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Diagnostic Significance of Molecular Genetic Markers in the Prognosis of the Breast Cancer Clinical Course

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Abstract

From year to year the awareness of the female population about the need for self-examination and clinical examination is increasing, diagnostic equipment is being improved and optimal diagnostic and treatment algorithms are being developed. The result of the work, ultimately, is a progressive improvement treatment results. Standard prognostic factors that predict the course of breast cancer include the following parameters: patient's age, tumor size, change in lymph and peripheral lymph nodes, histological type of tumor, degree of malignancy, estrogen and progesterone receptors.

Keywords: Estrogen, Progesterone, Breastcancer, Tumor, Lymphnode, Receptor.

Introduction. Breast cancer (BC) is still one of the main urgent problems of fundamental and clinical oncology, the intensive indicators of which remain the highest among malignant neoplasms in women.

According to a number of authors, in 2000, the average breast cancer incidence in Russia was 19.40%, in Moldova 22.90%, in Belarus 18.30%, in Georgia 36.00%, in Armenia 28.40%, in Kazakhstan 18.30%, in Uzbekistan 19.10% and is characterized by high neglect. (3)The incidence of breast cancer in women in Western countries is 5 times higher than in women living in Asian countries. In the western population, the incidence of breast cancer increases mainly in the postmenopausal age, while in Asian countries it is mainly in women under 50, i.e. at reproductive age.The morphological structure of breast cancer is important for prognosisdiseases. Most often, up to 80% is invasive ductal carcinoma. Special forms of invasive cancer, starting with lobular and lower, generally have a less malignant course than invasive ductal carcinoma, and therefore at one time were singled out into a special group. They make up about 15–20% of all neoplasms. Tumors of mixed histological structure are quite common. In such cases, predominance of some type of cancer is noted.On cell membranes there are special cytoplasmic proteins - receptors, which, when combined with hormones, can affect the rate of division of tumor cells. Determination of the level of

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steroid hormone receptors (estrogens, progesterone, etc.) allows predicting the course of the disease and judging the sensitivity of the tumor to hormonal treatment.

The morbidity of breast cancer (BC) in recent years has been steadily increasing [1,2]. The histological form of the tumor is one of the traditional morphological factors of the prognosis of the clinical course of breast cancer. Various morphological forms of breast cancer differ in the aggressiveness of the clinical course [11]. For example, it is known that the medullary breast cancer is characterized by a more conducive prognosis compared with other forms of breast cancer and an invasive lobular breast cancer metastasizes less often than an invasive ductal one [10]. According to the WHO data the most common histological form of breast cancer is invasive ductal. It occurs in 59% of cases. The second most breast cancer is invasive lobular breast cancer which makes up 25% of cases [3,9,11]. The leading factor in the mechanism of malignant cells transformation, in the biological behavior of already arisen tumors, is the increased proliferative activity of the tumor cells themselves [4-8,12]. Among the huge number of molecular biological studies related to the prediction of breast cancer and the search for factors predicting the sensitivity of the tumor to various methods of treatment, one should include an integral assessment of a huge number of molecular biological characteristics of neoplasms, which is represented by the classification of breast cancer, based on variations in the set of expressed genes and the correlation of genetic characteristics. tumors with long-term results. These characteristics also allow individualizing treatment and thereby improve its results [6,14]. In terms of choosing a treatment option and assessing prognosis, some molecular genetic parameters of the tumor are important, among which, first of all, the hormonal status of the tumor (ER / PR), HER-2 / neu, p53, Bcl-2, Ki-67 Surrogate isolation of the proposed subtypes of breast cancer, based on the immunohistochemical study of ER, RP and HER2neu, has come into practice: the luminal type is characterized as ER + HER2neu-, HER2neu + subtype - any values of ER and RP with overexpression of HER2neu. basal subtype - RE-RP-HER2neu-. Revision of the results of systemic therapy, depending on the tumor subtype, showed the predictive value of the new classification. The existing methods of risk estimate in patients with breast cancer are ineffective and insufficient. The significance of individual markers identified by immunohistochemistry remains controversial. The prognostic role of immunohistochemical methods of diagnosis in assessing the effectiveness of therapy and determining the prognosis of the disease after antitumor treatment requires clarification. Investigation of the ER / PR-status of breast cancer cells is performed by the immunohistochemical method in order to determine the indications for hormone therapy [17]. At the same time, immunohistochemistry helps in the choice of treatment for NPHT. Thus, with the neoadjuvant use of anthracyclines and taxanes in patients with breast cancer with ER (-), complete or partial morphological regression is more often recorded [13]. Interesting and conflicting results of studies on changes in the hormonal status of the tumor under the influence of chemotherapy.

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The aim of the study was to identify the expression of Published online at http://journal.sapub.org/ajmms Copyright ©2019 The Author(s). Published by Scientific & Academic Publishing

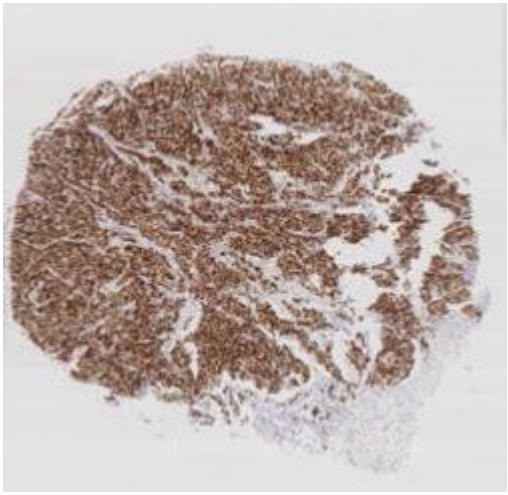
This work is licensed under the Creative Commons Attrihoweverion International License (CC BY). http://creativecommons.org/licenses/by/4.0/ molecular genetic markers and determine their diagnostic importance for prognosis the clinical course of breast cancer.

2. Material and Methods

200 patients with breast cancer of stage I-II admitted to the Department of Mammalogy of the Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology were included in the examined group. All patients underwent a comprehensive examination in the center. A cor-biopsy and histological examination were performed to clarify the nature of the mammary gland neoplasm. An avidin-biotin antibody imaging method was used for immunohistochemistry. Antibodies by "DAKO" company (Denmark) were used. ABC-Kit (universal) was used as a visualization system. DAB by Pharmingen was used to identify the color staining of the reaction result.

3. Results and Discussion

Histological form of the tumor	Numberofcases
Invasiveductalcancer	67%
Invasivelobularcancer	25%
Mucouscancer	3%
Tubularcancer	1%
Medullarycancer	2%
Otherforms	3%

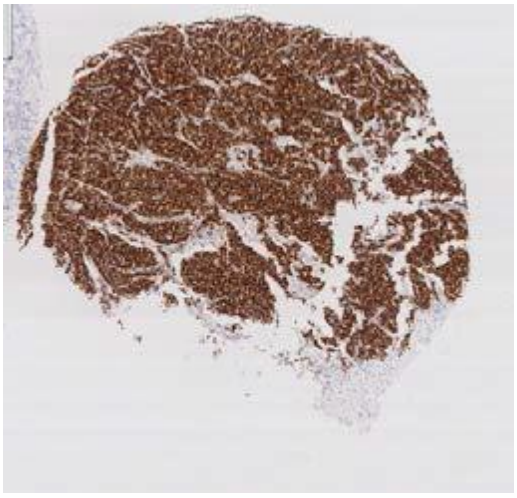


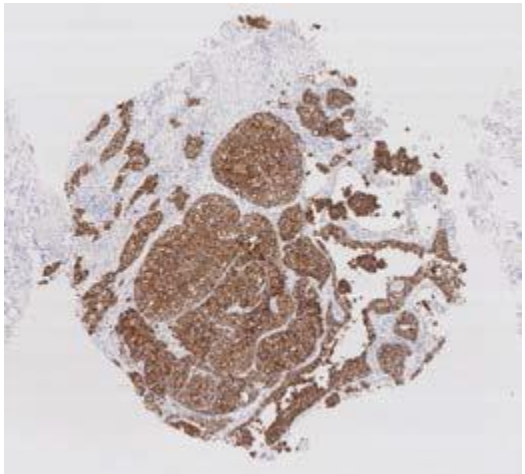
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The predominant histological form of breast cancer in our study was invasive ductal cancer which occurred in 67% of 326: Diagnostic Significance of Molecular Genetic Markers in the Prognosis of the Breast Cancer Clinical Course cases. Invasive lobular cancer was detected in 25% of cases. Mucous cancer was detected in 3%, tubular cancer - in 1%, medullary - in 2% of cases. Other forms made up 3% (Tab. 1).

Breast cancer forms of the third degree of malignancy occurred more often than others among the morphological forms of breast cancer and made up 56%. The 1st and 2nd degrees made up 12% and 32% respectively. Estrogen receptors were found in 53.5% of cases in our research. Depending on the level of ER expression 3 groups of patients with different ER-phenotypes of breast cancer were identified: ER-negative, ER-weakly positive and ER-positive. When comparing groups selected by the level of ER expression it was found that metastatic lesion of lymph node was significantly more often than single lesion in the group of patients with ER-negative tumors (59%) compared with the group of patients with ER-positive tumors (42%). The group of patients with ER- weakly positive tumors did not differ from the other two groups by this indicator. Moreover, multiple metastases in the lymph nodes among metastatic lesions cases were significantly more often in the group of patients with ER-negative tumors (89%) in compare with the groups of patients with ER-weakly positive tumors (63%) and ER-positive tumors (68%). These results, indicate that not only the presence of ER, however also the degree of their expression in a tumor can be an important factor in a more successful prognosis of the breast cancer clinical course than their absence. Progesterone receptors were found in 45% of breast cancer cases. When studying the relationship between the expression of ER and the expression of PR in breast cancer we identified four hormonal phenotypes of the tumor: ER + PR+ (34%), ER + PR - (13%), ER- PR + (9%), ER-PR-(44%). We found that the tumor phenotypes of ER-PR+ and ER-PR- are more malignant. In patients with such phenotypes of breast cancer metastatic lesions in the lymph nodes were significantly more often ($p < 0.05$) (Fig.1)





Hyper-expression of the HER2-neu oncoprotein was observed in 23% of cases. Tumors with the

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HER2-neu (3+) phenotype in our study were found with a frequency of 23% and with the HER2-neu (2+) phenotype - with a frequency of 25%. The results of our study testify that tumors with hyperexpression of the HER2-neu oncoprotein have a large lymphogenous metastatic potential in compare with negative HER2-neu tumors. The obtained results of Ki-67 in the study indicate that the level of this antigen expression is directly proportional to the degree of malignancy ($r = 0.28$, $p = 0.01$), the size of the tumor ($r = 0.42$, $p < 0.05$) and the number of affected lymph nodes ($r = 0.4$, $p < 0.05$). An important result, was the fact that breast cancer with weakly positive expression of PR was significantly different from PR-negative and PR-positive by Ki-67 index. In the group of patients with PR-weakly positive tumors the expression level of the Ki-67 antigen was significantly higher in compare with the groups of PR-negative and PR-positive breast cancer tumors (Fig.2).

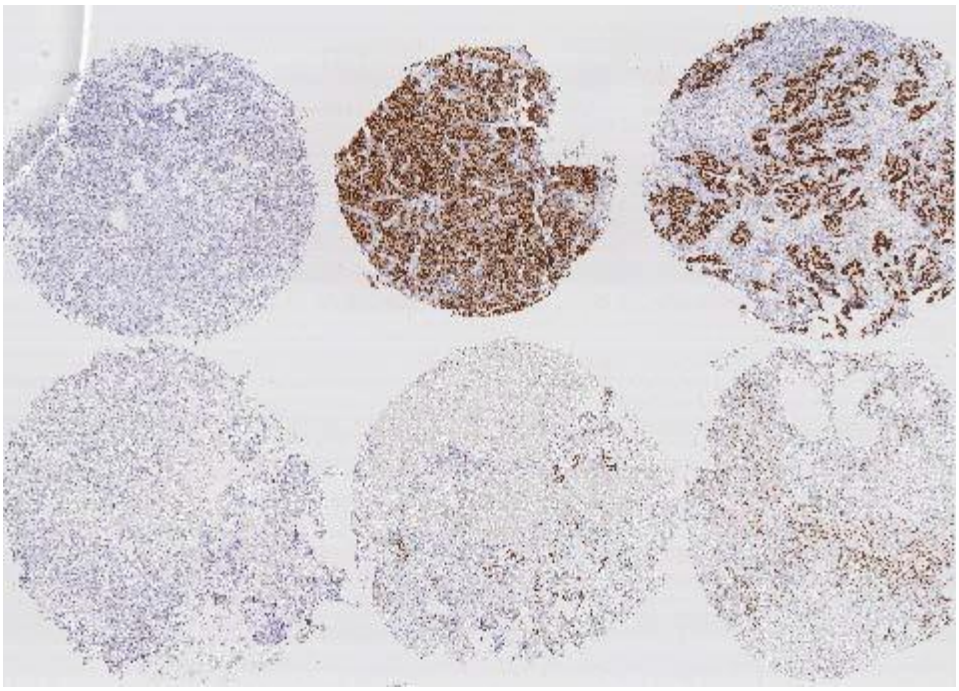


Figure 2. Fragment of the matrix stained with antibodies to estrogen receptors (ER)

4. Conclusions

Thus, tumors with reduced PR expression are characterized not only by high expression of the HER2-neu oncoprotein, however also by an increased level of cells proliferative activity. In this study we showed that the content and expression level not only of ER is an important prognostic factor of the breast cancer clinical course, however also the content and expression level of PR are key points in predicting the breast cancer course and can also serve as a predictive criterion for antitumor therapy. The prognostic importance of the content and expression level of PR (especially its decline) as a marker of an unfavorable prognosis and the breast cancer course is confirmed in the result of an integrated approach to this problem. The results of the study also confirm that the

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hyper-expression of the HER2-neu oncoprotein is an independent factor of a poor prognosis of the disease and is associated with the tumor high metastatic potential.

The lack of data on the biological heterogeneity of breast cancer in patients on the territory of Uzbekistan, the absence of a full-fledged laboratory for immunohistochemical research makes it hard to create effective screening and treatment programs. It is, of course, a huge social and economic problem in our region. The data on molecular genetic studies allow us to single out the heterogeneous biological phenotypes of this disease, which is the main one in modern oncology in choosing a treatment strategy in each specific case. The biological subtypes of the tumor exactly determine the tactics of treatment and the outcome of the disease. The biological heterogeneity of breast cancer remains insufficiently studied in Uzbekistan. The problem of breast cancer treatment is now becoming increasingly important due to the growth in the incidence rate which is proportional to the increase in life expectancy of the population of our country. This fact is aggravated by the late treatment of many patients. The issue of choosing a method of special therapy for this pathology, especially depending on the biological types of the tumor, remains controversial up to now. At the breast cancer there remains an unresolved question of risk stratification in patients depending on the presence and absence of prognostic significant clinical, biological, genetic factors, there is no clear data on the immediate and long-term results of treatment. Taking into account all mentioned above, this article is relevant, and the proposed development has a certain scientific interest, theoretical significance and importance for our further researches.

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