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Parathyroid cancer: parathyroid hormone as a predictor of malignancy

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Parathyroid cancer (PC) is a rare malignant disease that can be sporadic or connected with genetic syndromes. The incidence of PC among patients with primary hyperparathyroidism (PHPT) is not high and varies depending on the region. For example, in the USA it is nearly 1.0 % while in Japan and Italy, 5.0 % and 5.2 %, respectively [1, 2].

The clinical manifestation of PC is quite diverse and can mask different diseases. However, classical symptoms of PHPT with significant increases in calcium and parathyroid hormone (PTH) levels in the blood are still present.

Currently, no laboratory test diagnoses PC in the pre-operative period. A clinical presentation, with the combination of a significantly increased level of PTH and calcium, mainly allows to suspect PC in a patient with PHPT [3]. Rarely, clear-cell PC is aggressive with a poor prognosis [4—6]. The incidence of clear-cell PC is extremely low, only, isolated cases have been described in the literature [7].

To date, the recommended surgical treatment is en-block resection of the tumor, removing the unilateral thyroid gland and isthmus, involved muscles, tissues, and nerve, as well as group 4 lymphadenectomy. This en-block type of surgery provides significant advantages in the prognosis of the disease [4, 7].

At the initial presentation, it can be a challenge to differentiate between hyperparathyroidism caused by parathyroid carcinoma and that caused by benign adenoma. Because better prognosis and outcomes are associated with complete tumor resection during the primary operation, it is important to establish the correct diagnosis at the time of the initial encounter with the patient.

In this retrospective study, we compared the key laboratory preoperative parameters that characterize PHPT and PC.

Objective — to evaluate the diagnostic value of parathyroid hormone as a predictor of malignant parathyroid lesions.

MATERIALS AND METHODS

Design of the study: a single-center cohort retrospective study.

The study was performed at the Surgical Department of the Ukrainian Scientific and Practical Center of Endocrine Surgery, Transplantation of Endocrine Organs and Tissues of MoH of Ukraine from 2009 to 2017.

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We analyzed pre- and post-surgical examination data from 216 patients with PHPT. Increased levels of PTH and ionized calcium (Ca^{2+}) were diagnosed in all patients preoperatively. All patients were undergone parathyroidectomy. Following to post-surgical pathohistology, patients (n = 216) were divided into 2 groups: I group (n = 28) — the main group — patients with PHPT and postoperatively confirmed diagnosis of PC; II group (n = 188) — the comparison group — patients with PHPT and parathyroid adenoma.

The studied patients' age was 21 to 80 years old (mean age 55.1 ± 11.8 years old). In the I group, the mean age was 52.4 ± 12.8 years old (min-max 27—73 years old), males — 12 (42.9 %), females — 16 (57.1 %). The patients of the comparison group: mean age — 55.5 ± 11.6 years (min-max 21—80 years old), males — 10 (5.3 %), females — 178 (94.7 %).

According to the international TNM classification of PC, $T_2N_0M_x$ cancer (n = 10, 35.7 %) and $T_3N_0M_x$ (n = 18, 64.3 %) were diagnosed in the I group patients.

The study's **primary endpoint** was to identify and analyze the possibility of using preoperative PTH levels as a predictor of malignant processes.

The **secondary endpoints** were to find the correlation between tumor size, tumor weight, and laboratory findings, including the level of PTH and calcium in benign and malignant parathyroid lesions, and to analyze rare forms of PC.

The topical diagnosis was performed for precise preoperative parathyroid glands localization detection, using Toshiba NEMIO ultrasound (Japan) and Toshiba Aquilion CX CT Scanner (Japan).

Laboratory blood tests included preoperative PTH, total calcium, ionized calcium (Ca^{2+}), and inorganic phosphorus. The serum PTH test was performed by enzyme-linked immunosorbent assay using the immunochemical system ACCESS (by Beckman Coulter USA).

Table 1

The main laboratory parameters in the studied groups before operation

Parameter	Main group (n = 28)	Comparison group (n = 188)
PTH, pg/mL	857.7 (618.6; 1581.4) 280.8—5000.0	165.4* (118.0; 237.4) 71.4—3225.0
Ca^{2+}, mmol/L	1.79 (1.66; 2.11) 1.40—2.87	1.43* (1.38; 1.56) 1.09—2.33

Note. The data are presented as Me (Q1; Q3) and range.
* The difference between the groups is statistically significant (p < 0.001).

Post-surgical pathohistology of the parathyroid tumors was performed with routine histological samples examination (hematoxylin-eosin staining) and the immunohistochemical test for marker Ki-67. In order to minimize diagnostic errors, two independent experts examined histological specimens.

Statistical analysis. The database of the patients was processed using the software MS Excel 2013. AtteStat 13 and StatPlus 7 (Analyst Soft Inc.) were used in the calculations, and the operational characteristics of the diagnostic tests were calculated according to generally accepted formulas.

RESULTS

The determination of the level of PTH as a predictor of the malignant process can have a significant diagnostic value, regardless of the size and weight of the tumor. For this reason, the analysis of preoperative indicators of PTH and Ca^{2+} levels in the studied groups was performed (Table 1, Fig. 1).

The presence of significant differences between levels of PTH and Ca^{2+} in the studied groups is a necessary condition to analyze the possibility of using these indicators as predictors of PC. The ROC-analysis can be used as an additional criterion when deciding on the type of surgical treatment (Fig. 2, 3). In both cases the decision rule is «Positive if test value X i threshold T».

According to the official classification of the model AUC from 0,9 to 1,0 are considered as significantly different. Thus, both indicators can be used as predictors

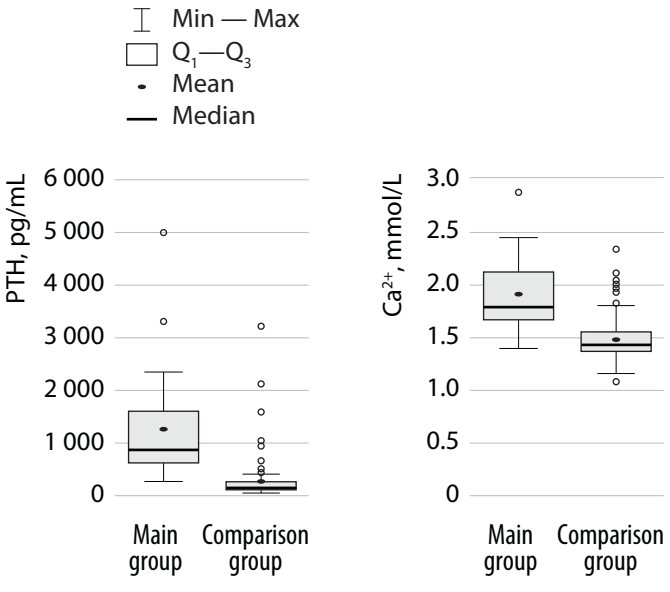

Fig. 1. *Comparison of preoperative PTH and Ca^{2+} levels in the studied groups*

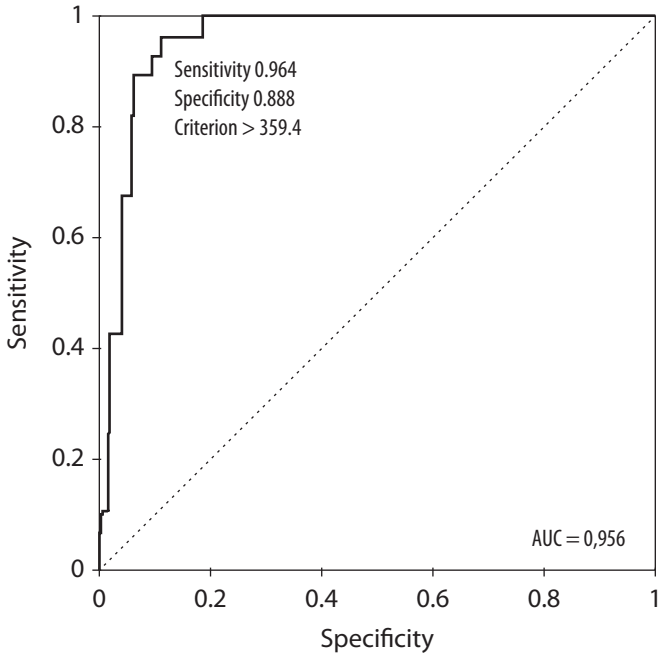

Fig. 2. *ROC-curve for the preoperative PTH levels*

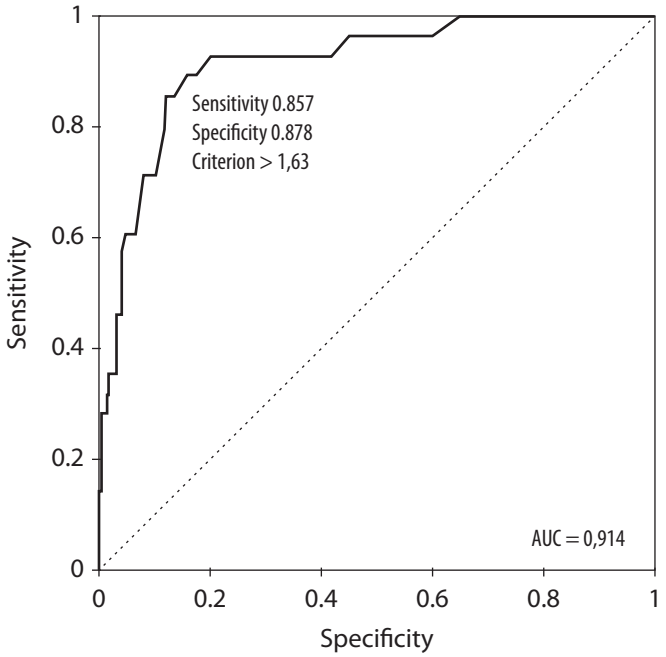

Fig. 3. *ROC-curve for the preoperative Ca^{2+} levels*

Table 2

Some operational characteristics of the test were calculated for some points of cut-off for PTH to determine the probability of a diagnosis of PC, pg/mL

Criterion	Sensitivity (95 % CI)	Specificity (95 % CI)	Accuracy	PPV	NPV
≥ 280.8	0.964 (0.896—1.000)	0.814 (0.758—0.869)	0.833	0.435	0.994
≥ 359.4	0.964 (0.896—1.000)	0.888 (0.843—0.933)	0.898	0.563	0.994
≥ 371.2	0.929 (0.833—1.000)	0.888 (0.843—0.933)	0.894	0.553	0.988
≥ 399.0	0.929 (0.833—1.000)	0.904 (0.862—0.946)	0.907	0.591	0.988
≥ 407.7	0.893 (0.778—1.000)	0.904 (0.862—0.946)	0.903	0.581	0.983
≥ 502.0	0.857 (0.728—0.987)	0.936 (0.901—0.971)	0.926	0.667	0.978
≥ 503.8	0.821 (0.680—0.963)	0.936 (0.901—0.971)	0.921	0.657	0.972
≥ 647.0	0.679 (0.506—0.852)	0.941 (0.908—0.975)	0.907	0.633	0.952
≥ 904.0	0.429 (0.245—0.612)	0.957 (0.929—0.986)	0.889	0.600	0.918
≥ 1237	0.357 (0.180—0.535)	0.979 (0.958—0.999)	0.898	0.714	0.911
≥ 1304	0.321 (0.148—0.494)	0.979 (0.958—0.999)	0.894	0.692	0.906
≥ 1500	0.286 (0.118—0.453)	0.979 (0.958—0.999)	0.889	0.667	0.902
≥ 1817	0.179 (0.037—0.320)	0.984 (0.966—1.000)	0.880	0.625	0.889
≥ 1900	0.107 (0.000—0.222)	0.984 (0.966—1.000)	0.870	0.500	0.881
≥ 2323	0.071 (0.000—0.167)	0.995 (0.984—1.000)	0.875	0.667	0.878
≥ 3306	0.036 (0.000—0.104)	1.000 (1.000—1.000)	0.875	1.000	0.874

Note. PPV — positive predictive value, NVP — negative predictive value.

of the presence of malignancy. Although, the indicator of preoperative PTH level is significantly more effective. For the fixed range of PTH level, we have calculated the operational characteristics of the test: sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic efficiency (Accuracy) which determine the probability of the detection of a malignant process in the tumor of the parathyroid gland (Table 2).

Attention should be paid to the lower threshold of PTH cut-off value of 280.8 pg/mL. When detected for the first time in this range there is a probability of PC (Se — 0.964, false negative rate — 0.036). However, the diagnostic value of this PPV of the result is low — 0.435 (this is the probability that a patient with this value of PTH really has cancer). Whereas the NPV is high (0.994).

The next significant cut-off threshold corresponds to PTH ≥ 359 pg/ml at which the Juden index is 0.853, i.e. the best ratio of sensitivity and specificity. Moreover, the third cut-off threshold at PTH > 502 pg/ml provides the best overall result of test efficiency (95 % confidence interval 0.926).

We also tested the hypothesis of correlations between PTH levels, linear tumor size, and weight, and between Ca^{2+} levels. The weight of the removed tumors ranged from 1.01 g to 92.53 g, the median value was 8.63 (5.09; 12.96) g, the size (by the largest linear) ranged from 20 to 67 mm, and the median value was 30.0 (25.5; 40.0) mm. Since the studied series of variables were not subject to the normal distribution, a nonparametric Spearman criterion was used for this purpose (Spearman rank correlation coefficient) (Table 3).

Thus, no statistically confirmed correlations between tumor size and weight and laboratory parameters were found in our study.

In 3/28 patients of the I group levels of PTH and Ca^{2+} were relatively low. The precise analysis of these cases revealed vague clinical presentation and clear-cell type PC. Previous ROC analysis showed that 2/3 cases of clear-cell PC were at the level of PTH between the second and third cut-off threshold (407 and 436 pg/mL (norm 15—65 pg/mL).

In the comparison group (II group), the Ki-67 protein expression was tested in patients with a threshold value of PTH > 510 pg/mL. The result was < 1 %, meaning one cell in the field of view (× 400 magnification), see Fig. 4.

Thus, considering, the immunohistochemical test result of ≤ 1 %, the degree of malignancy of the parathyroid adenoma remains low and does not depend on the level of PTH.

DISCUSSION

Parathyroid cancer is a rare disease and accounts for 1—5 % of all patients with PHPT. The solution to its preoperative diagnosis issues is still relevant [1]. The lack of reliable methods of preoperative diagnosis and intraoperative tumor verification encourages researchers to use additional criteria.

The analysis of age and gender of the patients in the group with a confirmed diagnosis of PC did not reveal any diagnostic predictability, which coincides with the data of other studies (mean age — 52.4 ± 12.8 years from 27 to 73 years, men — 12 (42.9 %), women — 16 (57.1 %). In contrast, benign parathyroid adenomas show a difference in occurrence rate regarding gender [8].

The presence of a correlation between the size of the parathyroid gland, its weight, level of PTH, and calcium gives controversial results in the differential diagnosis. In our study, we did not find clear correlations between PTH, calcium levels, linear size, and weight of the

Table 3

Correlations between tumor size, tumor weight a nd laboratory parameters

Indicator	PTH	Ca^{2+}
Tumor size	+0,203	–0,057
Tumor weight	+0,314	–0,288

Note. All p > 0.05.

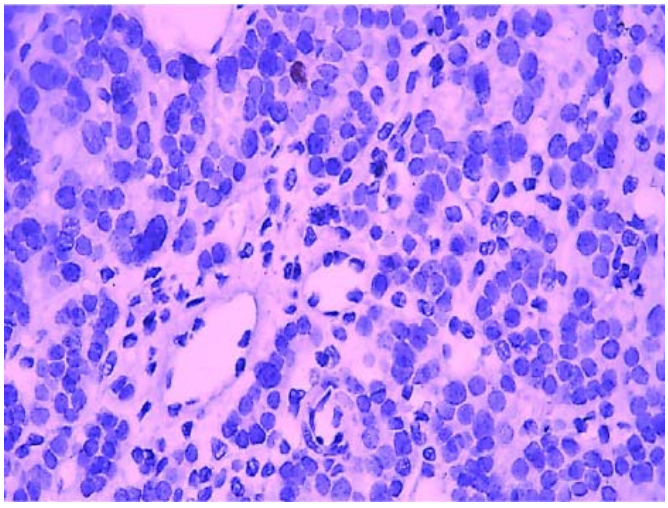

Fig. 4. *Expression of Ki-67 in parathyroid adenoma cells. Hematoxylin and eosin, × 400*

parathyroid tumor. Our results correspond with the studies of F. Ahmedi et al., who showed that PTH secretion does not depend on the total weight of the tumor [9]. However, a small case series study, by W. K. Cheah et al. revealed that there was an increased level of PTH with an increase in parathyroid volume [10]. Thus, the size of the tumor also cannot help in the diagnosis of PC in the preoperative stage.

A definitive intraoperative diagnosis of PC is also not ideal if clinical signs of malignancy are absent or vague. In the pathomorphological examination, the most reliable criteria for a malignant tumor are signs of extracapsular disease, vascular and perineural space invasion, spreading to the surrounding tissue as well as distant metastases [10—12]. Additional criteria for malignancy of the parathyroid tumor are the presence of characteristic bands, fibrosis, rosette formation, and high mitotic rate [13].

Immunohistochemistry with Ki-67 and cyclin D1 can be used to increase the accuracy of the differential diagnosis of carcinoma vs adenoma of the parathyroid gland. It has been suggested that a rise in the Ki-67 index increases the probability of malignancy. Ki-67 labeling index > 5 % can be regarded as a potential malignancy of the thyroid tumor [15, 16]. In our study, immunohistochemical test for Ki-67 was performed in patients (comparison group) with PTH higher than 510 pg/ml. The result was < 1 %, and didn't depend on the PTH level.

The lack of preoperative criteria for malignancy and the complexity of intraoperative diagnosis encourages researchers to use additional predictors of malignancy. The most informative in this scenario may be PTH. There are many studies that analyze the levels of PTH and the degree of benignity of the parathyroid gland. The result is only a statement of the fact that benign adenoma corresponds to the moderately increased level of PTH, and in PC it significantly increased [8].

In our study, we used ROC analysis to assess the possibility of using PTH levels as a predictor of malignancy. To assess the probability of PC diagnosis at different values of the PTH cut-off threshold, the corresponding operational characteristics of the test were calculated. Thus, the cut-off thresholds of PTH up to 288 pg/mL corresponded to benign parathyroid adenomas, however, the first case of clear-cell carcinoma of the parathyroid gland was observed at a value of PTH = 280.8 pg/mL. As can be seen, the levels of PTH and Ca^{2+} in cases of clear-cell PC (main group) are not significantly different from benign adenomas. Cases of clear-cell PC are extremely rare and can be distinguished from benign adenomas only in specific morphological features. H. Naganuma et al. gave a description of the first (according to the authors) case of clear-cell cancer with a level of basal PTH 137.0 pg/mL, and a vague clinical picture [11].

The clinical manifestations of parathyroid carcinoma largely depend on the level of PTH secretion. Thus, in the case of clear-cell PC, when levels of PTH and serum calcium are moderately increased, the clinical manifestations are not that obvious [17].

The first case of PC with a classic structure was observed at the level of PTH 502 pg/mL. The incidence of PC at the PTH ≥ 502 pg/mL cut-off thresholds was 78 % and reached maximum values at the level of PTH of more than 1200 pg/mL. These numerical cut-off thresholds cannot be constants — their values will unavoidably change as the main group is filled with new data.

Surgery is only radical treatment for PC, and aggressive primary management is crucial to reduce the chance of recurrence.

The recommended surgical treatment includes the en-block resection of the malignant parathyroid tumor with the adjacent thyroid gland and isthmus, skeletonization of the trachea, removal of tissue on the affected side with lymph nodes of group VI, as well as any muscle invaded by the tumor. Parathyroidectomy or subtotal resection, as well as any surgeries that may lead to a violation of the integrity of the tumor, in suspected PC are not recommended due to the risk of seeding and recurrence [18].

In our study, the volume of surgery among patients in the main group was not homogeneous and depended on the results of intraoperative frozen section, clinical data (the presence of obvious signs of extraorganic invasion), and basal PTH levels. In 11 (39.3 %) patients with moderately elevated levels of PTH (up to 500—600 pg/mL) and confirmed by the express histological diagnosis of parathyroid adenoma, only adenomectomy was performed. In more doubtful cases 7 (25 %) (atypical adenoma according to express histology, significantly elevated PTH levels) was performed adenomectomy with hemithyroidectomy. In 10 (35.7 %) cases, when clinical signs of extraorganic invasion or intraoperative histological verification of PC, en-block adenectomy was performed with ipsilateral hemithyroidectomy and central lymphadenectomy. Low «en-block» resection rates indicate a lack of informativeness of preoperative diagnosis, as well as erroneous intraoperative express histological

examinations, which have insufficient efficacy in the diagnosis of PC.

Subsequent follow-up of patients in the postoperative period showed free-recurrence results. Even though the PTH and serum calcium levels are within normal limits in patients that did not have en-block resection, and there is no evidence of locoregional recurrence, its potential risks still remain [1, 2, 18]. Further analysis of the data and more long-term follow-up are needed. Upon completion of the comprehensive study, the long-term results will be analyzed and presented as a publication.

It is difficult to evaluate the extent of the surgical intervention preoperatively. Thus, it is very important to have a comprehension of the morphological composition of the tumor. However, currently, it is impossible due to the ineffectiveness of puncture biopsy methods for verification of parathyroid tumors. In such cases, indirect signs of malignancy are important, namely — the level of PTH. Our study showed a tendency of the PTH level as a predictor of malignant process in the parathyroid gland; we believe that at levels of PTH ≥ 280 pg/mL it is advisable to plan surgery on the principles of oncology.

CONCLUSIONS

There were no statistically confirmed correlations between PTH, ionized calcium, and tumor size or weight in our study.

Most patients with benign parathyroid adenomas (70 %) were in the range of PTH values ≤ 280 pg/mL, which can be considered «safe».

The level of PTH ≥ 280 pg/mL suggests the potential presence of clear-cell PC. The PTH cut-off threshold ≥ 502 pg/mL potentially corresponds to the presence of parathyroid carcinoma with a classical histological structure, after which its incidence is 78 %.

Surgical approach in cases of PTH ≥ 502 pg/mL should be planned on the principles of cancer surgery.

Determining the predictors of PC requires further study.

Prospects for further research. The definition of PC predictors should be studied in multicenter prospective trials involving all possible methods of examination, including the use of molecular research. It is also advisable to evaluate patient-oriented long-term results of surgical treatment.

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Ethical aspects. *All procedures performed with the involvement of patient complied with the institution's ethical standards for clinical practice and the 1964 Declaration of Helsinki, as amended.*

Conflicts of interest: none.

Granting. *No granting is declared.*

Authorship contributions: *conception and design — O. A. Tovkai, V. O. Palamarchuk, S. H. Gychka, Y. Pavelko; collection and processing of material — V. V. Voitenko; statistical processing — V. V. Kuts; drafting the article — O. A. Tovkai, V. O. Palamarchuk, V. V. Voitenko, T. Y. Yuzvenko, S. I. Nikolaienko, Y. S. Kozachuk; critical revision of the article — O. A. Tovkai, V. O. Palamarchuk, Y. Pavelko.*

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ABSTRACT

The clinical manifestation of parathyroid cancer (PC) is quite diverse and can mask different diseases. Classical symptoms of primary hyperparathyroidism (PHPT) with significant increases in calcium and parathyroid hormone (PTH) levels in the blood are still present. Currently, no laboratory test can diagnose PC in the pre-operative period. A clinical presentation, with the combination of a significantly increased level of PTH and calcium, primarily allows suspicion of PC in a patient with PHPT.

Objective — to evaluate the diagnostic value of parathyroid hormone as a predictor of malignant parathyroid lesions.

Materials and methods. Pre- and post-surgical examination data from 216 patients with PHPT were analyzed. Increased levels of PTH and ionized calcium (Ca^{2+}) were diagnosed in all patients preoperatively. All patients underwent parathyroidectomy. Following to post-surgical pathohistology, patients (n = 216) were divided into 2 groups: I group (n = 28) — the main group– patients with PHPT and postoperatively confirmed diagnosis of PC; II group (n = 188) — the comparison group — patients with PHPT and parathyroid adenoma. The study's primary endpoint was to identify and analyze the possibility of using preoperative PTH levels as a predictor of malignant processes. The secondary endpoints were to find the correlation between tumor size, tumor weight, and laboratory findings, including the level of PTH and calcium in benign and malignant parathyroid lesions, and to analyze rare forms of PC.

Results. Preoperative levels of PTH and Ca^{2+} differed significantly between the study groups ($p < 0.001$). ROC analysis showed that both indicators can be used as predictors of the presence of malignancy. However, preoperative PTH level is significantly more effective. The sensitivity for PTH test in PC diagnosis was 0.964, and the specificity was 0.888. Attention should be paid to the lower PTH cut-off threshold of 280.8 pg/mL. For Ca^{2+} test, the sensitivity in PC diagnosis was 0.857, and the specificity was 0.878. Statistically confirmed correlations between tumor size and weight and laboratory parameters were not found in our study.

Conclusions. There were no statistically confirmed correlations between parathyroid hormone, ionized calcium, and tumor size or weight in our study. Most patients with benign parathyroid adenomas (70 %) were in the range of PTH values ≤ 280 pg/mL, which can be considered «safe». The level of PTH ≥ 280 pg/mL suggests the potential presence of clear-cell PC. The PTH cut-off threshold ≥ 502 pg/mL potentially corresponds to the presence of parathyroid carcinoma with a classical histological structure, after which the incidence is 78 %. Surgical approach in cases of PTH ≥ 502 pg/mL should be planned on the principles of cancer surgery. Determining the predictors of PC requires further study.

Keywords: parathyroid cancer, primary hyperparathyroidism, parathyroid hormone, ionized calcium, predictors.

РЕЗЮМЕ

Рак прищитоподібної залози: паратгормон як предиктор злоякісності

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Клінічні вияви раку прищитоподібних залоз (РПЗ) різноманітні та можуть маскувати інші захворювання. Класичними симптомами первинного гіперпаратиреозу (ПГП) лишаються значні підвищення рівня кальцію та паратгормону (ПГ) у крові. Нині жоден лабораторний тест не діагностує РПЗ у доопераційний період. Клінічна картина разом зі значно підвищеним рівнем ПГ і кальцію дає змогу запідозрити РПЗ у пацієнта з ПГП.

Мета — оцінити діагностичну цінність паратгормону як предиктора злоякісного ураження паращитоподібних залоз.

Матеріали та методи. Проаналізовано дані доопераційного та післяопераційного обстеження 216 пацієнтів із ПГП. У всіх пацієнтів до операції виявлено підвищені рівні ПГ та іонізованого кальцію (Ca^{2+}). Усім пацієнтам виконана паратиреоїдектомія. За результатами післяопераційної патогістології пацієнтів розподілили на дві групи: основну групу (n = 28) — пацієнти з ПГП та післяопераційно підтвердженим діагнозом РПЗ; група порівняння (n = 188) — пацієнти з ПГП і аденомою паращитоподібної залози. Первинною кінцевою точкою дослідження було визначення й аналіз можливості використання доопераційного рівня ПГ як предиктора злоякісних процесів. Вторинні кінцеві точки — виявлення кореляції між розміром пухлини, масою пухлини та лабораторними показниками, зокрема рівнем ПГ та Ca^{2+} при доброякісних і злоякісних ураженнях паращитоподібних залоз, зокрема при рідкісних формах РПЗ.

Результати. Виявлено статистично значущу різницю за доопераційними рівнями ПТГ та Ca^{2+} між досліджуваними групами ($p < 0{,}001$). ROC-аналіз показав, що обидва показники можуть бути використані як предиктори наявності злоякісної пухлини. Однак доопераційний рівень ПГ є значно ефективнішим. Чутливість ПГ щодо діагностики РПЗ становила 0,964, а специфічність — 0,888. Нижній поріг відсікання ПГ — 280,8 пг/мл. Для Ca^{2+} чутливість щодо діагностики РПЗ становила 0,857, специфічність — 0,878. Статистично значущих кореляцій між розміром і масою пухлини та лабораторними показниками не виявлено.

Висновки. Статистично кореляції між паратгормоном, іонізованим кальцієм та розміром і масою пухлини не виявлено. У більшості пацієнтів з доброякісними аденомами паращитоподібних залоз (70 %) значення ПТГ < 280 пг/мл можна вважати «безпечними». Рівень ПГ ≥ 280 пг/мл свідчить про потенційну наявність світлоклітинного РПЗ. Поріг відсікання ПГ ≥ 502 пг/мл потенційно відповідає наявності паратиреоїдної карциноми з класичною гістологічною структурою, після якого її частота становить 78 %. Хірургічний підхід у випадках ПГ ≥ 502 пг/мл слід планувати за принципами онкологічної хірургії. Визначення предикторів розвитку РПЗ потребує подальшого вивчення.

Ключові слова: рак паращитоподібних залоз, первинний гіперпаратиреоз, паратгормон, іонізований кальцій, предиктори.

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