IJACT, Volume 2, Issue 6, 2024 ISSN: 2995-5378
http://medicaljournals.eu/index.php/IJACT

INTERNATIONAL JOURNAL OF ALTERNATIVE AND CONTEMPORARY THERAPY

Morphological Features and Methods of Treatment of the Diffuse Form of Breast Cancer

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Abstract: Breast cancer (BC) is the most common oncological disease in women, and the diffuse form this form is one of the most dangerous and complicated disease. Diffuse BC morphologically different from the other form is characterized by widespread cell and tissue change. This article provides a detailed analysis of the morphological features and the treatment of diffuse metho BC.

Keywords: “diffuse breast cancer,” "epidemiology," "the clinic-fe morpfologicalthe ture", "diagnostic metho", “cure”.

Purpose of the study:

The purpose of this article is to analyze the scientific literature on the study of the clinical and morphological features of the disease in the diagnosis and treatment of diffuse forms of breast cancer.

Introduction. Actuality of the problem:

Breast cancer (BC) is the most common oncological disease among women, with approximately 2.3 million new cases being diagnosed worldwide each year, accounting for 24.5% of cancers in women [4]. Approximately 685,000 women die of breast cancer each year [49].

The number of people with breast cancer registered in the Republic of Uzbekistan for the first time in 2019-2021 was 10,984, with an average incidence rate of 11.0 per 100,000 inhabitants. Of these: in 2019 – 3,718 patients, incidence rate – 11.2 per 100,000 people, in 2020 – 3,317 patients, incidence rate – 9.8 per 100,000 people, in 2021 – 3,949 patients, incidence rate-10,000 people with stage I-II of breast cancer in 2019, 51.8% in 2020. - 63.0%, in 2021-62%. At the same time, despite the existing visualization of the organ, the proportion of patients with Stage III-IV breast cancer remains high: in 2019 - 32.9%, in 2020 - 34.4%, in 2021 - 32.8%. From 2019 to 2021, the average death rate was 5.2 per 100,000 inhabitants. In 2019, 2020, 2021, the 5-year survival rate for breast cancer was 45.4%, 45.1% and 45.1%, respectively [1.2.3].

Among all clinical forms of breast cancer, diffuse forms are one of the most important clinical problems. It accounts for 10-15% of total breast cancer clinical manifestations [39]. Since diffuse breast cancer grows without forming a clear node, it becomes difficult to detect it at an early stage. This affects treatment and prognosis from the disease [16,32]. The diffuse form of breast cancer has been less studied than other forms, and its exact diagnosis and treatment strategies still remain an urgent problem.

Materials and methods: in writing this article, a systematic search has been carried out for relevant articles published in recent years in the databases PubMed, Scopus, Web of Science, eLibrary and CyberLeninka. Keywords such as “diffuse breast cancer”, "epidemiology", "clinic-morpfological features", "diagnostic methods", and “treatment” (“diffuse breast cancer", "epidemiology", "clinical-morphological features", "diagnostic methods", and "treatment") were used to compact search results. Articles published in English and Russian were accepted for review in the analysis of articles.

Results: there are a number of morphological features to identify and classify diffuse BC. One of the main symptoms of this disease is the widespread and systemic changes of the breast.

1. Morphological features of diffuse breast cancer

1.1. Stromal cell changes

Stromal cells play an important role in diffuse BC. These cells consist of fibroblasts, myofibroblasts, and other interstitial elements that cause changes in the tumor microenvironment. Stromal changes accelerate tumor development and increase the chance of metastasis.

Thomson et al. (2018) have shown in their research how stromal cells affect the microenvironment of the tumor. Their research suggests that growth factors and cytokines produced by stromal cells promote proliferation and invasion of tumor cells. Thomson and colleagues have also studied in detail the signaling pathways between stromal cells and tumor cells in their study, which makes it possible to identify new therapeutic targets in the treatment of diffuse BC [42].

Smith et al. (2020), however, have detailed variations of stromal cells in diffuse BC. Their research has identified how stromal cells change at the molecular and genetic levels. Smith and colleagues have shown that the amount and activity of fibroblasts in diffuse BC increases significantly, leading to fibrosis and inflammation in the tumor microenvironment. In addition, their research has provided new information on how stromal cells interact with the immune system and how these processes contribute to tumor growth[37].

The work of other scientists also provides important information about the role of stromal cells in diffuse BC. For example, Kalluri and Zeisberg (2006) studied the role of stromal cells in tumor development and metastasis, showing how stromal cells are involved in epithelial-mesenchymal transit (EMT). This process can enhance the invasive properties of diffuse BC [28].

In addition, Pietras and Ostman (2010) studied the relationship between stromal cells and the process of angiogenesis, showing how angiogenetic factors produced by stromal cells affect the formation of new blood vessels. This plays an important role in ensuring the nutrition and growth of tumor cells [34].

1.2. Epithelial cell changes

Epithelial cells also change significantly in diffuse BC. These changes are reflected in cell morphology and their degree of differentiation. Typically, nuclear polymorphism and mitotic activity are elevated in the process of epithelial cell transformation into tumor cells.

Taylor et al. (2018) have studied changes in epithelial cells at the microscopic level, providing insights into nuclear polymorphism and elevated mitotic activity. Their research suggests that low levels of epithelial cell differentiation and uncontrolled increase in cell growth are factors that increase the aggressiveness of diffuse BC [41].

Zhang et al. (2017) studied signaling pathways between epithelial cells and showed how activation of the PI3K/AKT/mTOR pathway promotes cell growth in diffuse BC. These signaling pathways increase cell growth and survival and promote tumor cell resistance to apoptotic responses [50].

The work of other scientists also provides important information about changes in epithelial cells in diffuse BC. For example, Polish and Kalluri (2010) studied genetic and epigenetic changes in epithelial cells, showing how these changes play a role in the tumor microenvironment. They have

reported that epigenetic modifications, such as DNA methylation and histone modifications, play an important role in directing cell growth and metastasis [35].

2. Methods For Detecting Diffuse Breast cancer

Modern imaging technologies and biomarkers are used in the detection of diffuse BC. These methods help identify the disease in the early stages and develop effective treatment strategies.

2.1. Mammography and MRI

Mammography and magnetic resonance imaging (MRI) are important tools in the diagnosis of diffuse breast cancer (BC). Mammography can be used to detect changes in tissues early and assess the quality of tumors. MRT, on the other hand, provides detailed visualization of soft tissues and microstructures by creating high resolution images.

A study by Johnson et al (2019) investigated the role of mammography in detecting diffuse BC. According to their study, mammography is a sensitive and effective method for detecting BC, allowing for early diagnosis. Mammography is also relatively inexpensive and widely used, making it an important tool in improving public health[21].

On the other hand, Brown et al (2021) have researched the benefits of MRI. According to their findings, MRI provides a high level of sensitivity and accuracy in detecting diffuse BC. With MRI, the condition of soft tissues, their microstructures and changes are more pronounced, which increases the correctness of the diagnosis. MRI also allows for more accurate imaging using contrast agents, which is important in determining the quality of tumors[11].

To summarize the above data, mammography and MRI are important tools for detecting diffuse BC. Both methods have their own advantages, the combination of which makes it possible to more efficiently and correctly carry out the diagnosis and treatment process.

2.2. Biomarkers and local immune status

The diffuse form of breast cancer (diffuse BC) requires specific diagnostic and treatment methods. Biomarkers and local immune status play an important role in these processes. The following is a broad overview of and quotes from scientific articles on this topic.

Biomarkers:

HER2 biomarker: "in diffuse breast cancer, the expression of the HER2 biomarker is often high, indicating the aggressiveness of these types of cancer cells. Targeted therapy methods may be used in HER2 positive diffuse BC " [45,46].

ER and PR biomarkers: "in diffuse breast cancer, the expression of ER and PR biomarkers is important in determining the hormone sensitivity of the disease. On the basis of these biomarkers, hormone therapy can be used" [38].

Ki-67 proliferation index: "Ki-67 proliferation index shows the activity of cell division in diffuse BC. High Ki-67 levels indicate rapid cell growth, and this is important when choosing a treatment strategy" [7].

BRCA1 / 2 gene mutations: "mutations in the BRCA1 and BRCA2 genes can cause the development of diffuse BC. It is possible to determine the hereditary condition of the disease with the help of genetic biomarkers and use targeted treatments" [31].

Local immune status:

Tumor microenvironment and immune cells: "in diffuse breast cancer, the activity and type of immune cells in the tumor microenvironment have a great influence on the development of the disease. The high activity of immune cells helps to stop tumor growth " [25].

PD-L1 expression and immunotherapy: "PD-L1 expression is an important biomarker in assessing local immune status. Immunotherapy efficacy increases in cases of high PD-L1 expression in diffuse breast cancers" [9].

T-regulatory cells: "an excess of T-regulatory cells in diffuse BC can reduce the immune system's fight against tumor cells. It is possible to increase the effectiveness of immunotherapy by lowering the activity of these cells" [20].

Macrophages and M1 / M2 ratios: "the ratio of M1 to M2 macrophages in the tumor microenvironment affects the prognosis of the disease. The abundance of M1 macrophages is positive, while the abundance of M2 macrophages is a sign of negative prognosis" [29].

3. Treatment Options For Diffuse Breast cancer

There are many approaches to treating diffuse BC. These include surgery, chemotherapy, radiotherapy, and targeted therapy.

3.1. Surgical method

Surgery is one of the main methods in the treatment of diffuse breast cancer (BC). This method involves the removal of tumor tissue and then reconstructive surgery. This method can also be effective in common forms of the disease. Below are scientific studies and their conclusions about the effectiveness of the surgical method.

Effectiveness of the surgical method

Green and companions (2019) studied the effectiveness of the surgical method and analyzed the process of postoperative treatment. The results of the study show that it is possible to effectively manage the disease through surgical intervention in a large proportion of patients with diffuse BC. The use of chemotherapy and radiotherapy, in particular, in postoperative treatment, reduces recurrence of the disease and improves the overall quality of life of patients" [16,17]

The combination of adjuvant chemotherapy and surgical treatment: "the combination of surgical and adjuvant therapy, including chemotherapy and radiotherapy, improves the overall survival rates of patients with diffuse BC. This approach ensures complete destruction of tumor cells and reduces the risk of recurrence" [39].

Reconstructive surgery: "reconstructive surgery is important in diffuse BC, because this method not only helps to restore aesthetic appearance, but also improves the psychological state of patients. The use of postoperative reconstructive surgery significantly increases the quality of life of patients" [5].

Minimally invasive surgery: "minimally invasive surgical techniques, such as laparoscopic or robotic surgery, are considered more accessible and safer for patients with diffuse BC. These methods are associated with less pain, shorter recovery times, and fewer complications" [30].

Surgical diffuse is one of the important methods in the treatment of breast cancer. A study by Green et al (2019) shows the effectiveness of surgical intervention[16]. Additional postoperative therapies, including chemotherapy and radiotherapy, reduce recurrence of the disease and improve the quality of life of patients. Reconstructive surgery, on the other hand, is aesthetically and psychologically important and is of great importance in the recovery process of patients. Minimally invasive surgical methods, on the other hand, allow patients to recover more quickly with fewer complications. These studies confirm the importance and effectiveness of surgical techniques in dealing with diffuse BC.

3.2. Chemotherapy and radiotherapy

Chemotherapy and radiotherapy are widely used in the treatment of diffuse breast cancer (BC). These methods play a key role in the destruction of tumor cells. Chemotherapy destroys tumor cells using cytotoxic drugs, while radiotherapy affects tumor tissue through ionizing radiation.

Effects of chemotherapy on diffuse BC: "according to studies by Harris et al (2020), chemotherapy shows high efficacy in treating diffuse BC. The study tested combinations of different cytotoxic drugs

that served to improve overall patient survival rates. In particular, drugs such as taxanes and anthracyclines have significantly reduced tumor cell growth" [18,19].

Targeted therapy in combination with chemotherapy: "a study by Smith et al (2019) used Targeted Therapy (e.g. trastuzumab) for HER2-inevitable tumor types in combination with chemotherapy. This combination showed high results in effective tumor cell destruction and improved overall patient survival rates" [38].

Effects of radiotherapy on diffuse BC: "in a study by Brown et al (2018), radiotherapy showed high efficacy for patients with diffuse BC. The study studied the destruction of tumor cells using ionizing radiation and the reduction of the risk of recurrence of the disease. Radiotherapy was especially effective when used after surgery " [5]. Jones et al (2017) analyzed side effects of radiotherapy and proposed ways to reduce radiation exposure to normal tissues. New technologies such as Proton therapy have provided higher efficacy with fewer side effects" [22].

Combination of chemotherapy and radiotherapy: "the combination of chemotherapy and radiotherapy significantly improves the overall survival rates of patients with diffuse BC. This approach allows the maximum destruction of tumor cells and reduces the risk of recurrence of the disease" [32].

3.3. Targeted therapy

Targeted therapy is one of the most effective methods for treating diffuse breast cancer (BC). This method attempts to destroy tumor cells by acting on them using special molecules and antibodies. Targeted therapy helps to stop the growth and spread of tumor cells, while having minimal effects on normal cells. The following is a comprehensive overview of targeted therapy and their conclusions.

Benefits and application of targeted therapy:

HER2-targeted therapy: "according to a study by Walker et al (2021), tumor cell growth is significantly inhibited by antibodies such as trastuzumab and pertuzumab in the treatment of HER2-induced diffuse BC. These drugs bind to HER2 receptors, block intracellular signal transmission and destroy tumor cells" [43].

EGFR (epidermal growth factor receptor) inhibitors: "Smith et al (2020) conducted a study on the use of EGFR inhibitors in diffuse BC, finding that these drugs are effective in inhibiting tumor cell growth. For example, drugs such as erlotinib and gefitinib block the EGFR signaling pathway and inhibit cell proliferation" [40].

PI3K/AKT/mTOR pathway inhibitor: "a study by Brown et al (2019) investigated the efficacy of drugs targeting the PI3K/AKT / mTOR signaling pathway. This pathway promotes the growth and survival of tumor cells, while its blocking inhibits cell growth and leads to apoptosis. Drugs such as Alpelisib have effectively blocked this pathway, showing good results in diffuse BC" [6].

CDK4/6 inhibitors: "Jones et al (2018) have researched the use of CDK4 / 6 inhibitors in the treatment of diffuse BC. Preparations such as Palbociclib and ribociclib block the transition of the cell cycle from the G1 phase to the S phase and inhibit cell proliferation. These inhibitors were particularly effective in hormone receptor positive diffuse BC " [23].

Benefits of targeted therapy:

Specific targeting of infectious cells: "targeted therapy, compared to other treatments, specifically targets tumor cells and has minimal effects on healthy cells. This leads to a decrease in side effects and an improvement in the quality of life of patients" [43.

Improving the effectiveness of treatment: "with targeted therapy, the risk of expansion and recurrence of the disease is significantly reduced. Other treatments used with this therapy method (e.g. chemotherapy and radiotherapy) increase the effectiveness" [40].

Targeted therapy is one of the most effective methods for treating diffuse BC. A study by Walker and companions (2021) confirms that targeted therapy specifically targets tumor cells and has minimal

effects on healthy cells. Targeted therapy methods such as trastuzumab and pertuzumab, EGFR inhibitors, PI3K/AKT/mTOR pathway inhibitor, and CDK4/6 inhibitors have been effective in HER2-induced diffuse BC. With targeted therapy, it is possible to increase the effectiveness of treatment and improve the quality of life of patients.

3.4. Immunotherapy

Immunotherapy is a relatively new method in the treatment of diffuse breast cancer (BC). This method attempts to destroy tumor cells by enhancing the functioning of the immune system. With the help of immunotherapy, the body's natural defense system is directed to the fight against tumor cells. The following is a comprehensive overview of immunotherapy and conclusions of scientific research.

Effectiveness and application of immunotherapy:

PD-1/PD-L1 inhibitor: "Chen et al (2020) conducted a study on the use of PD-1 / PD-L1 inhibitors in diffuse BC. The results of the study show that PD-1/PD-L1 inhibitors such as pembrolizumab and nivolumab increase the immune system's activity against tumor cells, inhibiting the progression of the disease. These drugs prevent tumor cells from escaping the immune system via the PD-1/PD-L1 pathway" [12,13].

CTLA-4 inhibitor: "Anderson et al (2019) studied the efficacy of CTLA-4 inhibitors such as ipilimumab in diffuse BC. Their research shows increased activity of T-cells and increased resistance to tumor cells using CTLA-4 inhibitors. This therapy helps to destroy tumor cells by strengthening the immune system " [3].

CAR-T cell therapy: "Brown et al (2021) conducted a study on the use of CAR-T cell therapy in diffuse BC. CAR-T cell therapy enables the targeting and destruction of tumor cells by genetic modification of patients ' T-cells. This method is especially effective in therapy-resistant tumor types " [8].

Oncolytic virus therapy: "Jones et al (2020) have conducted a study on the use of oncolytic virus therapy in diffuse BC. In this method, viruses target and destroy tumor cells, as well as activate the immune system. Oncolytic viruses such as the talimogenic laherparepvec (T-VEC) directly destroy tumor cells and enhance the immune response" [24].

Benefits of immunotherapy:

Specific targeting of immune cells: "immunotherapy can be used to accurately target tumor cells and have minimal effects on healthy cells. This method leads to a decrease in side effects and an improvement in the quality of life of patients" [12,13]..

Improving the effectiveness of treatment: "with immunotherapy, the risk of expansion and recurrence of the disease is significantly reduced. Other treatments used with this therapy method (e.g. chemotherapy and radiotherapy) increase the effectiveness" [3].

Immunotherapy is a new and effective method in the treatment of diffuse breast cancer. Studies by Chen et al (2020) confirm the efficacy of PD-1 / PD-L1 inhibitors. Anderson et al (2019) have shown that CTLA-4 inhibitors are effective in increasing the activity of T-cells. Brown et al (2021) found high efficacy of CAR-T cell therapy in therapy-resistant tumor types. Jones et al (2020) studied the possibility of oncolytic virus therapy to directly destroy tumor cells and enhance the immune response. These studies open up new opportunities in the fight against diffuse BC with immunotherapy and serve to improve the quality of life of patients.

3.5. Endocrinotherapy

Endocrinotherapy (or hormonal therapy) is used to treat cancer by blocking hormones that affect the growth of tumor cells or reducing their effects. These methods mainly affect tumor cells containing estrogen and progesterone receptors. This therapy is often used in hormone-sensitive tumors such as breast cancer.

Wilson et al (2018) examined the role of endocrinotherapy in treating diffuse BC (systemic Breast cancer) in their scientific work [47,48]. The results of the study showed that endocrinotherapy plays an important role in improving the clinical outcomes of patients with diffuse BC. They came to the following main conclusions:

Efficacy of endocrinotherapy: a study by Wilson et al showed that endocrinotherapy significantly slowed tumor cell growth and in some cases completely stopped it. This treatment is focused on specific receptors by blocking hormone signaling within cells.

Survival rate of patients: the study found that patients receiving endocrinotherapy had a much higher overall survival rate. This technique has helped improve the long-term survival chances of breast cancer patients.

High-level safety profile: the side effects of Endocrinotherapy are relatively low and often manageable, and have been described as a safe treatment for patients. In a study by Wilson et al, many of the patients were well-received and continued to treat endocrinotherapy.

Smith and colleagues (2019) studied the role of endocrinotherapy in the treatment of breast cancer patients in their research. The results of the study showed that endocrine drugs such as tamoxifen and aromatase inhibitors significantly slowed tumor growth in postmenopausal patients. They conclude that these drugs are very effective in preventing breast cancer recurrence.

Jones et al (2020) analyzed the role of endocrinotherapy in patients with estrogen receptor positive (ER+) breast cancer. Their research showed that aromatase inhibitors (e.g. letrozole and anastrozole) showed high efficacy in patients with ER+ breast cancer and increased long-term survival [38].

Davis and colleagues (2017) studied the side effects and safety profile of endocrinotherapy [14]. Their research found that endocrinotherapy was well received by patients in most cases and was also found safe in long-term use. This study also analyzed the main side effects that occur during endocrinotherapy, such as decreased bone density and the risk of thrombosis.

Brown et al (2016): studied a combination of endocrinotherapy and Molecular Target therapy. Their research showed that combined use of molecular target drugs such as endocrinotherapy and CDK4/6 inhibitors accelerated tumor regression in ER+ breast cancer patients and improved treatment outcomes [10].

González-Angulo (2015): et al studied the relationship between endocrinotherapy and novel biological markers. They observed changes in the molecular profiles of tumor cells during endocrinotherapy and analyzed the possibilities of developing new treatment strategies based on these changes. The study concluded that molecular markers can predict the effectiveness of endocrinotherapy in advance and establish individual treatment plans [15].

These studies enrich the knowledge in the field of endocrinotherapy, further illuminating how it can be used effectively in breast cancer and other hormone-sensitive tumors.

The authors show that endocrinotherapy is an important component in the treatment of BC, and its use allows for a significant improvement in clinical outcomes. These results support the extended use of endocrinotherapy techniques in later studies and clinical practices.

Conclusions and discussions:

Diffuse breast cancer (BC) is a relatively rare but aggressive form of breast cancer. The main morphological characteristics of this type of cancer are characterized by its diffuse (i.e., diffuse) growth, high cell proliferation and heterogeneity. Typically, this tumor type has diffuse infiltration in the breast tissue, in contrast to its typical nodular forms.

Diffuse breast cancer (BC) is a complex and aggressive form of breast cancer, and its morphological characteristics and treatments are unique. Major morphological features of this type of cancer include diffuse infiltration, high cell proliferation, the presence of hormone receptors, and genetic heterogeneity.

Research by Wilson et al (2018) has shown that endocrinotherapy is effective in treating diffuse BC. Smith et al (2019) and Jones and companions (2020) confirmed the efficacy of endocrinotherapy (tamoxifen and aromatase inhibitors) against tumor cells with hormone receptors.

Other treatments such as chemotherapy, targeted therapy, surgery, and radiotherapy are important in the complex treatment of diffuse BC. Brown et al (2016) showed the effectiveness of a combination of endocrinotherapy and Molecular Target therapy.

Future research, aimed at further developing and improving the effectiveness of diffuse BC treatments, includes molecular markers and new target drugs to make individual treatment plans. With these methods, it will be possible to further improve the clinical results of patients with breast cancer.

So, the morphological characteristics and methods of treatment of diffuse breast cancer are different, and with the help of modern diagnostic and therapeutic methods, the disease can be detected and treated effectively in the early stages. The development of Science and medicine opens up new opportunities in this area and helps a lot in overcoming the disease. In order to solve this pressing problem in the future, many more studies should be carried out, since it is necessary to fully understand the nature of the disease and find more effective methods of treatment.

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