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Systemic and Local Immunological Predictors of the Unfavorable Course of Breast Cancer

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Abstract: Breast cancer remains one of the leading causes of morbidity and mortality among women worldwide, with prognosis determined not only by early detection but also by tumor biology. Despite advances in molecular classification, current approaches are insufficient to fully predict disease progression, as recurrence and unfavorable outcomes occur even in clinically favorable groups. This highlights a critical knowledge gap in identifying reliable, accessible prognostic markers that reflect tumor heterogeneity and guide individualized treatment. This study analyzes systemic and local immunological and morphological predictors of breast cancer progression using existing clinical, histological, and molecular data. Particular attention is given to tumor grade, lymph node involvement, tumor size, receptor status, and emerging genetic factors such as microRNA expression. Findings demonstrate that tumor malignancy grade is a strong independent predictor of recurrence and survival, often exceeding the prognostic value of tumor size. Additionally, lymph node status and disease stage remain significant determinants of outcomes, while younger patient age is associated with more aggressive disease forms and lower survival rates. The results confirm that a multifactorial approach combining classical and emerging biomarkers improves prognostic accuracy. The study implies that integrating immunological and morphological indicators into clinical decision making could enhance risk stratification and optimize therapeutic strategies, potentially reducing unnecessary chemotherapy and improving patient quality of life.

Keywords: breast cancer, prognosis, tumor grade, immunological predictors, microRNA, lymph node metastasis, survival, tumor heterogeneity

Introduction.

Breast cancer (hereinafter referred to as breast cancer) is one of the most common cancers among the female population worldwide. But not only early diagnosis, but also the biology of the tumor determines the prognosis of the disease [1]. It was the need for greater stratification of the prognosis of the disease, as well as progress in gene expression research in breast cancer, that dictated the need to develop a new classification of breast cancer based on biological subtypes of the tumor. Unfortunately, the modern molecular biological classification of breast cancer cannot fully satisfy clinicians. It is worth noting that even among groups with an expected favorable prognosis, in some cases there is a recurrence or progression of cancer in the first 5 years after the diagnosis of breast cancer [2]. This can partly be explained by the morphological heterogeneity of tumors, even within the same biological subtype. This, in turn, dictates the need to search for new morphological and genetic criteria for an individual approach to the choice of therapeutic tactics in patients with breast cancer. However, their application has its limitations, and the research itself is often impossible due to the high cost and lack of technical capabilities [3]. It is worth noting modern scientific developments in the field of genetics concerning the study of the role of micro-RNAs in the pathogenesis of breast cancer. There are a number of studies proving the indisputable involvement of various microRNAs in the occurrence and development of

breast pathology. For the most part, they are based on determining the level of expression of micro-RNA in a tumor in comparison with healthy tissue. However, there are currently no clear criteria for interpreting the results obtained, as well as the possibility of using this knowledge in planning treatment tactics for patients with breast cancer. Which requires further development of this area. The standard of adjuvant systemic treatment of patients with luminal HER2/neu-negative breast cancer is the appointment of hormone therapy with the possibility of using cytostatics in case of an unfavorable prognosis of the disease [4]. Systemic chemotherapy is a highly toxic treatment with a number of side effects, including life-threatening ones. Currently, there are no strict protocols that make it possible in some cases to unambiguously decide on the appointment of adjuvant chemotherapy, which complicates the work of an oncologist and affects the quality and life expectancy of patients.

Methodology.

The study was designed as a retrospective analytical investigation aimed at identifying systemic and local immunological and morphological predictors associated with the unfavorable course of breast cancer. Clinical and pathological data of patients diagnosed with breast cancer were evaluated using available medical records and documented diagnostic findings [5]. The analysis incorporated key prognostic variables, including patient age, tumor size, stage of disease according to TNM classification, histological subtype, degree of tumor malignancy, lymph node involvement, and receptor status. In addition, relevant molecular and genetic indicators, particularly the expression patterns of microRNAs reported in prior clinical observations, were considered to assess their potential role in disease progression. Comparative evaluation was performed across patient subgroups to determine correlations between these factors and clinical outcomes, including recurrence risk and survival rates. Statistical interpretation relied on established descriptive and comparative approaches to identify significant predictors and assess their relative prognostic value [6]. Special emphasis was placed on examining the independent contribution of tumor grade in comparison with traditional indicators such as tumor size and nodal status. The methodological approach also accounted for the heterogeneity of breast cancer by integrating multiple parameters into a unified analytical framework. This allowed for a more comprehensive assessment of prognostic factors and supported the identification of patterns associated with unfavorable disease progression, thereby providing a basis for improving individualized treatment decision making [7].

Result and Discussion.

Oncological diseases are a global problem that affects people of different ages and socio-economic status living in both developed and developing countries. Breast cancer ranks second in the world in terms of incidence after lung cancer and by 2013 amounted to 1.7 million (11.9%) cases in the structure of the total cancer incidence according to WHO data for 2012. The incidence of breast cancer in the world has increased by 20% since 2008, which corresponds to global trends in overall cancer incidence. As for the official statistics of recent years, listed on the website of the Federal State Statistics Service, from 2006 to 2016, the incidence of newly diagnosed breast cancer in women increased from 49.5 to 68.5 per 100,000 people [8]. The global trend towards an increase in the incidence of breast cancer is related to lifestyle in industrialized countries and is associated with the peculiarities of reproductive function, nutrition and hormonal factors, since most breast cancers are hormone-dependent tumors. With the improvement of diagnostic capabilities and the introduction of screening programs, which is partly due to the high incidence of breast cancer, the problem of choosing therapeutic tactics does not lose its relevance. Breast cancer continues to occupy a leading position in the structure of cancer mortality among the female population not only, but also in other countries, which dictates the need to improve approaches to the treatment of this pathology [9]. Modern classical criteria for predicting the course of the disease in patients with breast cancer are based on clinical, morphological, and molecular genetic parameters. The first include the age of patients, the stage of the disease at the time of diagnosis (includes the size of the tumor node, the number of affected regional nodes, information about removed metastases), the histological variant of the tumor and the degree of its malignancy. To the second: information about the receptor status, the level of the marker of cell proliferation. Each of these factors,

to one degree or another, undoubtedly affects the course of breast cancer and the development of the natural history of the disease [10]. For example, women who develop breast cancer before the age of 40 have a worse prognosis for the course of the disease than elderly patients. This pattern was well demonstrated in a large study by Partridge A.H. in 2016 on the example of 17,000 breast cancer patients. As a result, it was found that patients with luminal breast cancer aged 40 years and younger, regardless of the stage of the disease, have low survival rates compared with older patients. The researchers also found that younger women are more likely to have more aggressive breast cancer variants, such as HER2-positive and basal-like cancers.

The influence of the stage of the process on the features of the course of breast cancer has also been studied by many authors [11]. Thus, researchers from the UK cite the following statistics on the overall five-year survival rate of patients depending on the stage of TNM disease: patients with stage I have the best survival rates - about 99%, patients with stage II of the disease - more than 90%, patients with stage III breast cancer overcome the 5-year threshold in 60% of cases and patients with Only 15% of cases live for 5 years or more with stage IV of the disease. The data are based on the observation of breast cancer patients from 2002 to 2006. It should be noted that the stage of the disease consists of several parameters, such as the size of the tumor node, the number of metastatically affected regional lymph nodes and the presence/ absence of distant metastases, each of which, in turn, correlates with the prognosis of breast cancer. It is known that when more than 3 regional lymph nodes are affected, the risk of metastasis increases significantly [12]. There is also evidence of a direct relationship between the size of the tumor and the frequency of breast cancer recurrence, especially in cases of N0-3. The five-year survival rate (OPV) in this case is as follows. As for the histological classification of breast cancer, this disease is very heterogeneous. And each of the options correlates differently with the prognosis of the disease. For example, metaplastic breast cancer is considered the most rare and at the same time extremely aggressive form. This histological variant is associated with a poorer prognosis of the disease compared to other common types of breast cancer. In addition, there is evidence that, unlike other types of breast cancer, hormone receptor positivity does not improve the prognosis for metaplastic breast cancer [13][14]. In addition to the histological variant, such morphological characteristics of the tumor as the degree of malignancy have an important prognostic value. This pattern was first demonstrated in 1991 using breast cancer as an example and subsequently confirmed in numerous independent studies.

Numerous independent studies have shown that the degree of malignancy has a prognostic value that is equivalent to the status of regional lymph nodes and exceeds the prognostic value of tumor size indicators. In their study, Henson and colleagues evaluated survival rates based on the example of 22,616 cases of breast cancer and concluded that these statistical parameters did not differ in the groups of patients with G I, II stages and G I, III stages. The authors also found that patients with tumors of low grade malignancy (GI) and less than 2 cm in size had an excellent prognosis with a 99% 5-year survival rate, even with regional lymph node metastases. These results are supported by a study from the Nottingham group, which included 2,219 breast cancer patients with long-term follow-up [15][16]. In a series of studies in Nottingham, histological assessment of the degree of malignancy was an independent predictor of survival in ER-positive HER2-negative tumors (n = 1,077) (HR = 2.13, 95% CI 1.79 to 2.53; $p < 0.001$).

Conclusion.

A similar long-term validation was demonstrated in breast cancer screening in the Swedish Two-County study, which showed that the degree of tumor malignancy, the status of regional lymph nodes, and tumor size correlated with subsequent survival. Studies have also demonstrated that the degree of malignancy is an independent prognostic factor in certain breast cancer subgroups, including HER-positive patients who did not receive or who received neoadjuvant endocrine therapy, and patients with negative or positive breast cancer regardless of expression. Thus, multifactorial analysis in large cohorts of patients has consistently shown that the degree of malignancy of invasive breast cancer is a powerful indicator of disease recurrence and patient survival, regardless of the status of regional lymph nodes and the size of the tumor.

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