Introduction

Papillary thyroid carcinoma (PTC) is the most frequently diagnosed malignant well-differentiated neoplasm originating from follicular cells of the thyroid gland. PTC is often coexisting with other benign thyroid pathology such as chronic lymphocytic thyroiditis, follicular thyroid adenoma, toxic thyroid adenoma, Graves’ disease, non-toxic multinodular goiter. PTC can be diagnosed in patients undergoing surgical treatment for hyperparathyroidism. However, the clinical and pathomorphological features of PTC in the presence of other benign thyroid or parathyroid pathology, as well as possible differences in surgical tactics, remain relevant as evidenced by previously published reports. The purpose of the study is to assess the prevalence and determine the differences in the clinical and pathomorphological parameters of PTC in the presence of benign thyroid and parathyroid pathology.

Materials and methods.

There were identified 91 patients with PTC, who underwent surgical treatment at the clinical bases of the Department of Surgery of the NSC “Institute of Biology and Medicine” of Taras Shevchenko National University of Kyiv.

Results.

In the studied PTC cohort, 31 (35 %) patients were without coexisted benign thyroid pathology and 60 (35 %) patients had it (PTC/coexisted). A statistically significantly higher number of mitoses per 10 high power fields in the PTC group were identified in 3 (10 %) patients, as compared to the absence of this pathohistological parameter in the PTC/coexisted (p = 0.037). Further analysis of these 3 cases showed that 4 mitotic figures were found in one PTC, and one mitotic figure in the other two cases per 10 high power fields (400×). Conclusions. Papillary thyroid carcinoma in patients with other benign thyroid pathology is associated with lower biological aggressiveness than PTC without comorbidity as evidenced by a lower frequency of mitotic figures per 10 high power fields. The presence of concomitant benign thyroid pathology can be considered as a favorable prognostic factor for patients with PTC.

Keywords: papillary thyroid carcinoma; accompanying thyroid pathology; mitoses per 10 high power fields (400×)

Papillary thyroid carcinoma coexisting with benign thyroid and parathyroid pathology: clinical and pathomorphological features

Abstract. Background. Papillary thyroid carcinoma (PTC) is the most frequent malignant neoplasm originating from follicular cells of thyroid gland. PTC is often coexisting with other benign thyroid pathology such as chronic lymphocytic thyroiditis, follicular thyroid adenoma, toxic thyroid adenoma, Graves’ disease, non-toxic multinodular goiter. PTC can be diagnosed in patients undergoing surgical treatment for hyperparathyroidism. However, the clinical and pathomorphological features of PTC in the presence of other benign thyroid or parathyroid pathology, as well as possible differences in surgical tactics, remain relevant as evidenced by previously published reports. The purpose of the study is to assess the prevalence and determine the differences in the clinical and pathomorphological parameters of PTC in the presence of benign thyroid and parathyroid pathology. Materials and methods.

important to stratify the risk of malignant nodules according to TIRADS classes when performing ultrasound diagnostics and to use the Bethesda system when performing fine-needle aspiration biopsy (FNAB) of thyroid nodules [8].

Despite the fact that stage and extrathyroid spread, loco-regional metastasis of PTC play a more significant role than the presence or absence of coexisted thyroid pathology, many studies have shown a lower proportion of carcinomas and microcarcinomas on the background of benign thyroid pathology, lower biological aggressiveness of PTC and better survival rates of patients with PTC in cases of coexisted benign thyroid pathology [9, 10].

Also, PTC can be diagnosed in patients undergoing surgical treatment for hyperparathyroidism [11]. However, the clinical and pathomorphological features of PTC in the presence of other benign thyroid or parathyroid pathology, as well as possible differences in surgical tactics, remain relevant, as evidenced by previously published reports [12].

The purpose of this study was to assess the prevalence and determine the differences in the clinical and pathomorphological parameters of the PTC in relation to the presence of benign thyroid and parathyroid pathology.

Materials and methods

In the study there were identified 91 patients with PTC, who underwent surgical treatment at the clinical bases of the Department of Surgery of the Institute of Biology and Medicine of Taras Shevchenko National University of Kyiv.

Clinical and pathomorphological parameters of patients were obtained from medical records of inpatients, data of histopathology were also used for analysis. Preoperative examination of the patients included hormonal studies, clinical chemistry, ionized calcium. Ultrasound examination of the thyroid gland was performed in all patients using the TIRADS scale. FNAB was performed in all patients with verified PTC and TBSRTC categories 1–6. Ionized calcium levels were measured preoperative-ly and 24 hours postoperatively, and parathyroid hormone (PTH) levels were determined 48 hours postoperatively. During all operative interventions, the capsule dissection technique was used. During operations, all parathyroid glands were identified and mobilized, both recurrent laryngeal nerves were visualized.

Intraoperative frozen section was performed in the case of TBSRTC categories 3–5, as well as in the presence of a unilateral PTC lesion without reliable data on loco-regional 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 loco-regional metastasis to the lymph nodes of the neck (LR-MET). 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 spread to the loco-regional lymph nodes. I\textsuperscript{131} ablation was prescribed after total thyroidectomy, suppressive TSH therapy was carried out in all cases.

The volume of operative and postoperative treatment was carried out taking into account the recommendations of the ATA [12]. I\textsuperscript{131} ablation was prescribed when performing thyroidectomy, presence of extrathyroid invasion, or metastases. The diagnosis was verified histopathologically according to the WHO classification of endocrine tumors [13]. 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 parathyroid glands was performed using Fluobeam 800 or Fluobeam LX systems (Fluoptics, France) equipped with a laser NIR camera, a console for

### Table 1. Analyses of the clinical and histopathological characteristics of the cohort

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PTC/coexisted (n = 60)</th>
<th>PTC (n = 31)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>51 (85)</td>
<td>17 (55)</td>
<td>ns</td>
</tr>
<tr>
<td>Males</td>
<td>9 (15)</td>
<td>34 (45)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean age at diagnosis, years (range)</td>
<td>43.5 (20–76)</td>
<td>46.7 (25–71)</td>
<td>ns</td>
</tr>
<tr>
<td>Mean size of carcinoma, cm (range)</td>
<td>1.03 (0.15–4)</td>
<td>1.21 (0.2–3.8)</td>
<td>ns</td>
</tr>
<tr>
<td>Invasion to blood vessels</td>
<td>3 (5)</td>
<td>3 (10)</td>
<td>ns</td>
</tr>
<tr>
<td>Invasion to lymphatic vessels</td>
<td>26 (43)</td>
<td>13 (42)</td>
<td>ns</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>Number of mitoses per 10 high power fields (400×)</td>
<td>0</td>
<td>3 (10)</td>
<td>0.039</td>
</tr>
<tr>
<td>Macroscopic extrathyroid spread</td>
<td>6 (10)</td>
<td>4 (13)</td>
<td>ns</td>
</tr>
<tr>
<td>Microscopic extrathyroid spread</td>
<td>10 (17)</td>
<td>4 (13)</td>
<td>ns</td>
</tr>
<tr>
<td>Multifocality</td>
<td>21 (35)</td>
<td>10 (32)</td>
<td>ns</td>
</tr>
<tr>
<td>Metastases to local lymph nodes</td>
<td>25 (42)</td>
<td>10 (32)</td>
<td>ns</td>
</tr>
<tr>
<td>Extranodal spread</td>
<td>3 (5)</td>
<td>2 (6)</td>
<td>ns</td>
</tr>
<tr>
<td>Psammoma bodies in lymph nodes</td>
<td>3 (5)</td>
<td>1 (3)</td>
<td>ns</td>
</tr>
<tr>
<td>Relapse of PTC</td>
<td>4 (6)</td>
<td>3 (10)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Notes: data are presented as n (%) unless stated otherwise; ns — non-significant at statistical analyses (p > 0.05).
Results

In the studied cohort of 91 patients, 31 (35 %) patients with PTC were without coexisted benign thyroid pathology and 60 (35 %) patients were with PTC coexisted with benign thyroid pathology (PTC/coexisted). The main studied characteristics of the patients are presented in Table 1.

In both groups PTC was diagnosed mainly among females: 55 % in PTC and 85 % in PTC/coexisted (p > 0.05). The mean age of patients at the time of surgery was 46.7 years in PTC and 43.6 years in PTC/coexisted (p = 0.043). Analysis of data between groups did not reveal a significant statistical difference between TIRADS classes and TBSRTC categories. The following proportion of TIRADS classes was found in the PTC group: TIRADS5 — 3 (10 %), TIRADS4 — 17 (56 %), TIRADS3 — 11 (34 %), TIRADS2 — 0; and in the PTC/coexisted: TIRADS5 — 1 (1.5 %), TIRADS4 — 43 (72 %), TIRADS3 — 15 (25 %), TIRADS2 — 1 (1.5 %). The TIRADS data are also consistent with further analysis of the TBSRTC categories data using the Bethesda system. In the PTC group, there were following proportion of Bethesda classes: TBSRTC category 6 — 26 (84 %), TBSRTC category 5 — 4 (13 %), TBSRTC category 4 — 1 (3 %), TBSRTC category 3 — 0, TBSRTC category 2 — 0; in the PTC/coexisted: TBSRTC category 6 — 41 (68 %), TBSRTC category 5 — 9 (15 %), TBSRTC category 4 — 6 (10 %), TBSRTC category 3 — 2 (3 %), TBSRTC category 2 — 2 (3 %).

Most patients in both studied groups underwent complete removal of the thyroid gland: thyroidectomy was performed in 47 (78 %) cases in patients with PTC, while hemithyroidectomy was performed in 13 cases (22 %); in the PTC/coexisted thyroidectomy was performed in 30 cases (56 %). Central neck dissection was performed in 30 (100 %) patients with PTC, and in 19 (32 %) patients with PTC/coexisted (p > 0.05). Lateral neck dissection was performed in 7 (23 %) patients with PTC, and in 19 (32 %) patients with PTC/coexisted (p > 0.05). Frozen section pathology was performed in 17 (28 %) patients with PTC/coexisted, in 16 (28 %) patients with PTC (p > 0.05). Lateral neck dissection was performed in 7 (23 %) patients with PTC, and in 19 (32 %) patients with PTC/coexisted (p > 0.05). Frozen section pathology was performed in 17 (28 %) patients with PTC, and in 14 (23 %) patients with PTC/coexisted (p > 0.05).

The analysis of the data showed that among 60 patients with PTC/coexisted, in 17 (28 %) patients PTC coexisted with two or more benign pathologies of the thyroid gland: FTA + DTG in 1 (1.7 %) patient, FTA + NTMG in 1 (1.7 %) patient, FTA + CLT in 8 (13 %) patients, CLT + NTMG in 6 (10 %) patients, FTA + CLT + NTMG in 1 (1.7 %) patient (statistical difference was found). In one case (1.7 %) PTC was coexisted with NTMG and parathyroid adenoma. Among PTC/coexisted cases the following coexisting were identified: 33 cases of PTC with CLT, 18 cases of PTC with FTA, 24 cases of PTC with NTMG, 3 cases of PTC with DTG, 1 cases of PTC with TTA (statistically significant no difference was found).

The mean size of the carcinoma was slightly larger in PTC — 1.21 cm, than in PTC/coexisted — 1.03 cm (p > 0.05). As showed in Table 1, the invasive characteristics of PTC did not differ in the studied groups, multifocal growth was also determined statistically equally in both groups, locoregional metastasis was also diagnosed with a statistically equal frequency.

A statistically significant higher number of mitoses per 10 high power fields in the PTC group were identified in 3 (10 %) patients, as compared to the absence of this pathohistological parameter in the PTC/coexisted (p = 0.037). Further analysis of these 3 cases showed that 4 mitotic figures were found in 1 PTC, and 1 mitotic figure in the other two cases per 10 high power fields (400×).

Discussion

The absence of a statistical difference in relation to the TIRADS analysis data (statistically similar findings) indicate a relatively equal frequency of detection of thyroid nodules to be suspicious for a malignant process by means of ultrasound at the preoperative stage, both in case of PTC and PTC/coexisted. Attention should be paid to the presence of TBSRTC category 2 and 3 in the PTC/coexisted and their absence in the PTC group of a patient, which indicates the clinical significance of the presence of other thyroid pathology in terms of the accuracy of preoperative diagnosis.

The absence of a statistical difference according to the Bethesda analysis (statistically similar finding for TBSRTC category, p > 0.05) indicate a relatively equal frequency of detection of PTC (TBSRTC category 6) or nodes suspicious for a malignant process (grade 5) using FNAB in both studied groups.

Higher number of mitoses per 10 high power fields indicates a higher biological aggressiveness of PTC, as it is frequent feature of poorly differentiated thyroid carcinoma. The number of mitotic figures more than 3 per 10 high power fields (400×) is one of the characteristics of poorly differentiated thyroid carcinoma [16, 17]. The absence of the above-mentioned mitotic figures in the PTC/coexisted cohort may indicate a mild biological aggressiveness of the carcinoma, which is also consistent with the data of our previous studies [14, 15].

In the study of PTC and poorly differentiated thyroid carcinoma, K.S. Wong et al. also showed that a greater number of mitotic figures in the PTC was associated with a both worse prognosis and survival, indicating the importance of this histopathological feature in assessing the biological aggressiveness of the tumor [18]. Also, similar results were shown in the study of anaplastic thyroid cancer conducted by B. Xu et al., where the presence of mitotic figures was also proven as a sign of biological aggressiveness of the tumor [17]. Also, the study by J. Tong et al. also showed the importance of determining mitoses in poorly differentiated carcinoma [16]. In the context of the above-mentioned data from literature sources, the absence of mitotic figures in the PTC/coexisted cohort indicates a better clinical course of papillary carcinoma in patients with the presence of other thyroid be-
nign pathology [16–19]. Multivariate logistic regression did not show a significant difference between the parameters in the studied groups.

Conclusions

Papillary thyroid carcinoma in patients with the presence of other thyroid benign pathology is associated with lower biological aggressiveness than PTC without accompanying pathology; as evidenced by a lower number of mitotic figures per 10 high power fields. The presence of concomitant benign thyroid pathology can be considered as a favorable prognostic factor for patients with PTC.

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Папілярна карцинома щитоподібної залози на тлі добрякісної тиреоїдної та паратиреоїдної патології: клінічні й патоморфологічні особливості

Резюме. Актуальність. Папілярна карцинома щитоподібної залози (ПКЩЗ) є найбільш частою злоякісним новоутворенням, що походить із фолікулярних клітин щитоподібної залози. ПКЩЗ часто діагностується на тлі іншої добрякісної патології щитоподібної залози: хронічного лімфоцитарного тиреоїдиту, фолікулярної аденоми щитоподібної залози, токсичної аденоми щитоподібної залози, хвороби Грейвса (дифузний токсичний зоб), нетоксичного багатовузлового зоба. Мета: оцінити поширеність та визначити відмінності клініко-патоморфологічних показників ПКЩЗ на тлі іншої добрякісної патології щитоподібної залози. Матеріали та методи. Ідентифіковано 91 хворого з ПКЩЗ, які проходили оперативне лікування на клінічних базах кафедри хірургії ННЦ «Інститут біології та медицини» Національного університету імені Тараса Шевченка (Київ). Результати. У досліджуваній групі ПКЩЗ 31 (35 %) пацієнт не мав супутньої добрякісної патології щитоподібної залози та 60 (35 %) пацієнтів мали. Статистично вірогідно вищу частоту мітозів на 10 полів зору великого збільшення (400×) виявлено в 3 (10 %) пацієнтів із ПКЩЗ порівняно з відсутністю цього патогенетичного параметра в осіб із ПКЩЗ на тлі іншої патології (p = 0,037). Подальший аналіз показав, що 4 мітотичні фігури були знайдені в одному із цих трьох випадків ПКЩЗ і один мітоз — в інших двох випадках на 10 полів зору при великому збільшенні (400×). Висновки. Папілярна карцинома щитоподібної залози на тлі іншої добрякісної патології щитоподібної залози асоціюється з нижчою біологічною агресивністю, ніж ПКЩЗ без супутньої патології, про що свідчить менша кількість мітотичних фігур на 10 полів зору великого збільшення. Наявність супутньої добрякісної патології щитоподібної залози можна розглядати як сприятливий прогностичний фактор для хворих на ПКЩЗ.

Ключові слова: папілярна карцинома щитоподібної залози; супутня тиреоїдна патологія; фігури мітозів на 10 полів зору великого збільшення (400×)