THE ISSUE OF MULTIPLE PRIMARY TUMORS AMONG ONCOPATHOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM (REVIEW)

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Abstract: *in the last decade, in the field of oncology, there has been an increasing interest in the study of issues related to the problem of multiple primary malignant tumors (MPMT). Many researchers agree that polyneoplasias are most often found in women, which is associated with an increase in the incidence of hormone-dependent tumors of the reproductive system, which is functionally represented by the mammary glands, uterus and ovaries. The development of comprehensive examination methods, including molecular genetic studies, contributes to the identification of synchronous MPMT of the female reproductive system. In our studies, metachronous tumors prevailed among MPMTs in breast cancer (65.7%). The most common metachronous cancer of the uterine body (37.1% of cases). Determination of the level of specific tumor markers allows you to monitor in advance the development of MPMT in this category of patients. Thus, each of the tumors of the female reproductive system should be considered as an indicator of the risk of the others, which should lead to a state of rapid response to the entire well-functioning system of dispensary registration, observation and use of a full range of special methods of clarifying diagnostics.*
Keywords: *uterine cancer; cervical cancer; ovarian cancer; mammary cancer; multiple primary malignant tumors.*

ПРОБЛЕМА ПЕРВИЧНО-МНОЖЕСТВЕННЫХ ОПУХОЛЕЙ СРЕДИ ОНКОПАТОЛОГИИ ЖЕНСКОЙ РЕПРОДУКТИВНОЙ СИСТЕМЫ (ОБЗОР)

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Аннотация: *первично-множественные злокачественные опухоли (ПМЗО) представляют существенную проблему в современной онкологии. При этом большая часть таких полинеоплазий встречается у женщин и проявляется, как правило, при развитии гормонозависимых опухолей репродуктивной системы, таких как рак молочной железы, матки и яичников. Согласно результатам наших исследований, среди 35 больных РМЖ, у 12 (34,3%) обнаруживались синхронные опухоли, а у 23 (65,7%) впоследствии развились метахронные опухоли. Совершенствование современных методов молекулярно-генетической диагностики способствует более глубокому пониманию механизмов развития ПМЗО. Обзор данных литературы позволяет сделать заключение, что каждую из опухолей женской репродуктивной системы следует рассматривать как индикатор риска возникновения и других онкопатологий, а эффективное диспансерное наблюдение и определение уровня специфических онкомаркеров позволяет во многих случаях заблаговременно контролировать развитие ПМЗО у данной категории больных.*
Ключевые слова: *первично-множественные злокачественные опухоли, рак молочной железы, рак тела матки, рак шейки матки, рак яичников.*

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In the last decade in the field of oncology, there has been an increasing interest in the study of issues related to the problem of multiple primary malignant tumors (MPMT). This is due, first of all, to the widespread increase in the number of patients with this type of oncological pathology. In recent years, the growth rate of MPMT has increased several times, and their frequency has increased from 3-6% to 13% [3,7]. The factors influencing the growth of the incidence of polyneoplasias are an increase in the average life expectancy, an increase in the intensity of carcinogenic effects, urbanization, the accumulation of hereditary burden, and an improvement in the diagnosis of oncological diseases [2,8]. The growth of such oncopathology is also influenced by the conducted chemoradiation therapy of the primary tumor, which increases the likelihood of developing metachronous tumors in the presence of other predisposing factors [5].

Many researchers agree that polyneoplasias are most often found in women, which is associated with an increase in the incidence of hormone-dependent tumors of the reproductive system, which is functionally represented by the mammary glands, uterus and ovaries. It is assumed that a similar effect of estrogens is associated with their stimulating effect on the processes of cell proliferation in these organs. It has been shown that some polymorphisms of

gene variants, the products of which are involved in the synthesis of androgens and estrogens, can increase the risk of neoplasms of the reproductive sphere [6, 10]. Malignant tumors of the reproductive system are the most frequent in the structure of oncological morbidity in women and their total share exceeds 35% [7].

The rate of multiple primary malignant neoplasms of the female reproductive system ranges from 0.8% to 12.6% of all cases of cancer of these localizations [11]. This variability can be due to a number of reasons, first of all is associated with diagnostic errors, when the second tumor can be regarded as a metastasis of the first. In addition, a significant proportion of patients die from the progression of the primary cancer before the latent period of the development of the second tumor expires [12].

Recently, there has been a significant increase in the incidence of MPMT in the elderly: according to different authors, it ranges from 1.3 to 11.6%, increasing in proportion to age, it was noted that among patients who died at the age of 70-73 years, MPMT was found in 13.5%, 80-90 years old - in 14% and over 90 years old - in 22%. Therefore, with uterine bleeding in the menopausal period, an urgent examination of women is indicated for the detection of tumors in the mammary gland, cervix and uterus, in the ovaries [7,13].

Currently, MPMT is understood as the independent emergence and development of two or more neoplasms in one patient. In this case, not only different organs of different systems can be affected, but also paired organs, as well as one organ multicentrically. A combination of two tumors predominates in the structure of polyneoplasias. Cases of triple localization occur in 5-8% of cases [16]. The presence of four, five, six or more tumors in one patient is rare and seems to be casuistry. An important point in the classification of multiple tumors is the time of their occurrence. Classically, MPMTs are divided into synchronous (occurring simultaneously) and metachronous (occurring at regular intervals) according to the time of occurrence. Synchronous-metachronous and metachronous-synchronous types of occurrence can occur in triple or more combinations of tumors [4].

The issue of the time boundary between the synchronicity and metachronism of the development of malignant tumors has been open for a long time. In nowadays, most authors consider the most reliable, albeit rather conditional, interval for the appearance of the second metachronous tumor, the period of more than 6 months from the establishment of the diagnosis of the first [4]. At the same time, in the overwhelming number of observations (75-80%), metachronous tumors appear in terms of 3 to 15 years, although isolated cases of the occurrence of second tumors have been described at a later date [1]. At the same time, in essence, it is not possible to determine the exact boundaries. This is primarily due to the fact that with the simultaneous onset of the development of several tumors, one of them, having a more intense growth rate, manifests itself clinically faster and is diagnosed earlier. Therefore, it is more expedient to indicate not the timing of the occurrence of multiple tumors, but the timing of their detection [9,11].

In patients with uterine cancer (UC), the relative risk of breast cancer (BC) is 13.6 in the first year, 5.3 in the fifth, 3.9 in the tenth, and 3.0 in the fifteenth. In breast cancer patients, the relative risk of uterine cancer is 9.0 in the first year, 2.4 in the fifth, 2.2 in the tenth, and 3.6 in the fifteenth. Consequently, in patients with both breast cancer and uterine cancer, the risk of developing a second tumor is realized mainly in the first year due to synchronous polyneoplasias. Subsequently, over all 15 years, the excess of the expected probability over the observed one is significant ($p < 0.05$), which allows us to conclude that there is a higher risk of hormone-dependent polyneoplasias in patients with breast cancer and uterine cancer compared to the risk in a healthy woman [4,16].

Information about the relationship between the features of estrogen metabolism and the risk of hormone-dependent tumors, in particular breast cancer, uterine cancer, and ovarian cancer (OC), can be considered firmly established today [9,15]. Women with impaired fat and carbohydrate metabolism, obesity, diabetes mellitus and hypertension in the pre- and postmenopausal period are at risk of developing both single and MPMT of the mammary gland, uterus and ovaries. It is assumed that a similar effect of estrogens is associated with their stimulating effect on the processes of cell proliferation in these organs. The risk of developing breast cancer in daughters and sisters increases 3-7 times, it is believed that after the cure of this type of tumor, the risk of developing cancer of any localization increases 1.2 times, and after cervical cancer (CC) it increases 1.6 times [1.3].

In the literature, there are reports that the occurrence of polyneoplasias can also be influenced by the ecological state of the environment, smoking and alimentary factors [5,10]. Less severe disorders such as autoimmune diseases and age-related involution of the immune system may also increase cancer risk. Normal genetic variation also affects the effectiveness of anti-tumor immunity [4,11].

The incidence of multiple primary malignant neoplasms is not the same. However, there are certain patterns that indicate that the organs in which the majority of malignant solitary neoplasms initially arise are more often affected. About 23% of MPMT is in the mammary glands, and in 38% of cases the opposite mammary gland was the second tumor, in 28% - pelvic organs, in 14% - skin, colon tumors accounted for about 11%, in 5% - thyroid iron, and the least frequent (4%) - lung tumors [1,7]. The second and third places in terms of the frequency of lesions are shared by the skin and female genital organs (18% each). If the primary tumor is found in one of the pelvic organs, then in most cases the second focus is in the mammary gland - 26% of cases [9].

In patients with breast cancer, multiple primary tumors occur in 1.9-7.1% of cases. Moreover, breast cancer is most often combined with malignant tumors of the female reproductive system (33-42%): OC (15-17%), UC (12-14%), cervical cancer (10-12%). Colon and rectal cancer (12-13%), then stomach (14-15%) and thyroid gland (7.7%), is the next most common cancer. The rest of the localization of malignant tumors is described in single observations [13, 14].

Among patients with cervical cancer, the most frequent combination is noted with breast tumors, which confirms the hormonal dependence of malignant tumors of the cervix. In this category of patients, dysfunctions of the hypothalamus-pituitary-ovaries system are also observed, as evidenced by a high level of gonadotropins, monophasic or defective biphasic cycles, a high frequency of hyperplastic processes in the endometrium and cystic transformation of the ovaries, disturbances in the rhythm of excretion of steroid hormones with absolute or relative hyperestrogenism on the background of progestin deficiency [5,15].

The synchronicity of the development of UC and OC and the relatively short interval between the development of UC and BC indirectly indicate the common pathogenetic mechanisms of the development of these malignant tumors. It was found that the general risk factors for hormone-dependent tumors of the organs of the reproductive system are pronounced chronic hyperestrogenism, which is especially characteristic of patients with UC. The high content of progesterone receptors, the synthesis of which is stimulated by estrogens in patients with UC, BC and OC, is a positive prognostic factor that reliably correlates with higher 5-year survival rates. The diagnoses of multiple primary tumors, histogenetically related to the same germ layer, but having a different histological structure, are absolutely reliable. For example, squamous cell lung cancer and adenocarcinoma of the uterine body. Relatively reliable diagnoses of MPMT include cases of the same histological structure of the tumor, but its different differentiation [3,6,12].

The cases of MPMT with the same histological structure are doubtful. For example, squamous cell carcinoma of the vagina and squamous cell cervical cancer. In the latter cases, for a final judgment about the nature of the pathology, it is important to use clinical data, including information on the extent of the tumor process, the presence of regional and distant metastases from these neoplasms, as well as histological examination of not only the biopsy material, but also the entire removed tumor. The main criteria for this are infiltrating growth for the primary tumor and unicentric for the metastatic, the absence of a sharp transition of the tumor into normal tissue in the primary lesion and the presence of such a transition in metastasis [4,5,13].

The successes achieved in the treatment of cancer patients have posed a new important task - early detection of the primary metachronous tumor and the provision of adequate treatment. The development of a comprehensive examination contributes to the identification of synchronous MPMTs, when detected in one organ system, the symptoms can be so similar that it is not possible to distinguish one tumor from another. Only with a thorough, targeted examination is it possible to make the correct diagnosis, and in some cases the final data can be obtained only with surgery or autopsy [6,9,16].

An important role in the diagnosis of synchronous MPMT is played by the correct choice of the scope and methods of examination, based on the collection of anamnestic data and an adequate clinical examination [1,7]. If one of the suspected tumors is breast cancer, the recommended examination algorithm

should include: X-ray mammography, ultrasound computed tomography, scintimammography, magnetic resonance imaging, which allow to determine with high accuracy the nature of the tumor process. Cytological examination, highly informative in terms of diagnosis verification, is absolutely necessary, but sometimes contradictory in the differentiation of primary and metastatic tumors [3].

According to the mutational-somatic hypothesis of development, most tumors arise as a result of somatic mutations and must be monoclonal. Based on this, a number of researchers suggest that verification of genetic characteristics (disorders or polymorphisms) in tumor cells may be useful or decisive in differentiating multifocal malignant tumors from metastases of a single tumor [5]. This is important when choosing the appropriate tactics for the treatment of these diseases. Thus, the presence of terminal mutations in the BRCA1 and BRCA2 genes in breast cancer and OC indicate a high risk of developing these tumors in carriers of such mutations. For carriers of the pathological BRCA1 gene, the risk of developing breast cancer is 44-80%, and OC 15-60%. Moreover, the second tumor in such patients in 65% develops in the opposite mammary gland. Carriage of the BRCA2 gene is associated with a 55-85% risk of developing breast cancer [1,4,14].

One of the directions in the diagnosis of malignant tumors is the determination of tumor markers, that is, natural proteins secreted by tumor cells into the bloodstream [6,9]. The tumor markers have already found widespread use in diseases of the breast, ovaries, gastrointestinal tract organs, etc. in clinical practice. However, in the diagnosis of multiple primary tumors, laboratory determination of one marker does not allow the clinician to correctly assess the situation. This forces researchers to turn to the definition of a whole complex of markers that are most sensitive for suspected diseases. An increase in the levels of at least one or several of them will help guide the clinician to the idea of the possible existence of two tumor processes in the patient [11,14,17].

In addition to previously used markers for germ cell tumors, such as alpha-fetoprotein and chorionic gonadotropin, markers such as cancer-embryonic antigen, mucin-like cancer-associated antigen, high-molecular antigens CA-15-3, CA- 19-9, CA-125. The most studied and widely used marker is CA-125, which is found in more than 85% of patients with OC [5,9,13]. In this situation, tumor markers are an effective additional diagnostic tool, since their diagnostic sensitivity and specificity in a widespread tumor process in most cases exceeds 80-85%. This should influence the sequence of therapeutic measures in patients who received treatment for hormone-dependent malignant neoplasms, such as breast cancer, cancer, cervical cancer, ovarian cancer, which have a significantly higher risk of developing a metachronous tumor; regular determination of tumor markers can help identify these tumors at earlier stages. development and, thereby, determine the improvement of the forecast [5,7].

Determining the treatment strategy for metachronically and synchronously detected tumors is a much more complicated task than planning for one malignant neoplasm. Due to the variety of options for combining tumors, an

even more differentiated approach to the treatment of each patient is required. Considering the data of molecular genetic studies, it becomes possible to develop a modern strategy for the treatment of MPMT, the main position of which boils down to the fact that if the patient's condition allows, all tumors should be treated in parallel or sequentially [12].

Tumors, the occurrence of which is associated with the carriage of mutations in the BRCA1 / 2 genes, are characterized by aggressive rapid growth and a low level of differentiation of tumor cells. BC and OC in carriers of BRCA1 / 2 gene mutations are often detected at a very early age. The issue of the peculiarities of treatment of BRCA1 / 2-associated breast cancer and OC has been discussed in the scientific literature relatively recently. According to the ESMO recommendations, it is necessary to abandon organ-preserving operations, the decision on surgical treatment should be based on the same parameters as for sporadic cancer, taking into account the higher risk of bilateral cancer and ipsilateral recurrence [3,14].

In recent years, convincing data have begun to accumulate, indicating a special spectrum of chemosensitivity of hereditary breast cancer. It is assumed that BRCA1-associated breast cancer is characterized by resistance to the “gold standard” of breast cancer therapy - drugs from the taxane group. At the same time, they demonstrate an extremely pronounced regression in the treatment of cisplatin, which is widely used to treat other tumors, but is not yet included in the standards of therapy for breast carcinomas. In addition to cisplatin, a promising treatment for hereditary cancers associated with mutations in the BRCA1 gene is the use of poly (ADP-ribose-) polymerase (PARP) inhibitors; clinical trials are underway in which an increase in the duration of relapse-free survival is expected. However, there are still no standards for chemotherapy regimens in patients with BRCA-associated breast cancer [5,10,14].

In our own research in the period from 2015-2020. There were 35 patients with breast cancer examined and treated in the chemotherapy department of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan. 12 (34.3%) of whom had synchronous tumors, and 23 (65.7%) subsequently developed metachronous tumors. The age was from 25 to 80 years old, the average was 53.2 ± 2.3 years. Stages II-III of the disease prevailed. Tumor markers CA-125, CA-15-3, CEA and CA-19-9 were determined by ELISA in the blood serum of patients with PMBC. The most common polyneoplasia was uterine cancer (UC), which occurred in 13 (37.1%) patients on average after 95 ± 6.3 months. after breast cancer treatment. After 74 ± 8.3 months. after treatment, 8 (20.0%) patients developed OC. In 2 (5.7%) after 83 ± 9.2 months colon cancer has developed. 8 (20.0%) had synchronous OC and 4 (11.4%) had uterine cancer. With MPMT of breast cancer and OC, the content of CA-125 was increased in 87.5% of cases with synchronous tumors and in 72.1% of cases with metachronous OC. There was also an increase in the level of CA-125 in 75.8% of cases with synchronous uterine cancer and in 68.3% - with metachronous uterine cancer. The level of CEA and CA-19-9 was increased in 100% of cases

with the development of colon cancer. Initially, the level of CA-15-3 in breast cancer patients was increased in 90.5% of cases. Determination of a wide range of tumor markers in breast cancer patients both during treatment and during the subsequent observation of treated patients can significantly help the timely detection of various secondary tumor processes.

Thus, MPMT of the reproductive system in women is currently a significant problem in modern oncology. It can already be considered an established fact that BC, UC, cervical cancer and OC are associated with each other in terms of multiple organ primary multiplicity [1,3,9]. The development of genomic research in molecular oncology makes it possible not only to understand the fundamental processes of carcinogenesis, but also to benefit practical medicine. Although it is too early to speak of a complete understanding of the mechanisms of malignant cell transformation, a lot of information has already been accumulated that can be applied in clinical practice. The study of the predisposition to oncological diseases gives direct access to preventive medicine. Determination of terminal mutations in families with hereditary oncological syndromes, in sick and asymptomatic carriers, will allow developing methods of preventing the disease and controlling its manifestation [10, 14]. Examination of blood relatives of patients in order to detect genetic changes in them and monitoring of healthy carriers of mutations is necessary for early and possibly preclinical diagnosis of oncopathologies [5,11]. This, in turn, allows, when studying the genetic aspects of malignant tumors of a multifactorial nature, to single out the criteria for identifying hereditary cancers, to form risk groups for the development of the disease, with the subsequent organization of a preventive cancer registry.

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