Multifocality as an adverse histopathological factor in papillary thyroid carcinoma

A. Dinets 1,2, M. Gorobeiko 1, Y. Pysmenna 1, A. Lovin 1, K. Abdalla 2, V. Hoperia 1

1 Taras Shevchenko National University of Kyiv, ESC «Institute of Biology and Medicine»
2 Verum Expert Clinic, Kyiv

Papillary thyroid carcinoma (PTC) is characterized by various clinical and pathomorphological features, such as metastases to the locoregional lymph nodes and radioiodine resistance. It could also be diagnosed as a microcarcinoma coexisting with other benign thyroid pathologies or as multifocal growth. Of these, multifocality in PTC is considered an unfavourable pathomorphological feature. However, the research findings are controversial.

OBJECTIVE — to investigate and evaluate the clinical and pathohistological features of multifocal PTC (mPTC) in comparison with unifocal (single nodule) PTC.

MATERIALS AND METHODS. Among the patients who underwent operative treatment at the clinical bases of the Department of Surgery, Institute of Biology, and Medicine at Taras Shevchenko National University of Kyiv, 91 were diagnosed with PTC and were included in the study.

RESULTS. Out of the 91 patients, 31 (34 %) had mPTC and 60 (66 %) had PTC. Bilateral mPTC was diagnosed in 23 (74 %) patients, which is in line with other studies. It is also worth mentioning, that 5 (16 %) patients were diagnosed with multifocal growth only at the stage of histopathology section, without preoperative or intraoperative evidence of multifocality. A significantly higher frequency of locoregional metastasis was found in the mPTC group in 17 (55 %) patients as compared to 18 (30 %) patients with PTC (p = 0.025). Lateral neck dissection was performed in 13 (42 %) patients with mPTC, and in 13 (22 %) patients with PTC (р = 0.0525). Frozen section pathology was performed in 17 (24 patients with mPTC, and in 4 (10 %) patients with PTC (p > 0.05).

CONCLUSIONS. A higher frequency of locoregional metastasis and a higher propensity for performing a lateral neck dissection are both indicators of a higher biological aggressiveness of the carcinoma in PTC multifocal growth.

KEYWORDS
papillary thyroid carcinoma, multifocality, lymphnode metastases.
cancer. It should be noted that multifocal carcinoma growth in one or both lobes of the thyroid gland is diagnosed relatively often [17]. However, the clinical and prognostic significance of multifocal PTC is still under clinical investigation. Although the presence of multifocal PTC is considered an unfavourable pathomorphological feature, the results of the studies are controversial. There are data showing a strong association between locoregional metastasis (central and lateral neck collectors) and multifocal PTC growth. Also, several studies show that patients may have a higher risk of PTC recurrence in the presence of multifocal growth [26]. Given the controversial issue of multifocal growth, further research into this pathomorphological feature of PTC is important.

**Objective** — to investigate and evaluate the clinical and pathohistological features of multifocal PTC in comparison with unifocal (single nodule) PTC.

**Materials and methods**

Clinical and pathomorphological parameters of patients were obtained from medical records of inpatients, extracts from inpatients’ charts, and data from histopathology were also used for analysis. Among the patients who underwent operative treatment at the clinical bases of the Department of Surgery, Institute of Biology, and Medicine at Taras Shevchenko National University of Kyiv, 91 were diagnosed with PTC and were enrolled in the study.

The preoperative examination of the patients included hormonal studies, clinical chemistry, and ionized calcium. An ultrasound examination of the thyroid gland was performed in all patients using the TIRADS scale. Fine-needle aspiration biopsy (FNAB) was performed in all patients with focal thyroid pathology, followed by cytological verification according to the Bethesda classification (TBSRTC categories 1—6). Ionized calcium levels were measured preoperatively and 24 hours postoperatively, and parathyroid hormone (PTH) levels were determined 48 hours postoperatively. The capsule dissection technique was used throughout all operative interventions. All parathyroid glands were identified and mobilized, and both recurrent laryngeal nerves were visualized during operations [8]. Intraoperative frozen section was performed in the cases of TBSRTC categories 3, 4, and 5, as well as in the presence of a unilateral PTC lesion without reliable data on locoregional metastasis. A volume of surgery less than total thyroidectomy was performed in patients with favourable 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 the PTC to the contralateral lobe, and the absence of locoregional metastasis to the lymph nodes of the neck (LR-MET). Dissection of the central compartment was performed in all patients with verified PTC and TBSRTC categories 3 – 6. Dissection of the central compartment was not performed in the absence of suspicion of PTC at the preoperative stage (TBSRTC category 2) or in the absence of macroscopic spread to the locoregional lymph nodes. 131I ablation was prescribed after total thyroidectomy, and suppressive TSH therapy was carried out in all cases. The volume of operative and postoperative treatment was determined taking into account the ATAs recommendations [18]. 131I ablation was prescribed when performing a thyroidectomy and in the presence of extrathyroidal invasion or metastases. The diagnosis was verified histopathologically according to the WHO classification of endocrine tumours [20]. 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. Visually identified parathyroid glands were examined to determine their autofluorescence in the near infrared region (NIR), and a surgical decision was made based on the findings. 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 adjusting the NIR signal, and a touch-screen monitor. The NIR assessment was carried out in accordance with previously published protocols [13—15]. Statistical analyses were performed using SigmaPlot v15 trial version. Non-parametric statistical methods were used for statistical data processing by applying the Mann-Whitney test and 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, 31 (34 %) had multifocal PTC (mPTC) and 60 (66 %) had PTC. The studied characteristics of the patients are presented in Table. Multivariate logistic regression did not show any associations between the parameters in the studied groups.

Females were diagnosed with PTC in 21 (67 %) cases, and 47 (78 %) patients were diagnosed with mPTC (p < 0.05). The mean age of patients at the time of surgery did not differ statistically. Analysis of data between groups revealed no significant statistical difference between TIRADS grades or TBSRTC categories. The following proportion of TIRADS classes was found in the mPTC group: TIRADS5
A. Dinets et al.

The majority of patients in both groups were treated using thyroidectomy, whereas hemithyroidectomy was performed in a smaller proportion of cases ($p > 0.05$). Patients in the mPTC group underwent thyroidectomy in 28 (90%) cases and hemithyroidectomy in 3 (10%) cases. Patients in the PTC group underwent thyroidectomy in 44 (73%) cases and hemithyroidectomy in 16 (27%) cases. Central neck dissection was performed in 28 (90%) patients with mPTC and in 57 (95%) patients with PTC ($p > 0.05$). Lateral neck dissection was performed in 13 (42%) patients with mPTC and in 13 (22%) patients with PTC ($p = 0.0525$). Frozen section pathology was performed in 17 (24%) patients with mPTC and in 4 (10%) patients with PTC ($p > 0.05$).

Bilateral mPTC was diagnosed in 23 (74%) patients, which is in line with other studies. It is also worth mentioning that 5 (16%) patients were diagnosed with multifocal growth only at the stage of histopathology section, without preoperative or intraoperative evidence of multifocality. A significantly higher frequency of locoregional metastasis was found in the mPTC group in 17 (55%) patients as compared to 18 (30%) patients with PTC ($p = 0.025$).

Discussion

There was no statistical difference in TIRADS data analysis (i.e., statistically equal rates), indicating a relatively similar rate of detection of suspicious nodules by preoperative US in both mPTC and unifocal carcinomas (i.e., PTC).

In this study, we showed similar results for cytological data (no statistical difference) according to Bethesda classification, indicating a relatively equal (statistical) frequency of mPTC and PTC (TBSRTC category 6) or suspicious for malignancy (TBSRTC category 5) nodes by FNAB.

In addition, it should be noted that in 5 (16%) patients, multifocality was diagnosed only at the stage of histopathology section, without preoperative or intraoperative evidence of multifocality, indicating a possible risk of such histopathological features in any PTC. We showed a higher frequency of locoregional metastases in the mPTC group, which is consistent with our previous studies as well as the studies of other authors showing a higher frequency of locoregional metastases in cases of multifocality [2–5, 28]. Analysis of our data based on the results of neck dissection shows a statistical tendency ($p = 0.0525$) regarding the likely higher frequency of performing lateral neck dissection in the group of patients with mPTC compared with PTC and is consistent with data from studies in larger cohorts. In particular, an

<table>
<thead>
<tr>
<th>Index</th>
<th>mPTC (n = 31)</th>
<th>PTC (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females/Males</td>
<td>21 (67%)/10 (33%)</td>
<td>47 (78%)/13 (22%)</td>
</tr>
<tr>
<td>Mean age at diagnosis, years (range)</td>
<td>46.5 (25–68)</td>
<td>43.6 (20–76)</td>
</tr>
<tr>
<td>Mean size of carcinoma, cm (range)</td>
<td>1.1 (0.2–3.8)</td>
<td>1.1 (0.2–4.0)</td>
</tr>
<tr>
<td>PTC coexisting with benign thyroid pathology</td>
<td>21 (67%)</td>
<td>39 (65%)</td>
</tr>
<tr>
<td>Microcarcinoma</td>
<td>17 (55%)</td>
<td>34 (57%)</td>
</tr>
<tr>
<td>Invasion to blood vessels</td>
<td>3 (10%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Invasion to lymphatic vessels</td>
<td>17 (55%)</td>
<td>22 (37%)</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>2 (6%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Figures of mitoses per 10 high power fields (400x)</td>
<td>1 (3%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Microscopic extrathyroidal spread</td>
<td>4 (13%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Macroscopic extrathyroidal spread</td>
<td>3 (10%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>Metastases to local lymph nodes</td>
<td>17 (55%)</td>
<td>18 (30%)*</td>
</tr>
<tr>
<td>Mean size of lymph node metastases, mm (range)</td>
<td>10.2 (0.1–62.0)</td>
<td>4.7 (0.1–20.0)</td>
</tr>
<tr>
<td>Extranodal spread</td>
<td>1 (3%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Psammoma bodies in lymph nodes</td>
<td>1 (3%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Relapse of PTC</td>
<td>4 (13%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

Note: * The difference from the mPTC group is statistically significant ($p = 0.025$). Differences on other indicators are statistically non-significant ($p > 0.05$).
association between a higher rate of locoregional metastasis and mPTC was shown in a study by Zhang et al., where 460 patients were studied [28].

The study of multifocal growth in PTC remains an urgent problem in endocrine surgery, as evidenced by original studies, systematic reviews, and meta-analyses [9, 12, 19, 24, 27]. For example, in a meta-analysis conducted by Kim et al. (including 26 publications with a total of 33,976 patients), it was shown that multifocal PTC growth was associated with a higher risk of carcinoma recurrence but without a significant effect on survival. On the other hand, the original study by Omi et al. shows no prognostic value of the presence of multifocal dew in PTC compared with unifocal tumours [22]. Our results are consistent with the data of this meta-analysis and also demonstrate the importance of other pathomorphological characteristics of the tumour [19]. In line with Feng et al., we also showed the importance of considering multifocality and bilateral PTC thyroid involvement in routine clinical practice [12]. The results of this study support our findings regarding the consideration of possible multifocal PTC growth in terms of a higher risk of locoregional metastasis, which is in contrast with Ozdemir et al., who did not find a significant relationship between the risk of PTC metastasis and the presence of multifocal growth. The study by Wu et al. showed the association of PTC with autoimmune thyroiditis (i.e., PTC coexisting with other thyroid pathology) and the role of pathomorphological changes, in particular multifocal carcinoma growth, in the context of a worse prognosis for patients. Data from this study are consistent with our results, which also show a female predominance in the study cohort as well as a higher frequency of multifocal PTC growth in the background of chronic leukocytic thyroiditis (although without statistical difference) [27]. Our data are consistent with the results of the study by Ozdemir et al., which included 258 patients with PTC and showed that the frequency of metastasis to locoregional lymph nodes was not significantly increased in the presence of multifocal PTC [23]. It should be pointed out that the study by Machens et al. showed a relationship between the invasive characteristics of PTC, the biological aggressiveness of the tumour, and the risk of distant metastases [10, 21].

Conclusions
A higher frequency of locoregional metastasis and a higher propensity for performing a lateral neck dissection are both indicators of a higher biological aggressiveness of the carcinoma in PTC multifocal growth.

DECLARATION OF INTERESTS
The authors declare that they have no competing interests.

Funding. The study received no funding.

AUTHORS CONTRIBUTIONS
A. Dinets: project conception and design, data collection, analysis and interpretation of data, and drafting of the manuscript; M. Gorobeiko: project conception, write-up, critical revision of the manuscript, and final approval; Y. Pysmenna: acquisition of data, analysis and interpretation of data, preparation of figures, literature search, and write-up; A. Lovin: project conception and design, analysis, and write-up; K. Abdalla: project conception and design, analysis, and write-up; V. Hoperia: histopathology analyses, project conception, write-up, critical revision of the manuscript, and final approval.

REFERENCES
2. Дінець А, Гульчій М, Олійник О, Цимбалюк С. Нарушения паракаудального кровообращения в лягушке. Гонады с обозначением поражения. Проблемы онкологии и терапии рака щитовидной железы. 2013;2:20-5.
Мультифокальний ріст: неноситячий патоморфологічний чинник папілярної карциноми щитоподібної залози

А. Дінець 1, 2, М. Горобейко 1, Ю. Письменна 1, А. Льовін 1, К. Абдалла 2, В. Хоперія 1

1 Інститут біології та медицини, Київський національний університет імені Тараса Шевченка
2 Verum Expert Clinic, Київ

Папілярна карцинома щитоподібної залози (ПКЩЗ) має клінічні та патоморфологічні особливості, такі як мультифокалізм, метастази в лімфатичні вузли, резистентність до радіоактивного йоду, або може бути діагностичною метастазування в локорегіонарні лімфатичні вузли, резистентність до радіоактивного йоду, або може бути діагностичною метастазування локорегіонарних лімфатичних вузлів.

Мета — дослідити вплив мультифокалізму на біологічну агресивність папілярної карциноми щитоподібної залози, виявлення відносно біологічної агресивності мультифокалізму ПКЩЗ.

Матеріали та методи. Серед пацієнтів, яким проведено оперативне лікування на клінічних базах кафедри хірургії Інституту біології та медицини Київського національного університету імені Тараса Шевченка, у 91 діагностовано ПКЩЗ.

Результати. Пацієнтів розподілили на дві групи: 31 (34 %) віднесено до групи мультифокальної ПКЩЗ, 60 (66 %) — до групи уніфокальної ПКЩЗ. У 23 (74 %) хворих діагностовано білітарну мультифокальну ПКЩЗ. У 5 (16 %) пацієнтів мультифокальний ріст діагностовано лише на етапі планового патогістологічного дослідження за відсутності доопераційних чи інтраопераційних ознак мультифокалізму.

Висновки. Мультифокальний ріст ПКЩЗ асоціюється з вищою біологічною агресивністю карциноми, про що свідчить більша частота локорегіонарних метастазів та виконання латеральної дисекції шиї.

Ключові слова: папілярна карцинома щитоподібної залози, мультифокалізм, метастази в лімфовузли.