

**BREAST CANCER: MODERN ASPECTS OF DIAGNOSIS.
(LITERATURE REVIEW)**

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Summary

Breast cancer is a serious medical and social problem for most of the developed countries of the world. Analysis of the qualitative characteristics of diagnosis, staging and treatment of breast cancer will routinely confirm the achievability of reducing the risk of cancer recurrence with an appropriate standard of treatment.

Key words: breast cancer, diagnostics, qualitative indicators of cancer, HER2 status.

Relevance. Breast cancer takes the leading place among malignant neoplasms in women in all economically developed countries. So, in the EU countries, the risk of disease is 6-10 times higher than in the countries of Asia. In the United States, one in 28 women dies from breast cancer, and one in eight is at risk of the disease. In the CIS countries, more than 50 thousand new cases of breast cancer are registered annually, and mortality from this pathology ranks first.

According to EUSOMA, over the past twenty years in the United States and in some developed European countries, breast cancer mortality has been decreasing annually by 1-2%, thanks to early screening and continuous improvement of diagnosis and treatment [9]. In Uzbekistan, there is an increase in the number of patients with primary breast cancer per 100,000 women, which in the whole Republic of Uzbekistan was 6.6. In the regions of Uzbekistan, the greatest increase in the incidence was noted in the Republic of Karakalpakstan - 1.7 times, and in the city of Tashkent - 1.5 times. In 2018, 3,578 women with breast cancer were registered in Uzbekistan. Today, about 18,000 women have been diagnosed with breast cancer. The five-year survival rate is currently 45%, and the one-year mortality rate is 1.1% [5]. Breast cancer deaths also increased from 1985 to 2004, and the increase is greater in Bukhara and Surkhandarya. area - 3.9; 3.8 times, respectively. [9] Another important factor is the rejuvenation of the disease in our republic. According to European scientists, about 90% of newly diagnosed cancers are epithelial forms of cancer, among them, one of the most common is breast cancer (BC). In Western Europe, approximately 25% of breast cancer is diagnosed in women under the age of 50. Breast cancer in men is less common and accounts for only 1% [5,8]. Mammographic screening performed every two years in the age group from 50 to 69 years, reduces the death rate from cancer by 15%, but also increases the likelihood of overdiagnosis by 30% [4,8].

BREAST CANCER DIAGNOSIS

EUSOMA, with the participation of 24 leading experts in Europe, has published a Memorandum on Quality Indicators of Service Delivery to Breast Cancer Patients. EUSOMA experts identified 17 main characteristics for assessing the quality of care for breast cancer patients: 7 for diagnosis, 4 for local surgical treatment, 2 for systemic treatment and 4 for cancer staging. Below is an abbreviated version of the summarized qualitative indicators of breast cancer diagnostics developed by EUSOMA experts, which are recommended to all breast departments in Europe to control the quality of services provided. Monitoring of qualitative indicators will allow justifying the medical and economic costs of each service in relation to the clinical outcome. Indicators of mandatory breast cancer research methods:

- 1 Proportion of patients who underwent complete clinical and radiological diagnosis (preoperative mammography, ultrasound and clinical examination).
- 2 Proportion of patients who received specific diagnostic procedures (benign / malignant lesion ratio).
- 3 Proportion of patients with invasive or in situ breast cancer who were diagnosed prior to surgery.

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4 Proportion of patients with invasive cancer and prognostic / predictor parameters (PPP) - histological type, histological degree of maturity, estrogen receptors (ER), progesterone receptors (PR), HER2 status; Proportion of patients with invasive cancer and complete TPN - histological type, histological maturity, ER, CR, HER2 status, pathological stage (T and N), size in mm (for invasive component), peritumoral vascular invasion and distance to nearest radial edge; Proportion of patients with invasive cancer and TPN - dominant histological pattern, size in mm (best pathologic and radiologic assessment if stage 2), histologic maturity and distance to nearest radial margin.

5 Proportion of patients whose waiting time (between the date of the first diagnostic examination at the mammology department and the date of surgery or the date of initiation of treatment) is within 6 weeks.

6 Proportion of patients who underwent MRI (at least 5% of cancers examined before surgery).

7 Proportion of patients who received genetic counseling (proportion of cancers discussed).

The efforts of EUSOMA experts are aimed at achieving the final result by routine routine measurements and assessment of available indicators, which will ensure the quality of medical services provided by appropriate standards of diagnosis and treatment [9]. Annual mammography screening and magnetic resonance imaging (MRI) of the breast are recommended for women with a "very high risk" of developing breast cancer: positive BRCA-1 or BRCA-2 mutations, as well as other gene predispositions that increase the risk of developing breast cancer; untested carriage of a gene mutation, in carriers of the first degree of relationship; syndrome of hereditary breast cancer, when the cumulative personal lifetime risk is more than 25%. Mammography and MRI screening, with a lesser degree of evidence, is recommended for women at high marker risk, based on biopsy results (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ) and after chest radiotherapy (under 30 years of age or at least for the previous 8 years) [8]. ESMO experts recommend that breast MRI and mammography be performed annually in order to diagnose cancer at a more favorable, preclinical stage for women with a family history of breast cancer, regardless of the evidence of BRCA mutation carriage. In the case of test confirmation of BRCA carriage, patients are recommended prophylactic procedures [7,8]. The pathological diagnosis of breast cancer is based on a primary puncture biopsy obtained under ultrasound or stereotaxic guidance. The pathological conclusion should include: determination of the histological type; histological degree of maturity; immunohistochemical (IHC) assessment of estrogen receptor (ER) status using standard Allred or H-core methods; assessment of cancer aggressiveness by IHC assessment of progesterone receptors (PR) and HER2 expression. Routine cancer identification is aimed at determining the local-local spread of cancer, so there is no need for all patients to undergo comprehensive laboratory and radiological staging of cancer, since distant metastases are very rarely asymptomatic [7,9,10].

Additional tests, such as computed tomography (CT) of the chest, abdominal ultrasound or CT, and bone x-rays, are needed in patients with: clinically positive axillary nodes; with a large tumor formation (> 5 cm); with clinical symptoms or laboratory findings suggesting the presence of metastases [4,9]. Functional and anatomical characterization, such as positron emission tomography (PET) / CG, is required when conventional methods do not provide a definitive diagnosis. The use of PET / CT for staging local / regional spread of cancer is not advisable due to limited specificity compared to the "gold standard" axillary staging of breast cancer: sentinel lymph node biopsy (SLNB), which is mandatory if the involvement of axillary nodes is not proven [5,8,13]. Routine methods for determining the amplification status of the HER2 gene are fluorescent, chromogenic and silver in situ hybridization of the histological material of the primary tumor [4-12]. The choice of a reliable method for determining the status of the HER2 gene is very important in order to prevent overdiagnosis and over-treatment with anti-HER targeted agents. In the case of ambiguous HER (2+) IHC results, the analysis is recommended by one of the methods of in situ hybridization [7,8,9,15]. In the case of negative results of ER / PR and HER2 in the material of a puncture trephine biopsy, it is necessary to re-check the ER / PR and HER2 on the surgical material after tumor resection [19]. A complete postoperative pathologic evaluation of the surgical specimen should be performed according to the pTNM system. The final pathological diagnosis should be made according to the Classification of the World Health Organization with the analysis of the entire volume of the

resected tumor [14]. ER / ER status and HER2 are the most reliable and effective predictive markers of response to hormonal and anti-HER2 therapy. In addition, high ER expression may predict less benefit from chemotherapy [5,7,11]. A proliferation marker such as the Ki67 index can provide additional useful information about the aggressiveness of the process [7,8,13,21]. Following neoadjuvant systemic treatment, cancer response to treatment and the amount of residual disease are important predictors, but more convincing standardized biological markers are still needed. There are currently no universal guidelines for assessing the response to neoadjuvant treatment. Although there are many published results of scientific studies devoted to the study of the molecular panel of predictors of response to breast cancer treatment [5,6,7,8]. The original National Policy on Circulating Cancer Cells (Health Net, Inc. 2012) recommended the standard determination of circulating cancer cells by the US CellSearch (Veridex) system for the prognosis and monitoring of treatment, including metastatic breast cancer [6]. The latest statement from the National Policy on Circulating Cancer Cells (Health Net, Inc. 2014) recommends further research to investigate circulating cancer cells in all their possible meanings and available research options. Although noted, the great importance of circulating cancer cells in predicting the development of the disease and survival in some forms of metastatic cancer [23-31]. The authors of the publication warn that there are no proven definitive results in the literature, indicating the possibility of changing therapy and improving the results of treatment based on circulating cancer cells.

It is noted that the sensitivity of circulating cancer cells is relatively lower than that of some imaging techniques. In addition, the authors of the document argue that there are no data confirming the greater efficacy and clinical benefit of circulating cancer cells over other oncological biomarkers and, possibly, the results of the expected numerous ongoing clinical trials will determine the clinical role and importance of circulating cancer cells in cancer treatment [6,21]

The importance of micrometastatic dissemination and isolated circulating cancer cells for optimal cancer management is a matter of ongoing research [5,6,21].

Determination of the prognostic index - Nottingham Prognostic Index (NPI), which depends on clinical parameters (tumor size, involvement of lymph nodes and the degree of histological maturity of the cancer), will predict the likelihood of recurrence and mortality from breast cancer [20-23]. Interpretation is presented in table 2. The index can be calculated using the program: NPI calculator-Primed.info or by the formula: $NPI = [0.2 \times S] + N + G$, where

S is the size of the indexed formation in cm;

N is the number of involved lymph nodes:

0 = 1, 1-3 = 2, > 3 = 3

G - the degree of histological maturity of the tumor: GradeI = 1, GradeII = 2, GradeIII = 3

Table # 1. Nottingham Prognostic Index (NPI)

NPI scale	5-year survivalrate	NPI forecast
>/=2,0 до</=2,4	93%	Verygoodforecast
>2,4 до</=3,4	85%	Goodforecast
>3,4 до</=5,4	70%	Verygoodforecast
>5,4	50%	Badprognosis

The most important prognostic factors for early breast cancer remain the expression of ER / PR, the HER2 gene and proliferation marker, the number of regional lymph nodes involved, the histological variant of the tumor, the size, degree of histological maturity, and the presence of peritumoral vascular invasion [5,7,8,9,21].

CONCLUSION

The introduction of appropriate standards for the diagnosis and treatment of breast cancer and the analysis of quality indicators of service delivery to patients with breast cancer will reduce the risk of cancer recurrence. When analyzing the factors for the prognosis of breast cancer, it is necessary to take into account such indicators of the tumor as the morphological structure of the tumor, the degree of malignancy, the degree of differentiation

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of the tumor cell and, of course, its receptor status together with immunohistochemical markers of progression. The data obtained allow us, oncologists, to identify heterogeneous biological subtypes of breast tumors, which is the main one in modern oncology in choosing a treatment strategy.

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