвазія, мікроскопічна інвазія.

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