

Surgery

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THE RELATIONSHIP OF MICROSCOPIC INVASION
OF PAPILLARY THYROID CARCINOMA
IN PATIENTS WITH OBESITY*Dinets A.^{1, 2, 3}, Lurin I.^{3, 4}, Gorobeiko M.^{2, 3},
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Background. Papillary Thyroid Carcinoma (PTC) is the malignant neoplasm of thyroid gland constituting up to 80% of all thyroid cancer types. The relationship between PTC and obesity is not well investigated in Ukraine.

Aim. To investigate and evaluate the features of the microscopic invasive features of PTC in the obese and overweight patients and compare it with patients with PTC and normal weight.

Materials and Methods. This study enrolled 91 patients who were diagnosed with PTC. The patients were divided into a groups depending on their Body Mass Index (BMI): 20 patients with PTC and obesity (BMI >30 kg/m²), the 45 patients with overweight and PTC (BMI [25.0–29.9] kg/m²) and 26 patients with PTC and normal weight (BMI [18.0–24.9] kg/m²). A clinical data and histopathological parameters were retrieved from archived medical records. Written informed consent was to participated was obtained from all patient. Statistica 12 (TIBCO Software Inc., USA) and GraphPad Prism 10 (GraphPad Software, LLC, USA) statistical software were used for data analyses. Statistical significance was set at p<0.05. Ethical approval for the study was obtained the local ethical committee at Verum Expert Clinic. The study was conducted according to Helsinki Declaration and Ukrainian ethical standards.

Results. A statistically significant difference in the higher frequency of microscopic damage to the thyroid gland structures by PTC was detected in 6 (30.0%) patients with PTC with obesity, in 3 (6.0%) patients with PTC with overweight, and in 5 (19.0%) patients with PTC with normal weight (p=0.046). Further data analysis revealed a significantly higher frequency of the PTC perineural invasion in 3 (15%) obese patients with PTC, in 3 (2.2%) overweight patients with PTC, and in none of the patients with PTC and normal weight (p=0.031).

Conclusions. Patients with PTC and obesity have 1.57 higher frequency of microscopic invasion predominately due to perineural invasion of the carcinoma, which is aggressive biological characteristics of malignant neoplasm. The risk of PTC in the population with obesity should be taken into consideration by medical professional, and aggressive biological characteristics should be considered at follow up and management of the patients.

Keywords: neoplasm invasiveness, perineural invasion, body mass index, cancer risk factors.

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E-mail: andrii.dinets@kaunaas.com**Цитуйте українською:** Дінець АВ, Лурін ІА, Горобейко МБ, Хоперія ВГ, Абдалла КМ, Льовін АВ. Взаємозв'язок мікроскопічної інвазії папілярної карциноми щитоподібної залози у пацієнтів з ожирінням.

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Introduction

Papillary Thyroid Carcinoma (PTC) is frequent malignant neoplasm originating from thyroid follicular cell and constituting up 80% of all thyroid cancer cases [1; 2]. The PTC is also most frequent endocrine malignant neoplasm in Ukraine, which is in line with other geographical areas. Similar to other studies, this one also examines PTC in relation to other non-thyroid pathology, including coexistence with such a comorbidity as overweight and obesity [2].

Obesity is known risk factor for various malignant neoplasms, not just a diabetes mellitus type 2 [3]. Obesity is associated with an excess of white adipose tissue and obesity is determined by the calculations of the Body Mass Index (BMI) with $>30 \text{ kg/m}^2$ as obese, while the BMI range of $[25.0\text{--}29.9] \text{ kg/m}^2$ is considered as overweight, and BMI between 18 kg/m^2 and 24.9 kg/m^2 corresponds to normal weight. The results from different studies indicate the presence of various molecular mechanisms, associating with role obesity with certain types of malignant neoplasms, including PTC. There are changes in hormone concentrations, presence of chronic inflammation, oxidative stress, changes

in the carbohydrate metabolism (e.g., insulin resistance) [4].

There is a proven relation of obesity and thirteen distinct malignant entities as shown in basic, translational clinical studies, including research of PTC [5]. It is important to consider preventive measures in the population with obesity, and early detection of the PTC might be considered by simply performing prophylactic thyroid ultrasound, considering asymptomatic course of PTC. Out of various molecular-genetic mechanism contributing to the PTC carcinogenesis, there are some particular changes with distinct negative impact on the normal thyroid follicular cell proliferation and differentiation, as well as apoptosis mechanisms, increasing risk of malignant transformation to the PTC [6].

Another possible mechanism supporting the role of obesity in the development of various types of malignant neoplasms, including PTC, is the over-synthesis of estrogen, which is related to the aromatase activity of white adipose cells, and increased conversion of androgen to estrogen [7].

Also, when assessing clinical and clinical-morphological parameters, cohorts evaluate various indicators, taking into ac-

count modern clinical practices in various medical specialties, which may have an impact on all organs and systems, including in the context of the war in Ukraine [8; 9]. Chronic inflammation is pathologic feature associated with obesity and showing strong relation to support carcinogenesis, including development of PTC. Although obesity causes a moderate inflammatory process in the adipose tissue, it is characterized by the release of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6.

Research suggests various drugs against inflammation and oxidative stress in relation to thyroid cancer [10]. Previous publications to show the patients with PTC to frequently have elevation in the levels of inflammatory molecules, suggesting a potential link between obesity-induced systemic inflammation and the development of PTC [11]. There is a role of insulin resistance in oncogenesis, which is usually associated with obesity, and is also a significant risk factor for the development of PTC. Insulin resistance is associated with hyperinsulinemia, resulting promotion of cell proliferation and anti-apoptotic activity, which is increased risk of PTC development. Molecular-genetic changes in obese patients a well-studied, but the changes in pathohistological parameters are not well established, including Ukraine.

Aim of the study was to investigate and evaluate the features of the microscopic invasive features of PTC in the obese and overweight patients and compare it with patients with PTC and normal weight.

Materials and Methods

91 patients were identified for the study with diagnosis of PTC. These patients were surgically treated at Verum Expert Clinic (Kyiv, Ukraine). These 91 patients were divided into groups in relation to their weight for further evaluation. BMI was calculated in kg/m^2 . The study group constitutes patients with overweight and obesity based on their BMI. The BMI [18.0–

24.9] kg/m^2 was considered to be of normal weight, BMI [25.0–29.9] kg/m^2 was considered as overweight; and BMI >30 kg/m^2 was considered as obesity [12].

Various pathohistological and clinical parameters of patients were retrieved from the archived medical records. At preoperative stage, all patients with PTC underwent typical examination: thyroid hormones, clinical chemistry, ionized calcium as showed in our previous reports and suggested by local surgery protocols for the patients with thyroid and parathyroid lesions adopted by Verum Expert Clinic (Kyiv, Ukraine). Ultrasound examination of the thyroid gland was performed in all patients using the Thyroid Imaging Reporting and Data System (TIRADS) scale as suggested elsewhere [13].

Fine-needle aspiration biopsy was performed for all patients with thyroid nodules, followed by its cytological analyses by the TBSRTC (Bethesda System for Reporting Thyroid Cytopathology Bethesda) classification as described by Juhlin C.C. et al. [14]. Ionized calcium concentration was determined both preoperatively and 24 hours postoperatively, and parathyroid hormone levels was evaluated two days after operation.

All thyroid operative interventions were done by using the capsule dissection technique, which standard operative technique in most endocrine surgery centers, including Verum Expert Clinic as shown in our previous reports as well as by others [1; 2; 15]. During operations, all parathyroid glands were identified and mobilized, both recurrent laryngeal nerves were visualized according to the well-established technique. Dissection of central compartment was not performed in the absence of suspicion for PTC at the preoperative stage (TBSRTC category 2), in the absence of macroscopic extension to the locoregional lymph nodes at operation. Radioactive iodine ablation was performed after total thyroidectomy, suppressive thyroid-

stimulating hormone therapy was carried out in all cases. The volume of operative and postoperative treatment was carried out taking into account the valid recommendations of the American Thyroid Association at the time of operation [16].

The diagnosis was verified pathohistologically according to the WHO classification of endocrine tumors [17]. Fluorescence-guided surgery was performed for better verification of parathyroid glands in accordance with previously published protocols and equipment (Fluoptics 800 and LX (Fluobeam, France) available at Verum Expert Clinic (Kyiv, Ukraine).

Statistica 12 (TIBCO Software Inc., USA) and GraphPad Prism 10 (GraphPad Software, LLC, USA) statistical software were used for data analyses with application of only the following non-parametrical statistical tests: Kruskal-Wallis test and Fisher exact test (two-tailed); p value <0.05 was set as a cut off for statistical significance.

Ethical approval for the study was obtained the local ethical committee at Verum Expert Clinic. The study was conducted according to Helsinki Declaration (1964–2024) and Ukrainian ethical standards (Laws "On Protection of Human Rights in Biomedical Research" (2006) and "On Personal Data Protection" (2010)).

Written informed consent was obtained from all patients.

Results and Discussion

The group of patients with PTC and obesity comprised 20 (22.0%) patients, the group of patients with PTC and overweight were 45 (50.0%) patients, and the group of patients with PTC and normal weight were 26 (28.0%) patients ($p < 0.05$). The analyses of clinical and morphological features of the studied groups of patients are shown in *Table*.

According to our results, both obesity and overweight are frequently diagnosed more frequently in females as well as other clinical and histopathological parameters, which is in line with previously published reports [4; 5; 8; 18]. Among various pathohistological features, invasive characteristics of PTC are considered as one of the unfavorable features of PTC, which is considered as biologically aggressive characteristics (locoregional metastasis, multifocal growth, invasive cancer characteristics, larger size of tumor, higher recurrence rate, etc.) [19; 20].

The data revealed a 1.57 times higher incidence of microscopic extrathyroid spread in patients with PTC and obesity (30% of patients with PTC and obesity compared to 19% of PTC in patients with normal weight), which is consistent with

Table. Microscopical invasive characteristics analyses of the of the patients with papillary thyroid carcinoma in relation to the weight of the patients

Parameters	PTC obesity (n=20)	PTC overweight (n=45)	PTC normal weight (n=26)	p
Microscopic extrathyroid spread, abs. (%)	6 (30)	3 (6)	5 (19)	0.046
Invasion to blood vessels, abs. (%)	3 (15.0)	3 (6.0)	1 (3.0)	ns
Invasion to lymphatic vessels, abs. (%)	9 (45.0)	18 (40.0)	12 (46.0)	ns
Perineural invasion, abs. (%)	3 (15.0)	1 (2.2)	0 (0.0)	0.031
Figures of mitoses per 10 high power fields ($\times 400$), abs. (%)	2 (10)	0 (0.0–0.0)	1 (4.0)	ns

Notes: PTC – papillary thyroid carcinoma;

ns – non-significant at statistical analyses ($p > 0.05$).

the results of studies [4; 5; 18; 21]. Further analysis of data regarding the difference in the frequency of invasion into blood vessels, invasion into lymphatic vessels, assessment of figures of mitoses per 10 high ($\times 400$) power fields ($p > 0.05$).

However, the data analysis showed that among the mentioned morphological characteristics, perineural invasion was more common in obese patients. As the data analysis shows: perineural invasion was found in 3 (15.0%) patients in group of PTC with obesity, y 1 (2.2%) patients in group of PTC with overweight, and in none of the patients in group of PTC with normal weight ($p = 0.031$). These data are in agreement with other studies of perineural invasion, including in other malignant neoplasms, which confirms the need to take this pathomorphological feature into account in clinical practice. [22; 23].

Considering the short follow up time for the study cohort, it is important to mention about some possible risks for the patients with PTC and obesity in terms of possible recurrence rate.

Conclusions

Patients with PTC and obesity have 1.57 higher frequency of microscopic invasion predominately due to perineural invasion of the carcinoma, which is aggressive biological characteristics of malignant neoplasm. The risk of PTC in the population with obesity should be taken into consideration by a healthcare professional, and aggressive biological characteristics should be considered at follow up and management of the patients.

Conflicts of interests is absent.

All authors have consented to the processing of their personal data and the publication of the article.

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ВЗАЄМОЗВ'ЯЗОК МІКРОСКОПІЧНОЇ ІНВАЗІЇ ПАПІЛЯРНОЇ КАРЦИНОМИ ЩИТОПОДІБНОЇ ЗАЛОЗИ У ПАЦІЄНТІВ З ОЖИРІННЯМ

Актуальність. Папілярна Карцинома Щитоподібної Залози (ПКЩЗ) – це злоякісне новоутворення, яке становить до 80 % усіх типів раку щитоподібної залози. Зв'язок між ПКЩЗ та ожирінням в Україні недостатньо вивчений.

Мета. Дослідження та оцінка особливостей мікроскопічних інвазивних проявів ПКЩЗ у пацієнтів з ожирінням та надмірною вагою з порівнянням з пацієнтами з ПКЩЗ та нормальною вагою.

Матеріали та методи. У цьому дослідженні взяли участь 91 пацієнт з діагнозом ПКЩЗ. Пацієнтів було розділено на групи залежно від їхнього Індексу Маси Тіла (ІМТ): 20 пацієнтів з ПКЩЗ та ожирінням (ІМТ >30 кг/м²), 45 пацієнтів ПКЩЗ та надмірною вагою (ІМТ [24,0–29,0] кг/м²) та 26 пацієнтів з ПКЩЗ та нормальною вагою (ІМТ [18,0–23,9] кг/м²). Клінічні дані та гістопатологічні параметри були отримані з архівних медичних карт. Письмова інформована згода на участь була отримана від усіх пацієнта.

Результати. Статистично значуща різниця у вищій частоті мікроскопічного ураження структур щитоподібної залози при ПКЩЗ була виявлена у 6 (30,0%) пацієнтів з ПКЩЗ з ожирінням, у 3 (6,0 %) пацієнтів з ПКЩЗ з надлишковою вагою та у 5 (19,0 %) пацієнтів з ПКЩЗ з нормальною вагою (p=0,046). Подальший аналіз даних виявив достовірно вищу частоту периневральної інвазії у 3 (15,0 %) пацієнтів з ожирінням та ПКЩЗ, у 3 (2,2 %) пацієнтів з надмірною вагою та ПКЩЗ та у жодного з пацієнтів з ПКЩЗ та нормальною вагою (p=0,031).

Висновки. Пацієнти з ПКЩЗ та ожирінням мають у 1,57 разів вищий ризик мікроскопічної інвазії, переважно через периневральну інвазію карциноми, що є агресивною біологічною характеристикою злоякісного новоутворення. Ризик ПКЩЗ у популяції з ожирінням повинен враховуватися в рутинній клінічній роботі, а агресивні біологічні характеристики слід враховувати під час подальшого спостереження та лікування пацієнтів.

Ключові слова: інвазивність новоутворення, периневральна інвазія, індекс маси тіла, фактори ризику раку.

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