Clinical And Morphological Features In Diffuse Forms Of Breast Cancer: Results Of Digital Morphometry.

Yigitaliyev Alisher Bakhodir ugli[1], Tursunov Khasan Ziyayevich[2], Gafur-Okhunov Mirza-Ali Aliyarovich[3], Akhrayeva Dilnoza Bakhtiyarovna[4].

1. Assistant of the Department of Urology and Oncology of the Fergana Medical Institute of Public Health.
2. Head of the Department of Pathological Anatomy of Tashkent State Medical University, Doctor of Medical Sciences, Professor.
3. Head of the Department of Oncology of the Center for the Development of Professional Qualifications of Medical Workers, Doctor of Medical Sciences, Professor.
4. Assistant of the Department of Oncology of the Center for the Development of Professional Qualifications of Medical Workers, PhD.

Abstract.

In the study, tissue and cellular changes in diffuse forms of breast cancer (ductal, lobular, and inflammatory variants) were assessed using digital morphometry. Biopsy materials were scanned in the NanoZoomer system and analyzed using the QuPath and ImageJ/Image Pro Max programs. The main indicators were the proportion of stroma, excretory ducts, blood vessels, lobes, and the nuclear-cytoplasmic index (NCI).

According to the results, in the ductal variant, the proportion of stroma and excretory ducts increased, the lobules shortened, and the ALS decreased to 0.69. In the lobar variant, parenchyma predominates and angiogenesis increases (LAS - 0.61), and in the inflammatory form, vascular-inflammatory changes predominate.

In conclusion, digital morphometry is an effective method for differentiating diffuse phenotypes, assessing the level of cellular dedifferentiation and angiogenesis. The obtained indicators are recommended as an important prognostic criterion for making a clinical decision and determining the therapeutic orientation in breast cancer.

Keywords: breast cancer, diffuse forms, ductal invasive carcinoma, lobular invasive carcinoma, inflammatory variant, digital morphometry, nuclear-cytoplasmic index (NCI), angiogenesis, stroma, QuPath, ImageJ, NanoZoomer.

Introduction. Breast cancer (Breast cancer) is one of the oncological diseases with high histological and molecular heterogeneity. Modern classifications require precise identification of clinical and pathological phenotypes and the selection of appropriate individual therapy methods. According to the World Health Organization's classification in the 5th edition, among the morphological types of breast cancer, forms with a high probability of diffuse manifestations - ductal invasive carcinoma (IDC), lobular invasive carcinoma (ILC), and inflammatory breast cancer (IBC) - are of particular importance[1].

European clinical guidelines (ESMO) recommend combining morphological analysis with immunohistochemical and molecular profiling data in the diagnosis of breast cancer. Especially in cases with a diffuse phenotype, the assessment of angiogenesis, the degree of invasion, and stromal remodeling is an important criterion for clinical prognosis [2].

Inflammatory breast cancer is clinically characterized by a rapidly developing and aggressive course. In this case, a large part of the chest tissue is covered with inflammatory infiltration, which increases the risk of subjectivity in morphological assessment and requires a quantitative approach [3]. At the same time, E-cadgerin (CDH1) deficiency and a "discohesive" growth pattern are observed in lobar invasive carcinoma, which determines its diffuse distribution in the tissue [4].

It has been scientifically proven that stromal remodeling and angiogenesis indicators are directly related to the potential for invasion and metastasis of breast cancer [5,6]. The presence of a fibrotic focus in

IDC types is associated with a high risk of recurrence, while an increase in microvascular density (MVD) has a negative impact on overall survival [7].

In recent years, the introduction of digital pathology and artificial intelligence-based analysis systems (e.g., QuPath, ImageJ) has made it possible to analyze entire slide images accurately, quickly, and repeatably [8,9]. With the help of these platforms, the possibilities of determining tissue heterogeneity and the immune landscape through spatial quantitative assessment have expanded. However, the standardized analysis of morphometric indicators (stroma, excretory ducts, blood vessels, proportion of lobules, YAS) for diffuse phenotypes has not yet been sufficiently systematized [10].

Therefore, in this study, using the method of digital morphometry, the goal was to determine their clinical and prognostic significance by quantitative assessment of tissue histioarchitectonics and cellular parameters in ductal, lobular, and diffuse inflammatory variants.

Material and methods. For morphometric examination of glandular tissue in diffuse forms of breast cancer, micropreparations were taken from biopsy materials, pre-prepared from histological sections. In each case, at least 10 segments were scanned on a NanoZoomer, the measured areas were compared with each other, and the average values of morphometric indicators were obtained in numbers. Morphometric indicators mainly include the diameter of tumor cells, the nuclear-cytoplasmic index, the area occupied by the intermediate substance, the shape and size of the cells in the scar area, and other indicators. Thus, micropreparation sections made from tissue obtained in cases of diffuse breast cancer were obtained in the QuPath-0.4.0, NanoZoomer Digital Pathology Image program, and digital analyses of the tasks given on the values obtained in artificial intelligence without human intervention were obtained. The obtained values were denoted in μm, μm2, mm. It should be noted that in morphometric studies, the standard program Image pro max was mainly used. This was mainly used to determine the different echogenicity and cellular composition of tissue components in diffuse cancer, and to calculate the proportions of areas.

Results.

In inflammatory breast cancer, the presence of intraepithelial lymphocytes and neutrophils located between the lobules of the gland creates difficulties in determining the area occupied by atypical cells due to the clear depiction of the hypercellular picture of the gland. For morphometric verification, we preferred to check using the Image Pro Max software.

Table 1.

Morphometric indicators of tissue in invasive breast duct tumors are in μm, % and μm^2. 84000 μm^2 are given on the surface.

Area size	Nodular form	Diffuse forms	R ≥ 0.01* R ≥ 0.05**
Stroma %	30.12±1.01*	47.31±1.05**	0.01
Output road area%	13.39±1.01*	33.38±1.06**	0.01
Blood vessel area%	11.2±1.01*	5.66±1.04**	0.01
Piece area%	45.29±1.05*	13.65±1.07**	0.05
nuclear cytoplasmic index	0.83±0.03*	0.69±0.01**	0.05

In the diffuse form of the breast in the invasive type of the breast duct, as a result of the growth of the glandular epithelium mainly towards the stroma and mainly towards the blood vessels, the area occupied by the majority of the visual field at an area of 84000 μm2 was 5.66±1.04% compared to the control group. This also confirms that in epithelial tumors, the main part of the tissue consists of atypical cells, and the boundaries of the vascular wall, located between the interglandular spaces, are disturbed. In the control group, the area occupied by the vessels was 11.2±1.01%, and in this type of tumor, the area occupied by the vessels decreased by 2.0 times compared to the control group. This is explained by the fact that in the invasive variant of the duct of the diffuse form of the mammary gland, the majority of the field of view is occupied by an intermediate throma.

In terms of the area occupied by the stroma, in the control group this indicator averaged 11.2±1.01% on an area of 84000 μm2, while in the studied group this indicator was 47.31±1.05.

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This is clinically and morphologically explained by a sharp increase in connective tissue, consisting of various types of fibrous structures, in the interglandular space of invasive breast cancer with a diffuse form of the tumor.

This confirms our opinion that, as a result of the chronic course of the diffuse inflammatory process before the tumor process, reparative regeneration manifested in the form of substitution, which increased by 1.57 times compared to the control group.

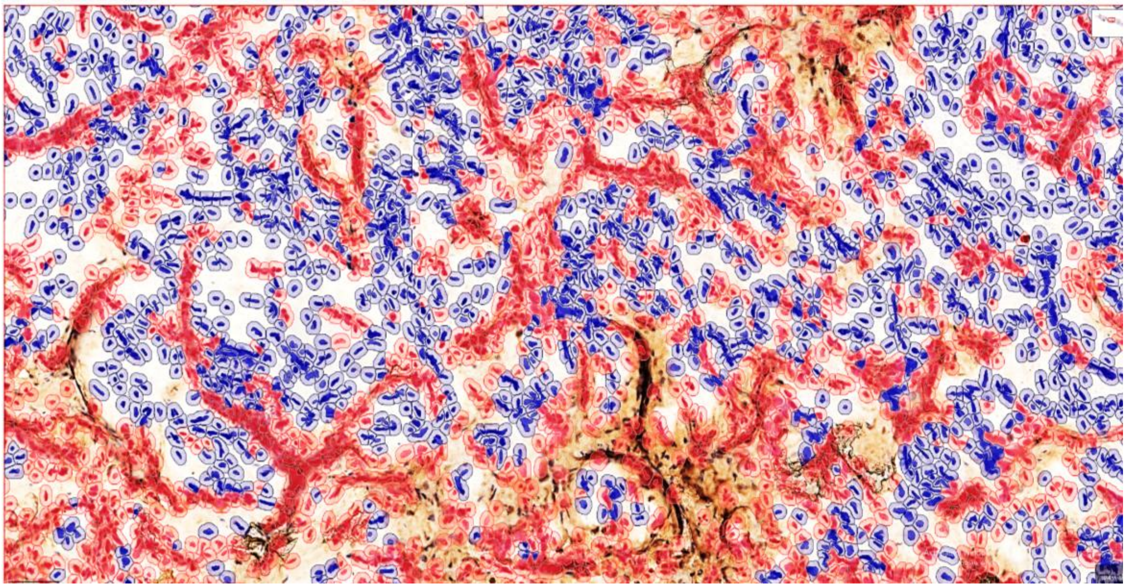

Figure 1. Morphogram showing the nuclear cytoplasmic index of epithelial cells in the ductal variant of diffuse breast carcinoma. Scanned in NanoZoomer. In the QuPath-0.5.0 (console) program, the cytoplasmic index of the nucleus was determined, and a microphotograph with average values was obtained. Dab chromogen. Size 10x20.

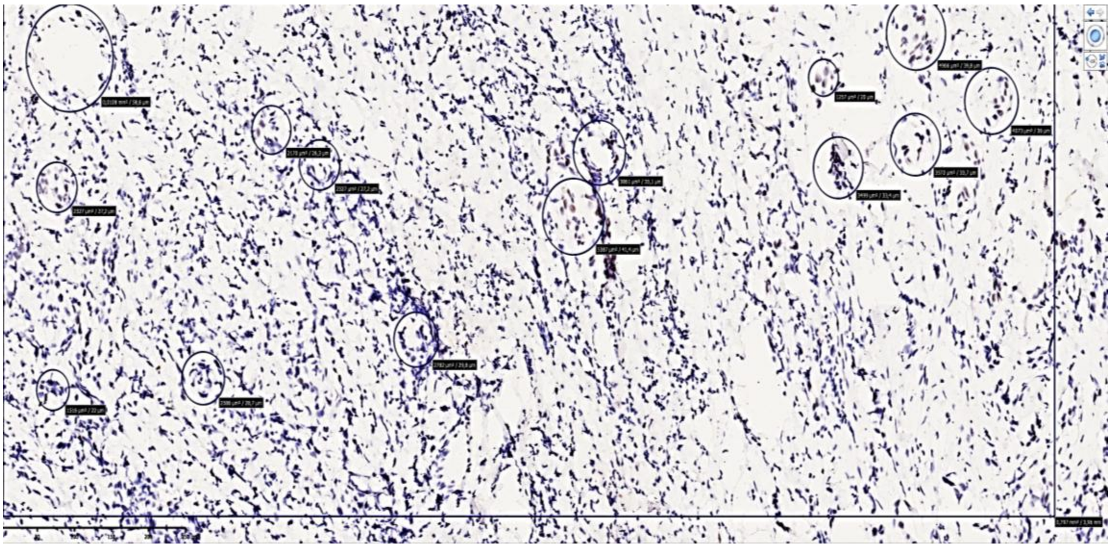

Figure 2. Morphogram of diffuse breast carcinoma in the ductal variant, in which the diameter and occupied area of the preserved lobules are separated by a circular border. Scanned in NanoZoomer. Image Pro Max was processed on an artificial intelligence platform and converted into a microphotograph. Dab chromogen. Size 10x20.

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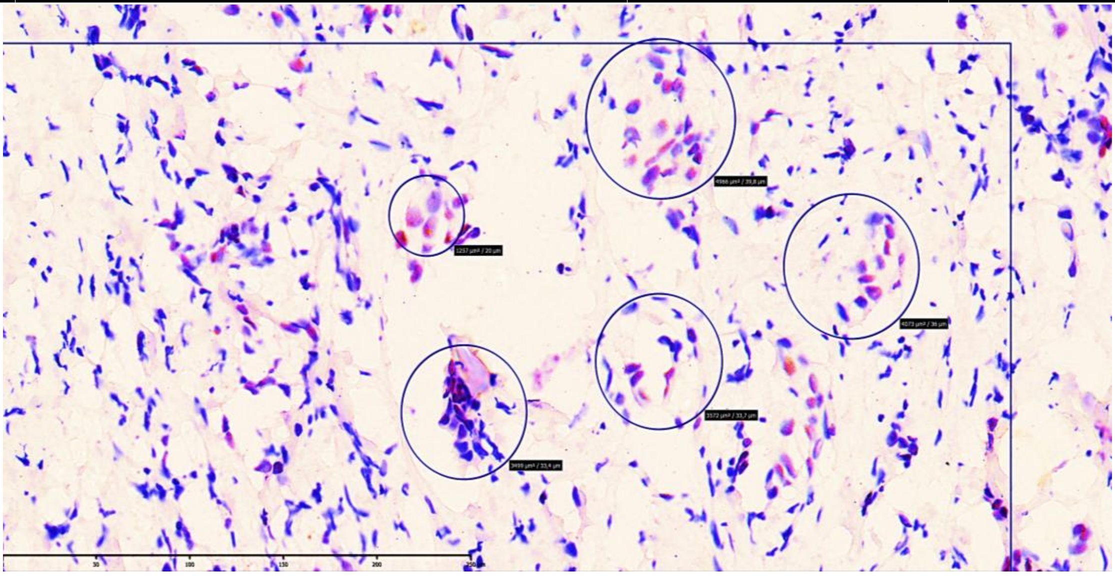

Figure 3. Morphogram of the ductal variant of diffuse breast carcinoma, in which the diameter and area of the preserved lobules are separated by a circular border. Scanned in NanoZoomer. Image Pro Max was processed on an artificial intelligence platform and converted into a microphotograph. Dab chromogen. Size 10x20.

In ductal invasive carcinomas of diffuse breast tumors, the area of the excretory duct in the control group averaged 13.39±1.01%, while in the diffuse form of ductal invasive carcinoma it was 33.38±1.06%, and most ductal ducts were detected in the field of view. This is characterized by an increase in the comparative ratio by 2.5 times.

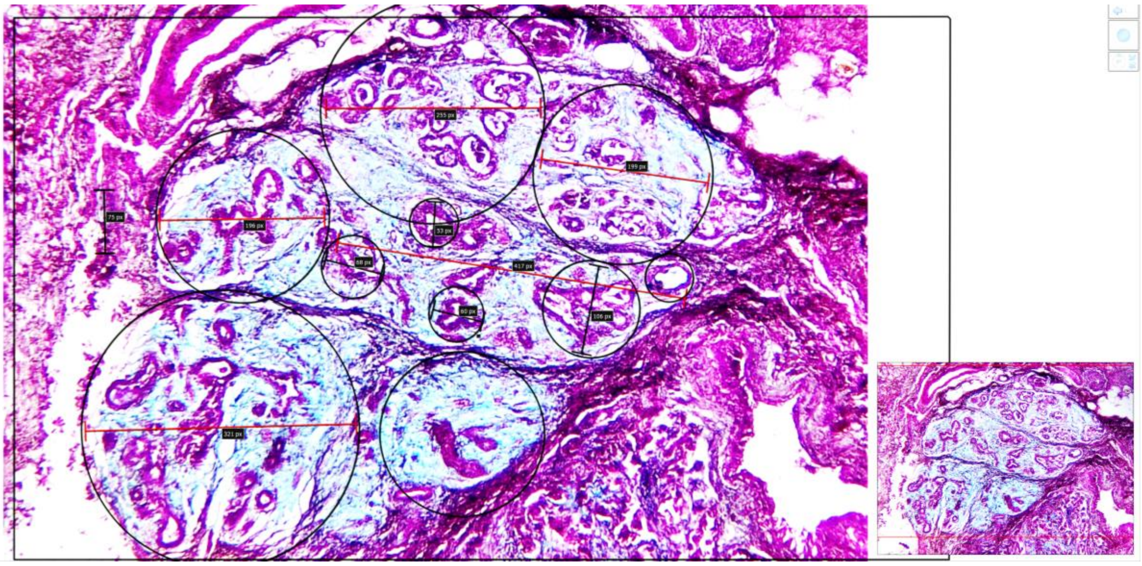

Figure 4. Morphogram of diffuse breast carcinoma in a lobular invasive variant, in which the diameter and area of the remaining lobules are separated by a circular border. Scanned in NanoZoomer. Image Pro Max was processed on an artificial intelligence platform and converted into a microphotograph.

The area of breast lobes in ductal invasive carcinoma was 13.65±1.07% on an area of 84000 μm2, while in the control group this indicator was 45.29±1.055, which confirms a decrease in the comparison indicator by 3.31 times. These changes in diffuse breast cancer and ductal tumors are mainly characterized by a sharp disruption of tissue histioarchitecture and the presence of excretory ducts in place of lobules. This indicates a violation of morphofunctional indicators of the mammary gland.

In the ductal variant of diffuse breast carcinoma, the average value of the nuclear cytoplasmic index was 0.69±0.01. In the control group, this indicator averaged 0.83±0.03, which is explained not by the enlargement

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of the nuclei of the epithelial cells, but by the fact that the volume of the cytoplasm is reduced and the volume of the nuclei does not change or is larger than in the control group.

Table 2.

Morphometric indicators of tissue in an invasive tumor of the lobular duct of the mammary gland in µm, % and µm². 84000µm² given on the surface.

Area size	control group	Study group	R ≥ 0.01* R ≥ 0.05**
Stroma %	26.2±1.80*	13.31±1.01*	0.01
Exit road area%	12.9±1.01*	14.02±1.05*	0.01
Blood vessel area%	3.8±0.97*	9.13±0.36*	0.01
Piece area%	45.29±1.05**	63.16±0.75**	0.05
nuclear cytoplasmic index	0.83±0.03**	0.61±0.03**	0.05

It was found that the average difference in YASI (nuclear cytoplasmic index) was 1.2 times. According to the difference in such morphometric aspects, the main changes were detected in all structures of the mammary gland, which is explained by a sharp change in the tissue histioarchitecture.

Conclusions. The use of digital morphometry in diffuse forms of breast cancer made it possible to quantitatively assess tissue and cellular changes. Using NanoZoomer, QuPath, and Image Pro Max programs, micropreparations prepared from each case were analyzed in a field of view of 84,000 µm2. This approach minimized the human factor and ensured repeatable and reliable results of morphometric indicators.

According to the obtained results, stromal remodeling and the predominance of the fibrous component were revealed in the ductal invasive diffuse phenotype. In this variant, the proportion of stroma was higher compared to the control group (47.31%), the dominance of the excretory ducts increased (33.38%), while the proportion of lobules sharply decreased (13.65%) and the proportion of blood vessels decreased by almost half (5.66%). A decrease in the nuclear-cytoplasmic index (NCI) to 0.69 is explained by the dedifferentiation of epithelial cells and a decrease in the parenchyma reserve.

In the lobular invasive diffuse phenotype, on the contrary, parenchymal structures predominate and angiogenesis increases. The proportion of lobules increased to 63.16%, the stroma decreased to 13.31%, and the area occupied by blood vessels increased to 9.13%. This indicates the activation of cell proliferation and the intensification of the neoangiogenesis process. A decrease in YASI to 0.61 reflects an increase in the level of dedifference.

In the diffuse inflammatory phenotype, the main morphological changes were characterized by a "vascular-inflammatory" profile. The area occupied by blood vessels was 10.43%, which is 2.7 times higher than in the control group. At the same time, inflammatory infiltration was 10.38%, and interstitial edema was 6.13%. These changes confirm the influence of inflammation on tissue architecture and the activity of immunological response reactions.

A decrease in the nuclear-cytoplasmic index in all diffuse forms compared to the control group (from 0.83±0.03 to 0.61-0.69) indicates an increase in cell dedifferentiation and tumor aggressiveness. Thus, a morphometric panel, consisting of such indicators as the ratio of stroma and parenchyma, the area occupied by blood vessels, and the lumen of the lumen, can be used as an important criterion for differentiating diffuse forms, assessing the degree of invasion, and making clinical decisions.

The results of the study showed that the introduction of digital morphometry as a standardized method plays an important role in the differential diagnosis of diffuse forms of breast cancer, in the selection of stroma-focused, antiangiogenic, or immunomodulatory therapy components in treatment tactics. At the same time, it is advisable to integrate this methodology into clinical practice through expanded sample size and multicenter studies.

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