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**The prognostic significance of a degree of ordering tissue structures
at invasive-lobular breast cancer**

ABSTRACT

A retrospective analysis of uneven distribution of tissue structures in breast cancer as a criterion for the prognosis is carried out. The standard statistical indicators which reflect variability of morphological parameters were applied. We found out the individual coefficient of variation of cancer structures in some optimal number of analyzed visual fields of the histology microslide to be the most informative and objective parameter statistically conjugated with the prognosis.

Keywords: prognosis of breast cancer, cancer structures, morphometry.

INTRODUCTION

Breast cancer in their clinical, morphological and molecular genetic features is a heterogeneous disease [11, 14]. Breast cancer has many subtypes which are different by its clinical outcomes. Morphological verification of breast cancer is 95.6%, within the same histological types and the same stage of the prognosis can vary significantly. It was suggested the set of morphological parameters for prognosis and risk of recurrence [3]. The interpretation of these parameters is quite complicated. In pathomorphology the best way to increase of the informational content is the unification of results using quantitative research methods [1, 16]. Of particular the prognostic interest represent the degree of ordering of the structure and components of the tumor tissue. The experience of the morphological study of micropreparations of different histological types of breast cancer and of cancer's structures that make up the tumor tissues, not only in different cases of observations, but also in the different fields of view of micropreparation of the one patient [15]. The number of cancer structures from observation to observation can vary by tens of times. A comparative study of breast tissue of patients with breast cancer before and after radiotherapy led to the conclusion that the damaging effect of radiation on the tumor leads to significant disturbances and changes of parenchymal-stromal relationship not only in the tumor tissues, but also in the surrounding tissues [2]. The absence of any strongly regularities of the heterogeneity of the distribution and the ordering of tissue structures lead to the conclusion that the need to find indicators that would adequately reflect this heterogeneity, and at the same time is sufficiently informative. In quantitative morphometric studies this group of indicators is parameters of the variability of variables and includes the

absolute difference between the extremes (maximum and minimum values), a relative measure of magnitude (relative difference of limits), standard deviation (σ), and finally, the coefficient of the variation (CV) [1]. The purpose of this study was to determine the variability of the distribution of the structural elements of the parenchyma and stroma of infiltrating lobular type of breast cancer and its covariation with prognosis.

MATERIALS AND METHODS

The material for the study included 69 biopsies of tumor tissue of patients with breast cancer at the age of $59,3 \pm 8,8$ years, which were treated in the Ulyanovsk Regional Clinical Oncology Center from 2004 to 2006. All permission on the research was granted by Ethical Committee of Ulyanovsk State University. For morphometric analysis were using methods described previously [8-9, 13]. For the estimate of the total score of malignancy used appropriate criteria [4-5, 10, 12]. The obtained data were processed using the software package Microsoft Excel 2003 and Statistica for Windows 8.0. (StatSoft Inc., USA).

RESULTS AND DISCUSSION

Preliminary univariate ANOVA analysis of variance by the criterion of five-year survival showed no significant differences in the group of patients who died of observations depending on the duration of their lives after moment when was diagnosed the breast cancer. Critical statistically significant differences were obtained only in the separation criterion five-year survival rate in the binary scale: "The patient is alive to the present (default value 0)" - "The patient died after 1-5 years after diagnosis (default value 1)." In accordance with the purpose of the study for identify the prognostic value of quantitative indicators characterizing the degree of ordering (or heterogeneity) structures were identified by their values for the above two groups of patients.

Table 1.

The main morphological features were the heterogeneity and disorder of the location of the cancer complexes in the stroma of tumor's. Their number varied in a wide range, from 38 to 898 structures in one field of view area of 0.152 mm^2 . As can be seen from Table 1, from of all of the analyzed indices of the individual variability greatest level of significance of differences were obtained for the mean value of the square deviations of the number of cancer's structures in the field of view. It was 20.22 ± 2.72 for patients with long-term survival over 5 years and 23.8 ± 2.49 for patients who died within 5 years after diagnosis of breast cancer ($p < 0.004$). The smallest statistically significant difference was observed for the absolute and relative difference of extremes (see Table. 1). Thus, the most informative and objective from a statistical point of

view, the parameter characterizing the degree of ordering and distribution of tissue elements in the tissue of the lobular type of breast cancer is an individual coefficient of variation of cancer structures (CV) in 30 fields of view. The substantial side of criteria, which were proposed by of different authors, depends on the skill and style of presentation of conclusion of a pathologist, often contains a large amount of special morphological information, and is difficult for understanding and summarizing for the clinician in matters of the medical tactics [3]. In recent years were undertaken intensive efforts to create of optimal pathologic assessment scales to improve diagnosis of breast cancer [6-7]. However, the methodological approaches implemented in them, based on standard statistical mean values of the variables or, more often, of the frequency. The interpretation of these data is of great complexity and is not devoid of abstraction for a particular patient. According to our results, the most objective measure of individual forecasting five-year survival for patients with lobular breast cancer option should be regarded the standard deviation of the number of cancer structures analyzed for the same number of fields of view. Other words, for patients with lobular infiltrative type of breast cancer having individual « σ » of the absolute number of cancer structures no more than "23" for 30 fields of view microscope slide, may be forecast 95% chance to five-year survival. In cases with individual variations of σ more than "32" five-year survival prognosis is unfavorable.

CONCLUSION

Summarizing the results of the study, it must be concluded that the a variant of infiltrative type of lobular breast cancer is characterized by of statistically significant differences in the degree of ordering of structures of cancerous tumor's tissue that can be highly reliable parameters for predicting the five-year survival rate of patients.

Table 1
Mean values and confidence intervals of parameters of the individual variability of the number of cancer structures determined in 30 fields of vision for each patient (the observation case)*

The parameter of the variability	Prognostic group	M $\pm$ m	95% confidence interval	Level of the significance of differences
Absolute difference of extremes	Survival over 5 years n=20	74.25 $\pm$ 11.32	50.57-97.93	p<0.021
	Survival less than 5 years n=8	123 $\pm$ 13.45	91.20-154.79	
Relative difference between the extremes	Survival over 5 years n=20	2.47 $\pm$ 0.38	1.69-3.26	p<0.021
	Survival less than 5 years n=8	4.1 $\pm$ 0.45	3.04-5.16	
Standard	Survival over 5	20.22 $\pm$ 2,72	14.53-25.92	p<0.004



deviation (σ)	years $n=20$			$p<0.013$
	Survival less than 5 years $n=8$	35.41 ± 3.17	27.92-42.90	
Coefficient of variation (CV)	Survival over 5 years $n=20$	8.80 ± 1.13	6.43-11.17	
	Survival less than 5 years $n=8$	15.21 ± 2.57	9.13-21.30	

Note: *- the parameter of the statistical variability which was obtained for the characteristic of each patient (for $n=30$ fields of vision) of the corresponding variable, was considered as the independent individual parameter

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