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Modern View on the Problem of Triple Negative Breast Cancer

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Relevance. Environmental pollution, repeated artificial termination of pregnancy, and improper use of medications create conditions for the development of breast cancer (BC). According to the World Health Organization, "... throughout the world, breast cancer ranks first among malignant neoplasms in women and is characterized by high mortality. According to statistics, about 1.67 million new cases are diagnosed annually in the world, more than 571 thousand women die from breast cancer..." [1]According to the literature, "...triple-negative breast cancer (TNBC) accounts for about 8-20% of all breast tumors, more often found in women before menopause, with early menarche, with the first pregnancy at an earlier age, with a short period of breastfeeding and increased body mass index ..." [2]. Frequent recurrence of the disease as a result of inadequate diagnosis and treatment, as well as the search for methods of its prevention are one of the pressing problems facing physicians.

Keywords: triple negative breast cancer, epidemiology, risk factors, molecular-genetic classification.

Epidemiology and risk factors for breast cancer

Currently, breast cancer is one of the five most common cancers in the world and the leading cause of death in women under 50 years of age. The detection of breast cancer during preventive examinations throughout the country remains low, and the indicator of stage IIIB - IV neglect, which is the leading criterion for the quality of diagnosis, on the contrary, is high. The real way to improve the results of treatment of breast tumors is early, and in some cases, preclinical diagnosis. In 25% of cases, breast cancer is diagnosed during reproductive age [1,5,6]. Every year, more than 1 million new cases of breast cancer are registered in the world; the highest incidence is observed in the USA, Canada, France, Israel, Switzerland, Spain, Finland, the Baltic countries, Australia and the Hawaiian Islands. Low incidence rates are observed in countries of Asia, Africa, South America - Japan, China, Mexico and Venezuela. According to the American National Comprehensive Cancer Registry (NCCN), one in 28 -women in the United States dies from breast cancer, and one in eight is at risk of developing the disease. In 2011 More than 230,000 women in the United States have been diagnosed with breast cancer. In the United States, in 2016 , there were 232,332 new cases and 39,620 [2,4].

According to data from the National Cancer Registry of Ukraine in 2016. 16,504 new cases of breast cancer were registered; in different regions of the country, the incidence varies from 30 to 61 cases per 100,000 women [9,14]. Every year in Ukraine, about 16,000 new cases of breast cancer are registered, and about 8,000 patients die from this disease [11].

In the structure of cancer incidence, breast cancer ranks first among the female population of Russia and the CIS countries. In Russia, at least 54,000 new cases of breast cancer are diagnosed annually [7; from 15-24, 10; c 71-74]. The highest rates were recorded in Moscow - 52.3 and St. Petersburg - 48.1 per 100 thousand women [1.12]. Its share ranges from 18-22% in Russia, Belarus, Kazakhstan and Kyrgyzstan to 25-33% in Uzbekistan, Azerbaijan and Armenia [5]. In 2010, standardized incidence rates fluctuated: 40-47.3 0/000 in Ukraine, Belarus, Russia, Armenia ; 24.6-36.4 0/000 in Azerbaijan, Turkmenistan, Kazakhstan ; 16.6-19.4 0/000 in Tajikistan, Uzbekistan .

In Uzbekistan, for several decades, breast cancer has consistently ranked first among cancer diseases in women and is one of the four most common cancer pathologies registered among the country's population [12].

[1]According to WHO annual accounting materials 2017.
[2]Zhukova L.G. Modern possibilities of metastatic breast cancer with a triple negative phenomenon // Proceedings of the Great RUSSCO Conference "Breast Cancer" - Moscow, 2014.-pp.235-241.

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The prevalence of malignant breast tumors is to some extent related to the demographic characteristics of the population. Breast cancer is the most common cancer among women in Uzbekistan [1,2]. The highest standardized incidence rates were registered in the city of Tashkent (25.5 0/0000), Bukhara (13.9 0/0000), Navoi (11.6 0/0000) and Tashkent regions (11.4 0/0000) and the lowest in Surkhandarya (6.3 0/ 0000) and Syrdarya (5.7 0/ 0000) regions [1, 9].

According to various authors, TN breast cancer occurs in 27-39% of breast cancer cases. The development of breast cancer is influenced by numerous factors: the state of the reproductive system, genetic, constitutional, nutritional, socio-economic, pathological processes associated with dysfunction of the hypothalamic-pituitary-ovarian system, concomitant diseases. The latter may include diseases of the thyroid gland with hypothyroidism, early obesity with the onset of menstruation before 12 years of age, and benign hyperplastic processes of the mammary glands [2,8].

The likelihood of developing TN BC is higher in women with early onset of menarche , young age (<50 years), African-American and Hispanic ethnic group, first pregnancy at a younger age, use of oral contraceptives before the age of 40 years, short period of breastfeeding [13].

At the same time, it has long been known that an increase in the number of full-term pregnancies contributes to the development of all subtypes of breast cancer, but not TN breast cancer, apparently being an exception to this rule. In addition, some studies have shown that pregnancy increases the chance of developing this subtype of breast tumors [6].

Results from studies examining this subgroup of diseases indicate a low chance of recovery for patients, as well as a tendency for patients with TNBC to have a negative outcome of the disease to a greater extent than those with other tumor subtypes, with worse OS rates and an increased risk of disease recurrence [8].

Among distant metastases, metastases are most likely to the brain and lungs, and less likely to the bones and liver. Observations of patients in this subgroup revealed that relapse of the disease usually develops within the first 3 years after completion of treatment [7,14].

Characteristics of triple negative breast cancer

Every year, more than 1 million new cases of breast cancer are diagnosed worldwide, of which approximately 170,000 patients are diagnosed with a triple negative phenotype [9, 14]. Most often, this type of tumor is observed in young patients (under 40 years of age) [2, 14] with preserved menstrual function [11].

Many studies have revealed a high incidence of this subtype of breast cancer in representatives of the African-American ethnic group [10]. Thus, information presented in 2006 by Carey L. _ A. _ et al . on San Antonio _ Breast Cancer Symposium , demonstrated a more than twofold prevalence of the incidence of breast cancer in this group of patients compared to the general population (47% and 22%) [5].

Clinically, tumors with a triple negative receptor phenotype are characterized by large sizes (more than 2 cm) [34, 77] and often involvement of regional (axillary) lymph nodes in the process [2].

Morphologically, the majority of cases of TNR (up to 90%) are represented by nonspecific invasive ductal carcinoma [108], rarer forms include medullary, metaplastic , secretory, adenoid cystic , invasive lobular and apocrine cancer [15]. This type of breast cancer often has a high grade of malignancy, cellular pleomorphism , a high mitotic index and contains necrosis in the center of the tumor [8,9].

TNR is characterized by a rather aggressive clinical course and an unfavorable prognosis, which is manifested by a high risk of distant metastasis [2,7] and low rates of overall and disease-free survival . survival compared to other breast cancer subtypes [6]. According to Lin et al ., in patients with triple negative receptor status , metastasis to the visceral organs (lungs and brain) is more often observed in comparison with patients with the ER +/ Her -2/ neu - phenotype, and bones are much less often involved in the process [6,9]. A number of studies have shown that a greater risk of relapse in TNR is observed in the first three years after surgery [15], while in patients with tumors with an ER-positive phenotype, local recurrence of the disease is most often observed between 5 and 10 years after surgical treatment [11,12].

Molecular genetic classification of breast cancer

At the beginning of the last century, it was enough to know that the patient had a malignant breast tumor, then they were prescribed a single treatment. Over time, observations have shown that patients with the same type of cancer demonstrate different prognosis, and the identification by pathologists of an increasing number of

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different morphological variants of the tumor over the past 50 years has led to discussion of the classification of breast cancer [7].

Currently, there are 20 major types and 18 minor subtypes of breast cancer, which were defined and included in the recently published WHO classification (2012) [5]. But despite this, there are doubts as to whether these variants are biologically significant or not? In addition, the definition of such a number of subtypes is the result of the pathologist's own vision . On the other hand, pathologists state that breast cancer is a heterogeneous disease with different histological and biological properties due to genetic, epigenetic and transcriptomic changes, with different clinical findings and treatment responses, and with several subtypes. This phenotypic difference influences the diagnosis, treatment, and therefore prognosis of breast cancer. The basis of all this chaos, apparently, is the lack of specific markers and an incomplete understanding of the development of breast epithelial cells [3,5]. With the development of molecular techniques such as gene expression profiling, “heterogeneity in the concept of breast cancer” has become generally accepted. Thus, a new classification of breast cancer began to develop, pathologists were introduced to the so-called new era of “molecular classification”, which was developed on the basis of the traditional old-fashioned “morphological” classification. With the introduction of this classification, targeted therapy and, more importantly, individualized treatment programs have become possible.

Invasive breast cancer is currently classified as nonspecific ductal carcinoma and a specific subtype. The subtypes of breast cancer have certain differences, while the nonspecific type includes all types of carcinomas except certain subtypes. Nonspecific invasive ductal carcinomas account for about 60–75% of all breast cancer cases. Specific types account for 20-25% of all, of which the most common are lobular, tubular, papillary and mucinous tumors [5,12].

Heterogeneity within the same tumor (intratumoral) or between morphologically similar tumors of the same type (intertumoral) is now well known and accepted.

Histological classification is related to the histological type of the tumor, as well as the presence of molecular changes, in particular, such as ER and EP including Her -2 amplification [13].

In the traditional approach, a number of powerful parameters, such as tumor size and the nature of its spread (in particular, the state of lymph node involvement), determine the stage of the disease, and these are important prognostic factors. The principles of the staging system , which can be applied to all cancer types and tumor, node, metastasis (TNM) parameters, were defined by Pierre Denoit and became widely accepted shortly thereafter [6].

Advances in the diagnosis and treatment of breast cancer, improved technology and increased knowledge of detailed assessment of tumor biology, the accumulation of new data showing that most prognostic factors are related to tumor biology, and, most importantly, the observation of very different survival rates in tumors with the same TNM group and the same histological type led to the search for alternative solutions.

Histopathological evaluation is very useful in the clinical management of breast cancer patients. However, significant differences were found among patients with the same histological subtype (eg, tubular carcinoma) and the same histological grade - same stage (eg, node-negative disease) in response to treatment and long-term survival, as well as the benefits of tamoxifen treatment in ER -positive patients and treatment with trastuzumab in patients with HER-2 amplification all support the belief that breast cancer is a heterogeneous group of diseases, indicating the importance of tumor biology in its treatment [7,11].

With the beginning of a new era in the study of breast cancer based on the use of high technologies, it became possible to determine prognostic factors. The development and study of genomic profiling and expression contributed to the development of breast cancer classification systems that incorporated tumor biology rather than morphology [13].

Studies have confirmed the idea that breast cancer is a molecularly heterogeneous disease with a different clinical picture, the presence of gene expressions that determine behavior about the tumor and the prognosis of the disease [14,17].

The first historical information about the “molecular classification” of breast cancer was provided by Peru and Sorley , which proposed a classification in 2000. showed the differences present in gene expression. Thus, breast cancer was divided into subgroups due to differences in expression.

- “ luminal ” – differentiates into 2 or 3 subgroups, reflects ER , ER regulatory genes and the expression of genes that are expressed in normal luminal epithelial cells;

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- " Her 2 positive" reflects amplification and overexpression ErB 2/ Her 2;
- "basal" (reflecting ER , PR and Her 2-negative expression of genes expressed in normal basal and/or myoepithelial cells of the breast);

These molecular subtypes were formed by differentiating numerous genes and dividing them into clusters to separate them into groups in terms of transcription [12]. Thus, there are three main subtypes that can be identified using only genes associated with ER and Her 2 phenotypes, rather than using hundreds of intrinsic genes [8,16]. These subtypes are ER- / Her 2- (basal-like), Her 2+ and ER +/ Her 2-, luminal A and B.

Currently, debates about the methods of molecular subtyping of breast cancer continue, but dividing them into luminal A and B, Her 2, basal and norm-like molecular subgroups turned out to be the most convenient and usable , since they represent different prognostic subgroups of tumors. The discovery of differences in response to therapy according to molecular subtypes has only increased the importance of this classification [17,19].

Thus, based on data from Her 2+ patients who were resistant to treatment with monoclonal antibodies (Herceptin) targeting the extracellular domain or who relapsed after treatment, possible causative mechanisms were explored. Part of Her 2+ patients with breast cancer who have a poor prognosis express the heterogeneous group of carboxy-terminal fragments of Her 2 [12,16].

Similar to histological evaluation, molecular tests are performed that show the average level of gene expression, and also that breast cancer is a heterogeneous disease [15,18].

Conclusions Patients with TN breast cancer have a more aggressive course of the disease, characterized by early progression after treatment, a high frequency of visceral metastases and metastases to the brain. In addition, unlike HER-2 positive and luminal subtypes, for the treatment of which targeted therapy can be used, the only treatment for TN breast cancer to date remains only chemotherapy. These features of the tumor and clinical course, as well as the limited therapeutic arsenal, determine the unfavorable prognosis of the disease, and, accordingly, the low survival rate of patients, even when treated in patients with early stages of the disease, especially in common processes. This requires the search for new approaches to treatment, as well as diagnosis, which was the main motive for conducting this scientific research.

List Of Used Literature:

1. Amos KD, Adamo B, Anders CK. Triple-negative breast cancer: an update on neoadjuvant clinical trials. Int J Breast Cancer. 2012;385978.
2. Hu R. et al. Androgen receptor expression and breast cancer survival in postmenopausal women // Clin. Cancer. Res. – 2011 Apr. – Vol. 17, N7. – P. 1867–1874.
3. McGhan L.J. et al. Androgen receptor-positive triple negative breast cancer: a unique breast cancer subtype // Ann.Surg. Oncol. – 2014 Feb. – Vol. 21, N2. – P. 361–367.
4. Banerji S., Cibulskis K., Rangel-Escareno C., Brown K. K., Carter S. L., Frederick A. M. et al. Sequence analysis of mutations and translocations across breast cancer subtypes. Nature 2012; 486: P. 405–9.
5. Barbie T. U., Alexe G., Aref A. R., Li S., Zhu Z., Zhang X. et al. Targeting an IKBKE cytokine network impairs triple-negative breast cancer growth. J Clin Invest 2014; 124: P. 5411–23.
6. Baselga J., Gomez P., Greil R., Braga S., Climent M. A., Wardley A. M. et al. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. J Clin Oncol 2013; 31:2586–92.
7. Bauer KR, Brown M, Cress RD, et al. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a populationbased study from the California Cancer Registry. Cancer. 2007; 109: P. 1721-1728.
8. Bethesda, MD, National Cancer Institute. Robertson, L., Hanson, H., Seal, S., Warren-Perry, M., Hughes, D., Howell, I…& TNT Trial TMG; BCSC (UK). (2012). BRCA1 testing should be offered to individuals with triple-negative breast cancer diagnosed below 50 years. British Journal of Cancer, 106(6), 1234-1238.

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Date of Publication:06-11-2023

9. Bidard FC, Conforti R, Boulet T, Michiels S, Delaloge S, Andre F. Does triple-negative phenotype accurately identify basal-like tumour? An immunohistochemical analysis based on 'triple-negative' breast cancers. Ann Oncol. 2012;18(7): 1285–6.
10. Atakhanova N.E, Almuradova D.M, Gaziev L.T, Sadullaeva N.I, Erkinova Ch.O. Androgen receptor values for prediction of survival of patients with three times negative breast cancer. World Bulletin of Public Health, 22, 140-142, 2023.
11. Almuradova D.M, Odilova Sh.Sh, Ubaydullaev I.A, Sharobiddinov B.B. Islamov S.B. A Modern Approach to Diagnosis and Treatment of Breast Cancer Releases. Central Asian Journal of Medical and Natural Science, 2(5), 294-298, 2021.
12. Khakimova G.G, Khakimov G.A, Khakimova Sh.G, Khakimov A.T, Almuradova D.M. Changes In Tumor Infiltrating Lymphocytes Of Peripheral Blood And Tissue During Chemotherapy In Patients With Gastric Cancer. The American Journal of Medical Sciences and Pharmaceutical Research. T 3 (03), 20-31, 2020.
13. MD Juraev, NE Atakhanova, DM Almuradova, LT Gaziev. Androgen receptor values for prediction of survival of patients with three times negative breast cancer. EPRA International Journal of Research and Development (IJRD) 8 (6), 104-106, 2023
14. M.N Tilyashaikhov, L.T Gaziev, A. Almuradov, D.M Almuradova. A Modern Approach to Diagnostics, Prediction and Course of Renal Cell Cancer. Annals of the Romanian Society for Cell Biology, 4429–4451, 2021.
15. Атаханова Н.Э, Алмурадова Д.М. Влияние экспрессии андрогеновых рецепторов на прогноз трижды негативного рака молочной железы. Клиническая и экспериментальная онкология. Т 10 (2), 112-115, 2022.
16. Atakhanova N.E, Almuradova D.M, Gaziev L.T, Ziyayev Sh.V. Results of Drug Treatment of patients with metastasis of triple times negative breast cancer. EPRA International Journal of Research and Development (IJRD) 9 (6), 125-128, 2023.
17. Atakhanova N.E, Almuradova D.M, Ziyayev Sh.V, Хамидов Х, Юсупов А. Значения андрогенных рецепторов для прогнозирования выживаемости больных трижды негативным раком молочной железы. International Bulletin of Medical Sciences and Clinical Research. 3 (6), 5-8 , 2023.
18. D.M Almuradova, D.I Mukumova, X.Kh Turaeva, Karlibaev A.O. Modern endocrine therapy in locally advanced estrogen or progesterone receptor-positive breast cancer. Образования и наука в XXI веке. 24 (2), 773-780, 2022.
19. Н.Э Атаханова, Д.М Алмурадова, И.А. Дудина. Молекулярно-биологические характеристики трижды негативного рака молочной железы. Российский биотерапевтический журнал. 17 (1), 23-27, 2018