THE PARTICIPATION OF IRISIN IN THE MECHANISMS OF WEIGHT LOSS IN OBESITY

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Abstract. In addition to the well-known basic functions, skeletal muscles can function as a secretory organ, stimulating the production and secretion of substances called myokines, which have a wide range of physiological effects and are able to regulate the homeostasis of peripheral tissues. Irisin is one of the most well-known myokines, produced mainly by muscles after physical exercise. It is believed to induce the conversion of white fat to brown fat in adipocytes, followed by an increase in mitochondrial lipid oxidation and a decrease in insulin resistance.

Irisin began to be researched recently, so the main laws and mechanisms of its action have not yet been sufficiently analyzed. In addition, the effects on the browning of white fat obtained in experiments on animals do not have clear confirmation in humans.

Obese subjects, both trained and untrained, have higher plasma irisin levels than normal-weight subjects.

In most studies, the immediate effect of a single exercise session is to increase circulating irisin levels in overweight individuals. The maximum concentration is observed between 1 and 2 hours after exercise. Protocols using high-intensity interval loads turned out to be the most effective.

The response of the human body to long-term exercise turned out to be more variable. Prolonged physical activity in obese and overweight individuals causes an increase in circulating irisin levels in both men and women. Probable changes in the level of irisin are registered after 6 months of classes. In individuals of normal body weight, exercise may cause a decrease in irisin levels (irisin resistance). The high heterogeneity of indicators of mRNA and protein irisin levels in tissues and blood in response to exercise depends on the type of tissue, type of object, and measurement method. Physical loads, which differ in direction, intensity and duration, are characterized by a unidirectional effect on the expression of irisin, but differ in the magnitude of the increase.

In most studies, changes in irisin levels were recorded in skeletal muscle, not blood plasma, which may be related to the duration of exercise exposure. Most often probable changes changes are established at the level of the protein itself by the method of Western blotting, and not at the level of mRNA. Additional use of recombinant irisin leads to improvement of lipid profile and insulin resistance.

Key words: myokines, irisin, obesity, physical activity, skeletal muscles.

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PREDICTORS OF UNFAVORABLE COURCE OF PAPILLARY THYROID CARCINOMA

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Determination of risk factors for metastasis and aggressive course of PTC is important in determining the scope of surgical treatment, namely the need for lymph node dissection in patients with this cancer.

Aim - to review the professional medical literature to determine the factors of unfavorable course of papillary thyroid carcinoma.

According to the results of studies, size of tumor larger than 1.0 cm and multifocal lesions can be considered an indicator of the aggressive course of PTC. AIT complicates the cytological diagnosis of nodal masses. A definite cause-and-effect relationship between AIT and PTC remains unclear. The basis for this relationship is the molecular, hormonal and histopathological similarity of these diseases. Galectin-3 is a regulator of normal cell proliferation, and its overexpression leads to malignant cell transformation and metastasis. The neoplastic transformation of benign

tissue is a complex process influenced by numerous factors. Humoral mechanisms of cancer development are associated with the IgG4 subclass. Regulatory cells that suppress the immune response, are playing an important role in avoiding the host's antitumor immune response. The BRAF mutation has also been shown to cause overexpression of many other molecular tumour markers, such as VEGF and MET.

The level of molecular genetic markers associated with participation in apoptosis, increased proliferation rate and angiogenesis, as well as the duration of inflammation can be used to establish the diagnosis, predict the course and assess the risk of PTC metastasis.

Key words: *thyroid glands, papillary carcinoma, combine pathology, metastasis, molecular markers.*

Connection of the publication with planned research works.

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Introduction.

Over the past 30 years, the incidence of papillary thyroid carcinoma (PTC) has increased rapidly [1]. The proportion of this disease among all newly diagnosed malignant tumors is 3.8% and 90.0% among all histologic forms of thyroid cancer (TC) [2, 3]. The incidence of thyroid cancer is growing faster than any other type of cancer. This phenomenon is associated with overdiagnosis due to improved diagnostic methods, high access to medical care, and, as a result, incidental detection of tumors in the setting of other diseases [4]. Although the overall rate of change in mortality in this category of patients is not high, the average annual relative increase in mortality is 1.1% per year [4]. The ten-year survival rate for middle-aged people with PTC is 80 to 95% [5]. Despite the fact that this type of tumor is inactive, metastasis to regional lymph nodes is associated with a high risk of recurrence [6, 7].

PTC is the most common form of thyroid malignancy and has complex etiologic and pathogenic mechanisms, which makes diagnosis and treatment a dilemma for the clinician. To date, the issue of choosing the optimal volume of surgical treatment in patients with PTC with different tumor sizes remains controversial. The latest guidelines of the American Thyroid Association (ATA) and the National Comprehensive Cancer Network (NCCN) consider a conservative approach to surgical treatment, considering lobectomy sufficient in low-risk patients, but in high-risk patients, thyroidectomy remains the standard. Nevertheless, many researchers are inclined to take a more aggressive approach in low-risk patients, justifying this by the high incidence of occult malignancies in the thyroid or regional lymph nodes, the risk of recurrence, and adverse outcomes.

Determination of risk factors for metastasis and aggressive course of PTC is important in determining the scope of surgical treatment, namely the need for lymph node dissection in patients with this cancer.

The aim of the study.

To review the professional medical literature to determine the factors of unfavorable course of papillary thyroid carcinoma.

Object and research methods.

To assess the clinical characteristics of patients with PTC, we used the methods of information search, content analysis, systematic, descriptive and generalization. For the systematic search, the results of fundamental and applied research by domestic and foreign scientists on the issue, scientific and methodological publications, dissertations from the repositories of medical and pharmaceutical universities of Ukraine and the PubMed database published before January 22, 2023 were used. The search was carried out using the keywords papillary carcinoma, thyroid gland, risk factors, metastasis, invasiveness, cytology, morphology, molecular genetic markers.

Main part.

According to the ATA recommendations, PTC has a low risk of metastasis, so it is considered inappropriate to expand the scope of surgery [8]. However, there are reports that 64.0% of patients with papillary carcinoma had metastatic lymph node involvement, and the presence of regional metastasis in 11.0% to 12.0% of cases is associated with a risk of recurrence [9, 10].

Sak S. D. in his study showed a relationship between high-risk disease and male gender, multifocal lesions, localization in the lower third of the thyroid lobe, superficial location of the tumor, and stromal fibrosis [11]. Other features that affect the clinical course of PTC may include age, size of the tumor, prevalence of the tumor process, and the presence of background pathology that affects the morphological properties of thyroid tissue.

Evaluation of these factors in the preoperative period is important for determining the risk of papillary carcinoma metastasis and choosing the scope of surgical treatment.

Ito Y. and Adam M. A. in their studies comparing the presence of metastases and the age of patients showed that patients younger than 45 years were more likely to have metastatic lesions of regional lymph nodes [12, 13]. Markovina S. et al. analyzed the clinical course of highly differentiated thyroid cancer and found that age over 45 years was associated with a more favorable prognosis [5]. Based on studies, the incidence of PTC metastasis ranges from 19.6% to 40.1% in patients younger than 45 years and from 22.4% to 34.3% in patients older than 45 years [5, 12, 13]. In addition, patients aged 45 years and younger were more likely to have extrathyroid spread [14].

According to the results of studies, in patients with a tumor size of more than 1.0 cm, the incidence of metastasis to regional lymph nodes ranged from 17.1% to 70.9%, while in patients with a tumor size of less than 1.0 cm from 5.1% to 38,4% [6, 15, 16, 17, 18]. At the same time, patients with a thyroid mass larger than 1.0 cm had a higher incidence of metastasis to the lateral lymph node group. Thus, in patients with PTC, a tumor size of more than 1.0 cm is associated with a higher risk of metastasis to regional lymph nodes [19].

A number of authors in their studies indicate a higher risk of papillary carcinoma (PC) metastasis in patients with multifocal tumors [15, 20, 21, 22]. Multifocal le-

sions play a particularly significant role in patients with PC with a tumor size of more than 1.0 cm [15]. Wang F. showed that multifocality is an independent predictor of PC metastasis [21]. However, the analysis revealed that there was no difference in regional lymph node involvement among patients with bilateral and unilateral lesions [23, 24, 25]. Thus, multifocal lesions can be considered an indicator of the aggressive course of PTC.

Capsular invasion and extrathyroidal spread of the tumour significantly increases the risk of PTC metastasis [26, 27, 28]. However, Furlan J.C. in his study indicates that there is no relationship between capsular invasion and metastasis, and the impact on survival rates in this category of patients [29]. However, most authors confirm that the presence of metastases in the regional lymph nodes is directly related to the degree of extrathyroidal spread. The prognosis for such patients is worse than in patients with only local microdilatation, which is detected by pathological examination [28].

In 71.0% of cases, PTC is combined with another thyroid pathology [30]. The most common background pathology is autoimmune thyroiditis (AIT), and the prevalence of this disease is constantly increasing. Its pathogenesis is a violation of immune tolerance to the thyroid gland. As a result, leukocytes penetrate the thyroid tissue and provoke the development of an autoimmune response. In fact, it is a destructive tissue-specific autoimmune disease with the presence of antibodies to thyroglobulin and antithyroid peroxidase [31]. The relationship between cancer transformation and inflammation has been described previously in other diseases, such as Helicobacter pylori induced gastritis and gastric cancer, chronic inflammatory bowel disease and colorectal cancer, chronic obstructive pulmonary disease and lung cancer [32, 33, 34]. Immune cells, namely tumour-associated lymphocytes, macrophages, mast cells and dendritic cells (DCs), have been identified in neoplastic lesions and are recognised as determinants of tumour growth [34].

AIT is a disease that is the most common cause of hypothyroidism, which in turn is associated with the development of PTC [28]. Constantly high levels of thyroid-stimulating hormone (TSH) stimulate epithelial cell proliferation, which leads to the development of oncological pathology in patients with hypothyroidism [35, 36, 37].

One study reported that the destructive or hypothyroid form of AIT (i.e., long-term course) may have protective properties in patients with PTC, whereas patients with euthyroidism have a higher risk of developing PTC. These observations demonstrate that the duration of inflammation may be a determining factor and explain the discrepancies in the results obtained when analysing the course of PTC in the setting of AIT by different researchers [31].

Of the analysed studies, half reported that patients with AIT had a tumour size of less than 1.0 cm [38, 39, 40, 41]. However, two studies indicated that vascular invasion was less common in patients with PTC without other pathologies [42, 43, 44]. No correlation was found with extrathyroidal spread [39, 42]. One study demonstrated a higher incidence of metastasis to the central lymph node group [41]. An increased relapse rate was also found in patients with AIT, but no correlation with mortality was found [43]. Some researchers have reported no negative impact of AIT on the course of PTC, so the relationship between AIT and the severity of PTC remains open and controversial [45].

AIT complicates the cytological diagnosis of nodal masses. Cellular atypia, anisonucleosis, and pleomorphism are observed in both AIT and PTC, so differential diagnosis in the case of a combination of these pathologies is more difficult [46].

Prolonged autoimmune inflammation weakens immune tolerance, contributing to cancer transformation, which is one of the reasons for the uncertain or false results of cytological examination in patients with AIT at the preoperative stage [47]. Follicular neoplasia is detected in the inflammatory infiltrate even without the presence of a tumour [48].

Inflammatory infiltration, angioectasia, and vascular proliferation, which are characteristic morphological features of AIT, can increase bleeding during fine needle aspiration biopsy (FBA). As a result, mixed components may be added to the cytological smears, which contributes to the uncertainty of cytological results [49]. In AIT, the frequency of false-positive and false-negative TAPB results is higher [50, 51].

Given the risks of capsular invasion, higher incidence of metastasis and recurrence, patients with AIT should be monitored by an endocrinologist, especially for patients with nodal masses. Although the protective properties of AIT have been reported in patients with PTC, smaller tumours, however, in this category of patients, tumours are more likely to have multifocal growth, so total thyroidectomy should be preferred for surgical treatment. The choice of lymph node dissection volume remains controversial, as the results of studies vary and there is no consensus on the effect of AIT on metastasis.

A definite cause-and-effect relationship between AIT and PTC remains unclear. The basis for this relationship is the molecular, hormonal and histopathological similarity of these diseases.

Galectins (S-type lectins) are an evolutionary family of lectin molecules that can also be expressed both intracellularly and in the extracellular matrix. They are functionally active in the transformation and regulation of cellular biological programmes. Galetin-3 recognises and binds galactosides on cellular glycoproteins and glycolipids, thus implementing cell signalling and receptor endocytosis [52]. During normal cell growth, galectin-3 is translocated to the cell nucleus. In malignant tumours, an alternative process of glycosylation occurs, which leads to an increase in the expression of specific galectins and their accumulation in the cytoplasm. As a result, it becomes possible to ensure such processes as adhesion and migration, and cell differentiation, gene transcription, cell cycle, and apoptosis are disrupted [53]. Galectin-3 has been found to be a physiological target for the transcriptional activity of p53, which activates the process of apoptosis. This means that after DNA damage, wild-type p53 does not activate the apoptotic programme in the cell, and galectin-3 remains activated [54]. Thus, galectin-3 is a regulator of normal cell proliferation, and its overexpression leads to malignant cell transformation and metastasis.

The value of this marker is that Galectin-3 is almost always expressed in well-differentiated thyroid carcinomas, is detected in the cytoplasm of malignant cells and is absent in the cytoplasm of normal thyrocytes [53]. The

immunocytochemical test with Galactin-3, according to the analyzed studies, has a high specificity, sensitivity, and diagnostic accuracy in the differential diagnosis of thyroid tumor lesions and benign lesions in ambiguous cases [55].

The incidence of the combination of PTC and multinodular goiter varies from 6.0% to 21.2% [56, 57]. The results of studies on the risk of PTC in patients with nodular goiter show either no relationship or a negative relationship [58, 59]. Barroeta J.E. et al. found that patients with a single thyroid nodule have a higher risk of PTC than patients with multiple thyroid nodules [59]. However, more recent studies have reported a higher risk of thyroid cancer in patients with multiple nodular lesions [60, 61].

The neoplastic transformation of benign tissue is a complex process influenced by numerous factors. Although molecular genetic markers for the diagnosis of PTC are not widely used in clinical practice today, the relationship between them and the aggressiveness of the disease, the degree of prevalence and metastasis is being actively investigated. Understanding the immunological mechanisms is important for controlling tumor progression. It is particularly important to identify relevant molecular markers in patients with an uncertain fine-needle aspiration biopsy result (atypia of undetermined genesis or follicular neoplasia) at the preoperative stage of the examination.

PD-L1 is a key regulator of the T-cell immune response and activation of peripheral tolerance. Disruption of the PD-1/PD L1 immune response pathway contributes to the apoptosis process. PD-1 is synthesized on active T-lymphocytes, and PD-L1 is synthesized on antigen-presenting cells. The PD-1 receptor is blocked by the PD-L1 protein of cancer cells, thus slipping out of immune control, which makes it possible for them to grow and invade [62, 63].

Humoral mechanisms of cancer development are associated with the IgG4 subclass, which is a counter-regulatory mechanism of inflammation [64]. Antibodies to IgG4 are pro-inflammatory, but when unstable disulfide bonds in the molecule are destroyed, their functions change - they become bispecific and unable to cross-link antigen, and thus create immune complexes [65]. An increase in IgG4 levels is associated with an attempt to reduce inflammation, while its decrease leads to the development of fibrosis [32]. In patients with PTC, high levels of IgG4 are associated with larger tumor size and metastasis, as it increases TGF-β levels [65].

The immune system restrains the development of malignant cell transformation through the immune surveillance system, but cancer cells adapt to avoid it. In patients with cancer, the innate immune system, including antigen-presenting cells (i.e. dendritic cells (DCs) and macrophages), and natural killer (NK) cells become tolerant. In addition, T cells, which form the basis of the immune response, undergo apoptosis or produce immunosuppressive cytokines, and as a result do not interact with antigen-presenting cells. As a result, an environment favorable to tumor growth is created [66].

During early tumour development, cancer cells present tumour-specific antigens (Ags) that are recognised by the immune system. Inflammatory cytokines such as interferon (IFN)-γ and interleukin (IL)-12 produced and released by the tumor attract NK cells and induce the maturation of DCs, which become capable of presenting tumor-associated Ags to T cells, leading to the destruction of tumor cells. All these processes are possible in the case of normal functioning of the immune system; in the case of an inadequate immune response, cancer cells are able to produce highly immunosuppressive cytokines such as TGFβ and IL-10, suppressing the T-cell response, inducing T-cell apoptosis, blocking DC maturation and, finally, inducing T-regulatory (Treg) cells, which further suppress the immune system. In this case, the growth and spread of malignancy occurs [66].

Regulatory Treg cells are a subgroup of CD4+ cells that suppress the immune response, playing an important role in avoiding the host's antitumor immune response [67]. Thus, the presence of Treg cells in peripheral blood, thyroid malignancy sites, and lymph nodes affected by the tumor is associated with its progression, aggressiveness, higher degree of invasion, greater risk of lymph node metastasis, and reduced survival [32, 67]. An increase in the number of Treg cells is also observed in patients with kidney, stomach, breast, lung, and hepatocellular carcinoma [67, 68]. However, the study did not refute the data that a higher percentage of recurrence and aggressive course of PTC may be associated with other clinicopathological factors, such as male gender, older age at diagnosis, larger tumor size, extrathyroidal enlargement, metastatic lymph node involvement, distant metastases, and advanced disease [67].

Cytotoxic T cells (CD4 CTLs), T follicular helper 2 (Tfh2), B cells and plasma cells play a leading role in the activation of proinflammatory cytokines. Tfh2 cells activate fibrosis development through IL4 activation, and plasma membrane B cells, presenting antigens to CD4+ cells, initiate the same process through IL1b, interferon gamma (IFN-γ) and TGF-β [32, 69]. Some surface antigenic molecules may promote tumour development and growth, for example, the expression of histocompatibility antigen class I, G (HLA-G), Fas ligand (FasL) and B71 homologue (B7H1) is associated with aggressiveness and unfavorable clinical presentation of PTC [31].

The transport of active molecules to other cells is provided by exosomes, and they also retain biological activity in antigenic presentation. In this way, they activate the inflammation process [70, 71]. Exosomes present antigens to dendritic cells and bind to TLR2/3, causing activation of dendritic cells through the NFκB pathway, leading to an imbalance of CD4+ T lymphocytes [72]. It is reported that a decrease in CD4+ leads to oncological transformation [73].

The role of interleukins (ILs) in the pathogenesis of PTC is actively discussed, namely, an increase IL6, IL10, IL12, and in 56% of patients, also high levels of IL17 and IL22 [74, 75, 76]. The occurrence of epithelial dysplasia leads to an increase in cytokine levels. However, the level of IL 35, a heteromeric protein consisting of two subunits, is downregulated by Epstein-Barr virus-induced gene 3, and IL-12a is downregulated. Its level is associated with the balance of T helper 17, which is a new line of CD4+ cells, and Treg cells, and it weakens their connection through the Wtn/β pathway [77]. When IL 4 levels increase in response to the presence of a tumour, proliferation processes are inhibited and the function of cytotoxic CD8+ T cells and the regulation of CD127 expression [31]. All of this leads to disruption of apoptosis and antitumour immunity, but their levels

change under the influence of any pathological process, making it impossible to use them for the specific diagnosis of oncological pathologies.

One of the best prognostic genetic markers is the BRAF mutation. It activates the BRAF kinase in the MAPK (mitogen-activated protein kinase) pathway, which contributes to the aggressiveness of papillary thyroid cancer [78]. The results of a multicentrical study showed a strong association of BRAF mutation with lymph node metastasis, extrathyroidal spread, advanced stages (III and IV) and disease recurrence [79]. The coexistence of this mutation with other mutations, such as amplification of RTK (receptor tyrosine kinase) genes, can double activate the MAPK and PI3K-AKT pathways. Such a combination of mutations is a factor in thyroid tumour progression and may potentially indicate a negative prognosis of PCa [79]. The BRAF mutation has also been shown to cause overexpression of many other molecular tumour markers, such as VEGF (vascular endothelial growth factor) and MET (N-methyl-N-nitrosoguanidine transforming gene of human osteosarcoma).

The presence of a BRAF mutation is associated with radioiodine-resistant metastases of the PCa [79]. Most often, radioiodine resistance is observed in the elderly or in low-grade thyroid cancer [80]. Refractory disease is usually aggressive. Therefore, the BRAF mutation status may also affect postoperative treatment, but there is not yet sufficient data to implement it in clinical practice. The study of BRAF mutations is currently at a rather early stage and requires further study to collect sufficient data to implement this method in clinical practice.

There are some similarities between BRAF and RAS mutations. The latter belongs to the family of GTP-binding proteins that regulate cell growth through the MAPK and PI3K-AKT pathways. Almost a third of patients with malignancies have a RAS mutation [81]. This mutation was first detected in a patient with thyroid cancer in 1988 [82]. Later, it was found that the RAS mutation was significantly more common in patients with low-grade carcinoma and anaplastic thyroid cancer than in patients with highly differentiated cancer. This suggests that this mutation is a marker of malignant progression rather than tumour appearance [83]. RAS mutations play a significant role in the activation of PI3K-AKT and MAPK pathways, altering GTP-binding affinity and intrinsic GTPase activity [84]. The majority of morphological subtypes of PTC (classic, encapsulated, high-grade, diffuse sclerosic) have a BRAF mutation, while invasive encapsulated follicular variant and follicular thyroid carcinoma have RAS mutation.

VEGF was identified 25 years ago and is known as a vascular permeability factor and a stimulator of endothelial cell proliferation. It is directly related to mitotic activity [85]. Although the action of VEGF is directed at endothelial cells, it has been shown to have an effect on other cell types. Tumour growth is directly related to the activity of neoangiogenesis. Overexpression of VEGF in most malignancies correlates with invasiveness, vascular density, metastatic lesions, recurrence, and poor prognosis [86]. An oncogenic RAS mutation can coordinate VEGF-driven signalling, which is responsible for cell proliferation, migration, and vascular permeability during angiogenesis. Increased expression of this factor is also observed in PTC [87]. Good vascularisation of the thyroid is a normal phenomenon, i.e. this factor is detected in unchanged thyroid tissue. It envelops the tumour with a thin layer, being in close contact with the neoplasm and stimulates its growth [88]. VEGF is located in the cytoplasm, and therefore its use in clinical practice is possible only for nodes containing colloidal fluid. This immunohistochemical marker can be used to determine the activity and invasive properties of the tumour, but not in all cases, which should be taken into account when choosing a method of differential diagnosis.

The molecular marker MET (mesenchymal-epithelial transition) plays an important role in cancer, activating signalling pathways to initiate cell migration, proliferation and angiogenesis [89]. MET activation, in turn, increases the expression of VEGF, thus this factor is involved in tumour formation, growth and invasion.

The apoptosis regulator B-cell lymphoma 2 (Bcl-2) inhibits this process. The Bcl-2 polymorphism changes its expression and leads to an imbalance in the mechanisms that regulate apoptosis. In malignant tumours, its expression is increased, and at high levels, loss of differentiation and resistance to treatment are observed. By protecting cells from apoptosis, Bcl-2 promotes tumour transformation [90].

B-cell activating factor (BAFF) is a member of the TNF ligand family and is produced by cells of myeloid origin, such as monocytes and dendritic cells, follicular cells, and T cells. It is a transmembrane protein that is released as soluble cytokine 2 after processing by furin, and is involved in B cell maturation, immunoglobulin switching, and antibody production. Its soluble form exists in the form of BAFF 3-mer trimers or in their complex. At high levels of BAFF, there is a high production of immunoglobulins, which leads to increased activity of the humoral immune system. The presence of inflammation stimulates the expression of BAFF by cells, which not only affects the function of B cells but also indirectly through the BCMA/BAFF-R pathway on T follicular helper cells [91, 92]. Since BAFF is directly related to the functioning of B cells, an increase in its level in patients with AIT and thyroid neoplasms indicates an aggressive course of PTC. This makes it possible to use it in clinical practice to predict the course of PTC in the setting of AIT.

Conclusions.

Based on the analysed studies of the literature data on the transformation of the PTC:

1. A decrease in the incidence of metastasis in patients under the age of 45 years was found. Tumour size of more than 1.0 cm increases the risk of tumour invasion into the thyroid tissue and extrathyroidal spread.
2. The level of molecular genetic markers associated with participation in apoptosis, increased proliferation rate and angiogenesis, as well as the duration of inflammation can be used to establish the diagnosis, predict the course and assess the risk of PTC metastasis.
3. The comparative analysis revealed a decrease in the effectiveness of preoperative detection of PTC in the setting of AIT, which encourages the use of more aggressive surgical tactics in the combination of these thyroid pathologies.

Prospects for further research.

To continue studying the relationship between papillary thyroid carcinoma metastasis and various factors, to study and implement molecular genetic markers for predicting the clinical course of thyroid cancer in clinical practice.

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ПРЕДИКТОРИ НЕСПРИЯТЛИВОГО ПЕРЕБІГУ ПАПІЛЯРНОГО РАКУ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Перцов В. І.

Резюме. *Вступ.* Визначення факторів ризику метастазування та агресивного перебігу папілярної карциноми щитоподібної залози є важливим для визначення об'єму хірургічного лікування, а саме необхідності виконання лімфатичної дисекції у пацієнтів з даним онкологічним захворюванням.

Мета. Провести огляд фахової медичної літератури для визначення факторів несприятливого перебігу папілярної карциноми щитоподібної залози.

Результати. У дослідженні Sak S. D. показано зв'язок високого ризику захворювання з чоловічою статтю, мультифокальним ураженням, локалізацією в нижній третині частки щитоподібної залози, поверхневим розташуванням пухлини та фіброзом строми. Згідно з результатами досліджень, розмір пухлини більше 1,0 см та мультифокальне ураження можна вважати показником агресивного перебігу ПТК. Автоімунний тиреоїдит ускладнює цитологічну діагностику вузлових утворень. Клітинна атипія, анізонуклеоз і плеоморфізм спостерігаються як при АІТ, так і при папілярній карциному, тому диференціальна діагностика при поєднанні цих патологій ускладнюється. Основою такого взаємозв'язку є молекулярна, гормональна та гістопатологічна подібність цих захворювань. Галектин-3 є регулятором нормальної проліферації клітин, але його надмірна експресія призводить до злоякісної трансформації клітин і метастазування. Неопластична трансформація доброякісної тканини є складним процесом, на який впливають численні фактори. Гуморальні механізми розвитку раку пов'язані з підкласом IgG4. Регуляторні Treg-клітини – це підгрупа CD4+ клітин, які пригнічують імунну відповідь, відіграючи важливу роль в уникненні протипухлинної імунної відповіді хазяїна. Повідомляється, що зменшення кількості CD4+ призводить до онкологічної трансформації. Також було показано, що мутація BRAF викликає гіперекспресію багатьох інших молекулярних пухлинних маркерів, наприклад таких як VEGF і MET.

Висновки. Рівень молекулярно-генетичних маркерів, асоційованих з участю в апоптозі, підвищеною швидкістю проліферації та ангіогенезу, а також тривалість запалення можуть бути використані для встановлення діагнозу, прогнозування перебігу та оцінки ризику метастазування ПТК.

Ключові слова: щитоподібна залоза, папілярна карцинома, поєднана патологія, метастазування, молекулярні маркери.

PREDICTORS OF UNFAVORABLE COURCE OF PAPILLARY THYROID CARCINOMA

Pertsov V. I.

Absrtact. *Introduction.* Determination of risk factors for metastasis and aggressive course of PTC is important in determining the scope of surgical treatment, namely the need for lymph node dissection in patients with this cancer.

Aim. To review the professional medical literature to determine the factors of unfavorable course of papillary thyroid carcinoma.

Results. A relationship between high-risk disease and male gender, multifocal lesions, localization in the lower third of the thyroid lobe, superficial location of the tumor, and stromal fibrosis was showing in Sak S. D.`s study. According to the results of studies, size of tumor larger than 1.0 cm and multifocal lesions can be considered an indicator of the aggressive course of PTC. AIT complicates the cytological diagnosis of nodal masses. Cellular atypia, anisonucleosis, and pleomorphism are observed in both AIT and PTC, so differential diagnosis in the case of a combination of these pathologies is more difficult. The basis for this relationship is the molecular, hormonal and histopathological similarity of these diseases. Galectin-3 is a regulator of normal cell proliferation, and its overexpression leads to malignant cell transformation and metastasis. The neoplastic transformation of benign tissue is a complex process influenced by numerous factors. Humoral mechanisms of cancer development are associated with the IgG4 subclass. Regulatory Treg cells are a subgroup of CD4+ cells that suppress the immune response, playing an important role in avoiding the host's antitumor immune response. It is reported that a decrease in CD4+ leads to oncological transformation. The BRAF mutation has also been shown to cause overexpression of many other molecular tumour markers, such as VEGF and MET.

Conclusions. The level of molecular genetic markers associated with participation in apoptosis, increased proliferation rate and angiogenesis, as well as the duration of inflammation can be used to establish the diagnosis, predict the course and assess the risk of PTC metastasis.

Key words: thyroid glands, papillary carcinoma, combine pathology, metastasis, molecular markers.

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DOES CRYOPRESERVATION UNIFORMLY AFFECT THE DNA FRAGMENTATION RATE OF SPERMATOZOA OF MEN WITH DIFFERENT STATES OF SPERMATOGENESIS? A SYSTEMATIC REVIEW AND META-ANALYSIS

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Cryotechnologies have become an integral part of infertility treatment methods. However, the question of the impact of cryopreservation on human sperm DNA fragmentation levels remains open. The aim was to conduct a systematic review and meta-analysis of studies on the effect of the cryopreservation method (a method of rapid cooling and vitrification) on the occurrence of DNA damage in spermatozoa of men with different states of spermatogenesis. The search was carried out in Medline, Embase, PubMed and Google Scholar databases. The results of 52 studies from 32 scientific papers were analysis in the present study. DNA damage in spermatozoa of men with different states of spermatogenesis was measured before and after cryopreservation using one of these methods: SCSA, SCD, TUNEL and Comet Assay. It was found that cryopreservation, regardless of the method used, leads to an increase of 7.73±2.04% in the DNA fragmentation rate of spermatozoa, regardless of the state of spermatogenesis of men. Cryopreservation increases normospermia sperm DNA fragmentation compared to pathospermia (SMD=8.76%, 95% CI 6.22 – 11.31%, p<0.00001 and SMD=4.01%, 95% CI 2.23 – 5.79%, p<0.00001, respectively). The greatest effect of cryopreservation on DNA fragmentation compared to fresh sperm was determined by the TUNEL method. Using this method, 8.08±2.38% of cells with the mentioned pathology were identified (SMD=8.08%, 95% CI 5.69 – 10.46%, p<0.00001). Determining the degree of DNA damage of spermatozoa before their banking can be a useful marker of the effectiveness of their cryopreservation, as it has prognostic value regarding the effectiveness of infertility treatment by assisted reproductive technology methods.