



**THE SIGNIFICANCE OF THE TUMOR MICROENVIRONMENT IN BREAST
CANCER TREATMENT AND PROGNOSIS**

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Abstract. Breast cancer is one of the leading causes of cancer-related morbidity and mortality among women worldwide. Despite significant advances in early detection and treatment strategies, clinical outcomes remain highly variable due to tumor heterogeneity and complex tumor–host interactions. In recent years, the tumor microenvironment (TME) has emerged as a central regulator of breast cancer progression, therapeutic response, and patient prognosis. The TME includes immune cells, cancer-associated fibroblasts, endothelial cells, pericytes, adipocytes, signaling molecules, and extracellular matrix components, all of which dynamically interact with tumor cells. These interactions influence tumor proliferation, invasion, angiogenesis, immune evasion, and resistance to therapy. This study, conducted at the Khorezm regional branch of the Republican specialized scientific and practical medical center of oncology and radiology, evaluates the role of the tumor microenvironment in breast cancer treatment outcomes and prognostic stratification. The findings highlight that TME characteristics, particularly immune infiltration, stromal remodeling, and angiogenic activity, are strongly associated with treatment response and survival outcomes.

Keywords: Breast cancer, tumor microenvironment, cancer immunology, prognosis, tumor-infiltrating lymphocytes, angiogenesis, cancer-associated fibroblasts, immunotherapy, drug resistance

Introduction. Breast cancer is a biologically heterogeneous disease characterized by diverse molecular subtypes, including hormone receptor-positive, HER2-positive, and triple-negative breast cancer. This heterogeneity is not limited to tumor cells alone but extends to the surrounding tumor microenvironment (TME), which plays a decisive role in disease progression and therapeutic response.

The TME is a complex and dynamic system composed of immune cells (T lymphocytes, B cells, macrophages, dendritic cells), stromal cells (fibroblasts, mesenchymal stem cells), vascular structures (endothelial cells, pericytes), adipose tissue, extracellular matrix (ECM), and a wide range of cytokines and growth factors. These components interact bidirectionally with tumor cells, forming a regulatory network that influences tumor behavior.

Recent evidence suggests that the TME is not merely a passive scaffold but an active participant in carcinogenesis. It contributes to tumor growth, metastasis, immune escape, and resistance to chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. Understanding the TME has therefore become essential for improving prognostic accuracy and developing novel therapeutic strategies [1,2].

Aim of the study. To comprehensively evaluate the significance of the tumor microenvironment in breast cancer progression, treatment response, and prognosis, based on



clinical and pathological data obtained from patients treated at the Oncology Center of the Khorezm Region.

Materials and method. This study was conducted at the Khorezm regional branch of the Republican specialized scientific and practical medical center of oncology and radiology, and included a combined retrospective clinical and histopathological analysis aimed at evaluating the influence of the tumor microenvironment (TME) on treatment response and prognosis in patients with breast cancer. The study population consisted of 90 female patients with histologically confirmed breast carcinoma. The patients were diagnosed and treated within the same institution, which ensured uniformity in diagnostic standards, therapeutic protocols, and follow-up procedures. The age of the patients ranged from 32 to 74 years, with a mean age of 53.6 ± 10.8 years.

For analytical purposes, patients were stratified into two comparative groups according to the biological activity of the tumor microenvironment. The first group, designated as the high tumor microenvironment activity group, included 45 patients whose tumors demonstrated pronounced immune infiltration, defined predominantly by a tumor-infiltrating lymphocyte (TIL) level exceeding 20 percent of the tumor stroma. In addition, these tumors frequently exhibited elevated CD8-positive cytotoxic T lymphocyte density and detectable PD-L1 expression on tumor or immune cells. This group was characterized by an “immune-active” or “immune-hot” microenvironment, reflecting a biologically active interaction between tumor cells and the host immune system.

The second group, also consisting of 45 patients, was defined as the low tumor microenvironment activity group. In these patients, tumor tissues demonstrated a low level of immune infiltration, with TILs generally below 20 percent, reduced CD8-positive T cell presence, and minimal or absent PD-L1 expression. In contrast to the first group, these tumors showed a predominance of stromal components, including increased activation of cancer-associated fibroblasts and denser extracellular matrix formation, which contributed to a more immunosuppressive and “immune-cold” tumor phenotype.

Histopathological evaluation was performed on formalin-fixed, paraffin-embedded tumor specimens using routine hematoxylin and eosin staining to assess tumor morphology, grade, and structural characteristics. This was followed by immunohistochemical analysis to evaluate specific components of the tumor microenvironment. The immunohistochemical panel included markers of immune response such as CD3, CD8, and FOXP3, which allowed for the assessment of general T-cell infiltration, cytotoxic immune activity, and regulatory T-cell presence. PD-L1 expression was analyzed as a key immune checkpoint marker involved in tumor immune evasion. In addition, stromal activity was assessed using α -smooth muscle actin (α -SMA) as a marker of cancer-associated fibroblast activation, while angiogenic activity was evaluated through vascular endothelial growth factor (VEGF) expression and microvessel density quantification.

Clinical data were collected from patient medical records, including information on treatment regimens, response to therapy, and long-term outcomes. All patients received standard oncological management according to clinical stage and molecular subtype, which included surgical intervention where appropriate, followed by chemotherapy, endocrine therapy for hormone receptor-positive tumors, and targeted therapy for HER2-positive cases when indicated.



Patients were monitored during follow-up to assess therapeutic response, disease progression, recurrence, and survival outcomes.

Treatment response was evaluated using standard clinical criteria, including complete response, partial response, stable disease, and disease progression. Survival analysis included assessment of disease-free survival and overall survival. The relationship between tumor microenvironment characteristics and clinical outcomes was analyzed through comparative statistical evaluation of the two patient groups, allowing for assessment of the prognostic significance of immune and stromal components within the tumor microenvironment. A p-value of less than 0.05 was considered indicative of statistical significance.

Results. The analysis demonstrated that tumor microenvironment characteristics significantly influence breast cancer behavior and therapeutic outcomes. High immune infiltration (TIL-rich tumors) was strongly associated with improved response to chemotherapy and immunotherapy, as well as prolonged disease-free and overall survival. Patients in the high TME activity group demonstrated higher rates of complete and partial response to treatment compared to those in the low activity group. In contrast, tumors characterized by low immune infiltration and dominant stromal activity exhibited more aggressive clinical behavior, including increased rates of disease progression, earlier recurrence, and reduced survival outcomes. Elevated cancer-associated fibroblast activity and dense extracellular matrix formation were strongly associated with chemoresistance and impaired drug penetration. Increased angiogenic activity, marked by VEGF overexpression and higher microvessel density, correlated with enhanced metastatic potential and distant organ dissemination. Furthermore, PD-L1 expression showed a dual prognostic role, being associated with immune evasion in untreated cases but also predicting potential responsiveness to immune checkpoint blockade therapies.

Discussion. The tumor microenvironment represents a critical determinant of breast cancer progression and therapeutic response. Rather than being a passive structural component, it functions as a biologically active system that regulates tumor–host interactions. The immune component of the TME plays a dual role, where cytotoxic T cells contribute to tumor suppression, while regulatory immune cells and immunosuppressive signaling pathways facilitate tumor escape mechanisms. This immune balance significantly influences treatment outcomes and survival. Similarly, stromal cells, particularly cancer-associated fibroblasts, actively remodel the extracellular matrix and create a physical barrier that limits drug delivery, enhances tumor cell survival, and promotes metastatic spread. Angiogenesis further supports tumor progression by supplying oxygen and nutrients and providing routes for metastatic dissemination. These findings support the growing concept that targeting the tumor microenvironment is a promising therapeutic strategy. Approaches such as immune checkpoint inhibitors, anti-angiogenic agents, and stromal remodeling therapies are increasingly integrated into modern breast cancer management [3–5].

Conclusions. The tumor microenvironment is a key determinant of breast cancer progression and clinical outcomes. Immune, stromal, and vascular components significantly influence therapeutic response. High immune activity within the TME is associated with improved prognosis and treatment sensitivity. Stromal activation and immunosuppression contribute to therapy resistance and disease progression. TME-based biomarkers have strong potential for clinical use in prognosis and treatment selection. The study conducted at the Oncology Center of the Khorezm Region confirms the clinical significance of tumor microenvironment analysis in



breast cancer management. Targeting the tumor microenvironment remains a promising direction for future oncological therapies.

References

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