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DIFFUSE CARCINOMAS OF THE BREAST: CLINICAL AND MORPHOLOGICAL PROFILING BASED ON QUPATH/IMAGEJ

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Abstract:

In the study, the clinical and morphological features of diffuse breast carcinomas (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 programs. Stroma, lobules, blood vessels, and the nuclear-cytoplasmic index (NCI) were measured as the main indicators.

According to the results, in the ductal variant, the proportion of stroma increased (47.31%), in the lobular variant, the activity of parenchyma and angiogenesis was high (63.16%, blood vessels 9.13%), and in the inflammatory variant, vascular-inflammatory changes prevailed. In all cases, a decrease in YAS (0.61-0.69) indicated cell dedifferentiation.

In conclusion, digital morphometry is a reliable method for morphological profiling of diffuse breast carcinomas, the results of which are targeted and have important prognostic significance in choosing the direction of individual therapy.

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 a group of neoplasms with high morphological and molecular heterogeneity, with different clinical course, prognosis, and response to therapy. The latest WHO classification (5th edition) updates the morphological criteria of clinical-value phenotypes such as invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), and inflammatory breast cancer (IBC), emphasizing the need for standardized assessment in forms prone to diffuse manifestations.[1] ESMO guidelines recommend integrating morphological inference with immunohistochemistry and molecular profiling, including systematic consideration of signs of invasion, angiogenesis, and stromal remodeling in diffuse phenotypes [2].

In clinical practice, IBC is characterized by a rapidly progressive, "erythema-edema" phenotype and extensive diffuse infiltration, which increases the risk of subjectivity in morphological assessment and requires a quantitative approach [3]. ILC is often accompanied by diffuse dissemination in the parenchyma due to the "discohesive" growth pattern characteristic of E-cadgerin (CDH1) dysfunction; this condition may be underestimated in conventional microscopy and cause difficulties in clinical and radiological correlation [4].

The potential for invasion/metastasis largely depends on stromal remodeling (e.g., a fibrous focus) and the activity of the vascular component. Meta-analysis and a series of studies have shown that the presence of a fibrotic focus in IDC is associated with a high risk of recurrence, while an increase in microvascular density (MVD) is inversely related to survival rates [5-6]. Therefore, the quantitative assessment of parenchymal-stromal ratios and vascular composition plays an important role in the differentiation of diffuse phenotypes and predictive stratification.

In recent years, the development of digital pathology and open-source image-analysis platforms (QuPath, ImageJ) has made it possible to perform rapid, accurate, and repeatable morphometry on full-slide images (WSI); the possibilities of spatial quantization of

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immune landscape and tissue heterogeneity have expanded [7-9]. At the same time, the issue of a stable correlation of the standardized morphometric panel (stroma, lobes, excretory ducts, vascular fraction, and nuclear-cytoplasmic index - NCI) for diffuse breast cancer phenotypes with clinical-aggressive and therapeutic orientations remains insufficiently systematized [10].

In this article, quantitative characteristics of tissue histioarchitectonics and cellular parameters in diffuse variants of IDC, ILC, and IBC are presented using digital morphometry based on QuPath/ImageJ; the obtained indicators (stroma/parenchyma ratios, vascular component, and YAS) are compared from the point of view of clinical interpretation, and profiling criteria are proposed [1-2,7-10].

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 the conducted studies, it was established that in lobular invasive breast cancer, the morphometric aspects of the tissue are also characteristic, accompanied by an increase in the proliferative activity of the epithelium of the lobules and an increase in the size of the lobules.

In the lobular invasive variant of diffuse breast cancer, one of the main features is that due to the fact that the main part of the tissue stroma is occupied by lobular structures, the area occupied by the stroma on an area of 84000 μm2 averaged 13.31±1.01%, while in the control group this indicator was 26.2±1.80%. This, according to the comparison indicator, confirms an increase in the cellular composition of the mammary gland with a 1.99-fold decrease in stroma.

At 84000 μm2 along the excretory tract, the area occupied by this indicator was 14.02±1.05% in the studied group and 12.9±1.01% in the control group. This, in turn, was considered statistically significant, since it was less than 10% by comparison.

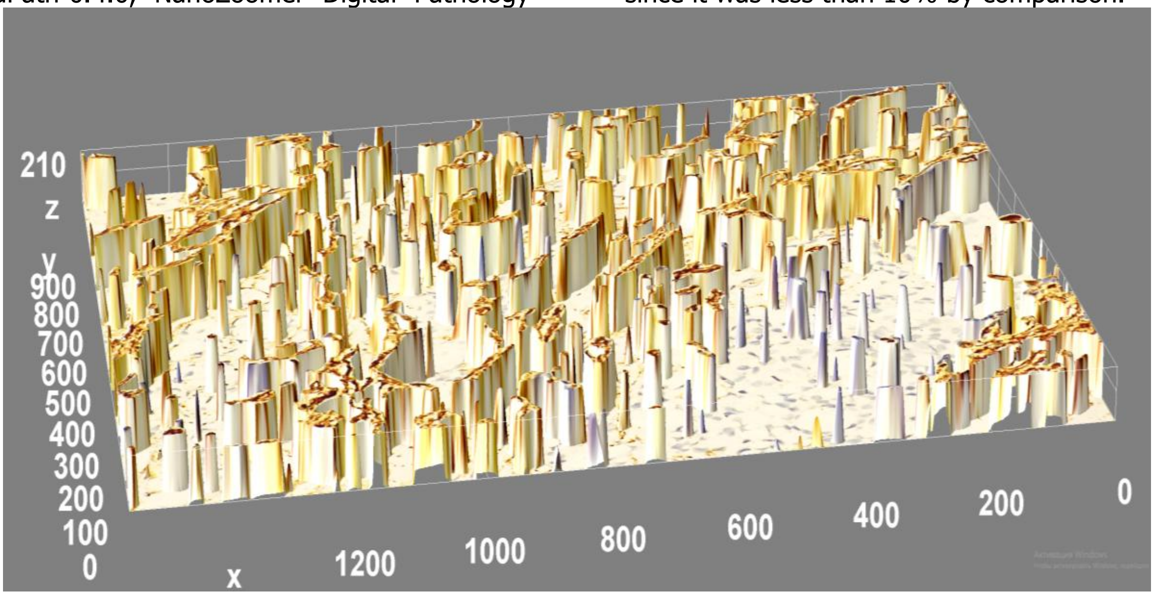

Figure 1. In diffuse breast carcinoma, a confocal image of the tumor stroma and a volumetric view of the area occupied by fibrous structures in the tissue cavities are reflected. Scanned on NanoZoomer. QuPath-0.5.0 was loaded into the ImageJ program and the spatial shape was measured.

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In diffuse carcinoma, the average area occupied by blood vessels on an area of 84000 μm2 was 9.13±0.36%, while in the control group this indicator was 3.8±0.97%. In terms of statistical significance, an increase in the area occupied by vessels by 2.4 times confirms the ongoing process of neoangiogenesis. This is due to the fact that in the above immunohistochemical studies, high vascular expression was also observed in nodular variants, namely, in the diffuse lobular form of breast cancer, multiple branching foci of blood vessels were detected in the perimeter and center of the lobules, which also confirms the sharp progression of the invasive process.

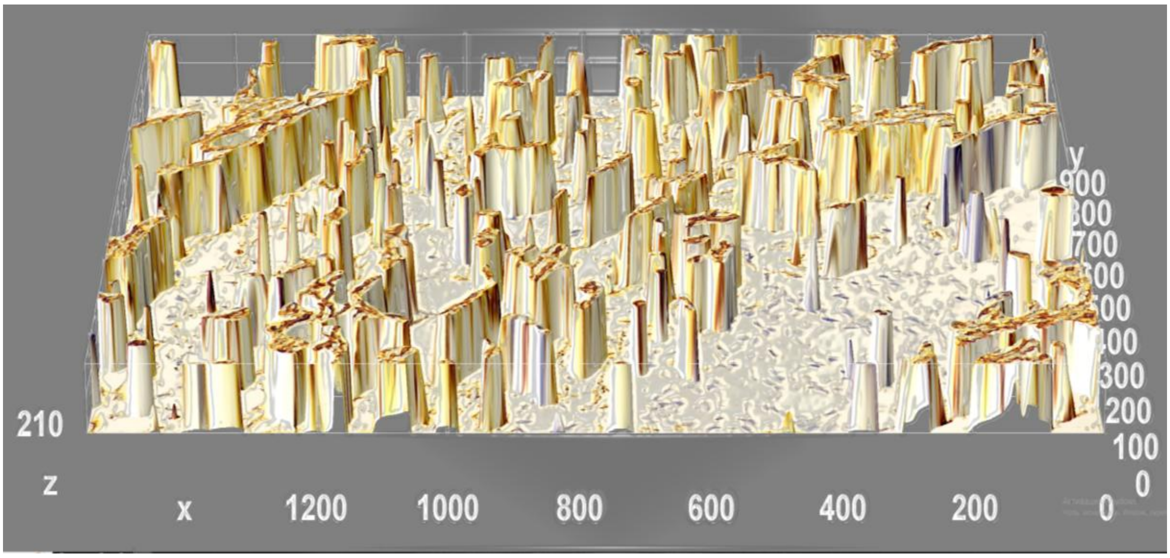

Figure 2 Confocal dot image of diffuse breast carcinoma. The volumetric appearance of the wall thickness of the gland and the volumetric appearance of the area occupied by the vessels in the lumen are reflected. Scanned in NanoZoomer. QuPath-0.5.0 was loaded into the ImageJ program and the spatial shape was measured.

In terms of the area occupied by the lobules, in the control group this indicator was 45.29±1.05%, while in the studied group this indicator was 63.16±0.75%, and from a clinical and morphological point of view, the presence of multiple nodules in this type confirms the occurrence of a hyperplastic process in the lobules. At the same time, when comparing the obtained numerical indicators, it was found that it increased by 1.4 times compared to the control group. This also proves the volume increase of the particles through numbers.

Table 1.
Morphometric indicators of tissue in inflammatory breast cancer are % and μm². 84000 μm² is given on the surface.

Area size	Nodular form	Diffuse form	R ≥ 0.01* R ≥ 0.05**
Stroma %	26.2±1.80*	27.22±1.05**	0.01
Output road area%	12.9±1.01*	12.13±1.02**	0.01
Blood vessel area%	3.8±0.97*	10.43±1.08**	0.01
Piece area%	45.29±1.05**	33.71±1.05**	0.05
inflammatory cells	-	10.38±0.03**	0.05
interstitial edema	-	6.13±0.08**	0.05

According to the nuclear cytoplasmic index, in the diffuse form of the breast, it averaged 0.61±0.03 in the epithelial cells of the lobules, while in the control group this indicator was 0.83±0.03. According to the comparison indicator, it was found that it increased by 1.36 times, which proves that when assessing the degree of cellular atypia and cell dedifferentiation, even the presence of hyperchromic nuclei is the basis for assessing proliferative activity, it decreased compared to the control group.

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In our next group, the inflammatory variant of the diffuse form of the mammary gland was mainly characterized by the presence of foci with completely altered histioarchitectonics and neutrophils, rich in lymphocytes, and other types of mesenchymal cells in the stroma. This, in turn, led to a change in the ratio of other components (parenchyma and stroma, adipose tissue, mesenchyme) in the studied tissue in the field of view of 84000 µm2, mainly due to inflammatory foci. This, unlike the 2 variants mentioned above, is presented in Table 3 in the following morphophometric indicators.

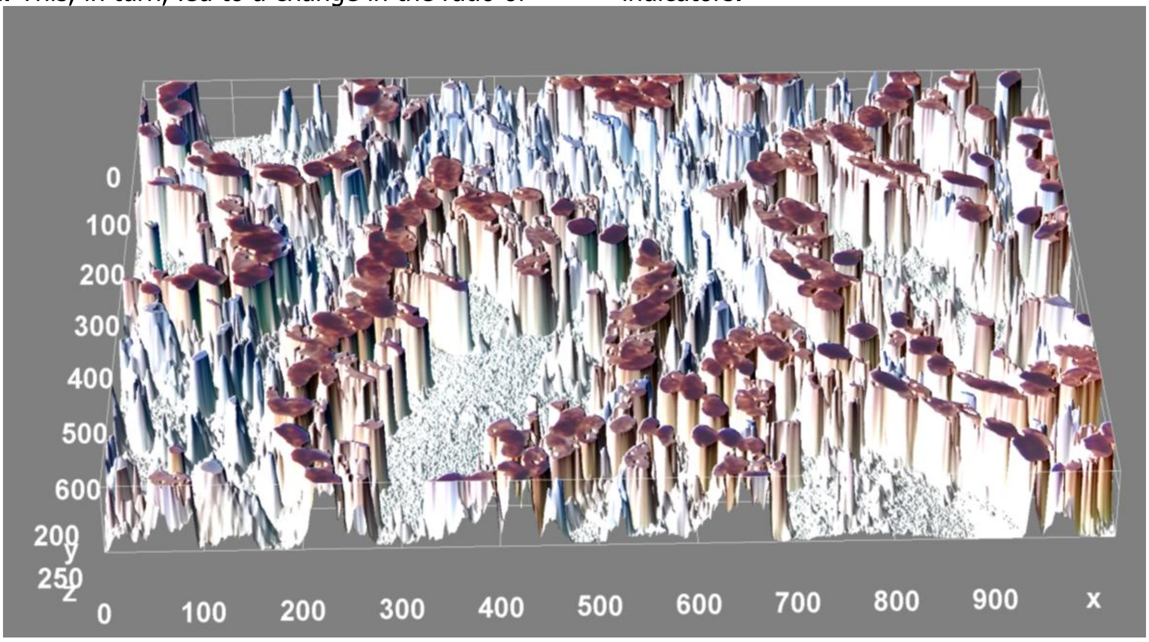

Figure 3. Diffuse breast carcinoma is a carcinoma of the excretory duct. A confocal dotted image of the ducts and areas occupied by the tissue stroma are presented. Scanned on NanoZoomer. QuPath-0.5.0 was loaded into the ImageJ program and the spatial shape was measured.

The area occupied by the stroma was 27.22±1.05%, which differed by 5% compared to the control group, which was not statistically significant. In terms of the area occupied by the excretory duct, it was not statistically significant, as the difference was up to 5% compared to the control group, which amounted to 12.13±1.02% of the area of 84000 µm2. This is explained by the fact that no differences were found in the severity of changes in the ducts of the stroma and ducts of the glandular duct in the variant of breast cancer infection compared to the control group. In terms of the area occupied by blood vessels, the area of 84000 µm2 was 10.43±1.08 5, and due to the predominance of inflammation in this process, vascular fullness was formed due to foci of angiogenesis, while in the control group it was 3.8±0.97%, which confirms an increase in the comparison indicator by an average of 2.74 times.

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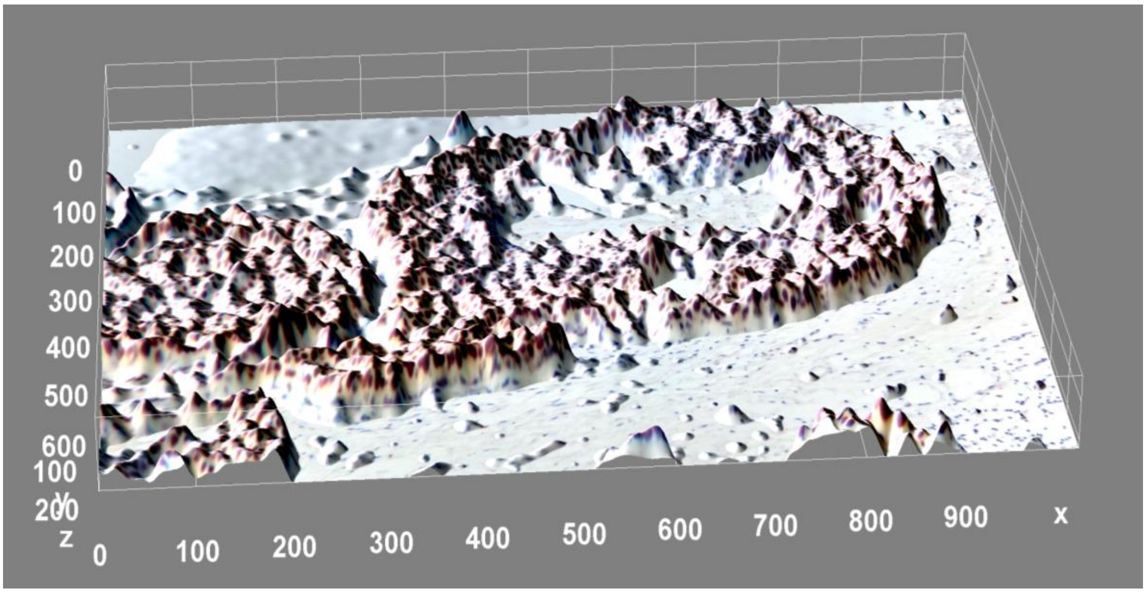

Figure 4. Confocal dot image of the inflammatory variant of diffuse breast carcinoma. In the perimeter of the inflammatory foci and lobule, small areas are reflected, occupied by the stroma and surrounding inflammatory infiltrate. The volumetric appearance of the area occupied by the vessels and intermediate edema is reflected. Scanned on NanoZoomer. QuPath-0.5.0 was loaded into the ImageJ program and the spatial shape was measured.

In terms of particle area, the area of 84000 μm2 was 33.71±1.05%, while in the control group this indicator was 45.29±1.055. This was characterized by a decrease in the comparative indicators by 1.34 times due to the appearance of secondary changes in the tissue due to inflammation, foci of necrosis.

The area occupied by lymphocytes, neutrophils, macrophages, and other cells with inflammatory infiltrate in pathological foci on an area of 84000 μm2 was 10.38±0.03%. This confirms the presence of vasodilation, interstitial edema, mesenchymal response reactions due to inflammatory infiltration in all areas of the breast.

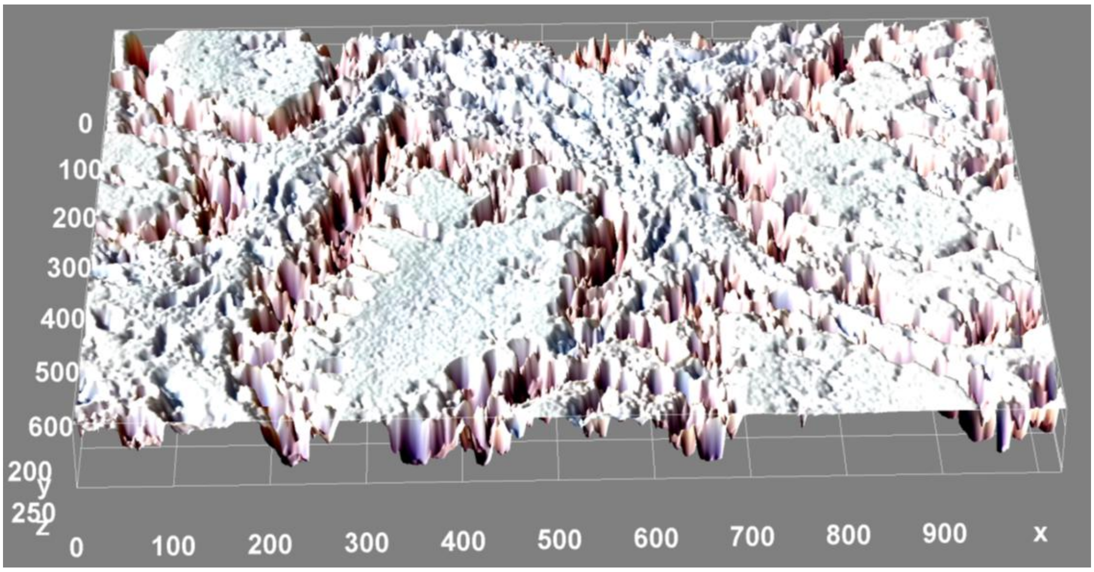

Figure 5. A confocal dotted image of diffuse breast carcinoma and a volumetric view of the area occupied by the vascular lumen are reflected. Scanned on NanoZoomer. QuPath-0.5.0 was loaded into the ImageJ program and the spatial shape was measured.

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At the same time, it was established that in diffuse breast cancer, the presence of interstitial edema formed as a result of inflammation, the area of 84000 μm^2, amounted to 6.13±0.08%.

Thus, according to the ratio of the main components of the tissue in diffuse breast cancer, in the invasive variant of the excretory duct, the main changes were manifested by an increase in the stroma by 2 times compared to the nazaort group, and a decrease in the area occupied by the gland lobules by 3.31 times compared to the control group.

The main features of the lobar invasive variant were a sharp decrease in stroma on an area of 84000 μm2 due to the fact that the main part of the tissue stroma is occupied by lobar structures, which amounted to 13.31±1.01%, a decrease in stroma by 1.99 times compared to the control group was manifested by an increase in the cellular composition of the breast.

In the inflammatory variant of diffuse breast cancer, the main feature was that intermediate edema in the areas where the tumor was detected was detected in 6.13±0.08% compared to the control group, and the inflammatory infiltrate tissue was 10.38±0.035. This was characterized by the fact that in diffuse breast cancer, the area occupied by all stromal components was 2.74 times greater than in the control group.

CONCLUSION. The applied digital morphometry protocol (NanoZoomer-QuPath/ImageJ/Image Pro Max) allowed for accurate and reproducible clinical and morphological profiling of diffuse breast carcinomas. Quantitative analysis revealed specific tissue "traces" of each diffuse phenotype: in the lobular-invasive variant, an increase in the proportion of parenchyma (lobes up to 63.16%), a sharp decrease in stroma (13.31%) and an increase in the proportion of blood vessels (9.13%) showed increased neoangiogenesis and proliferative activity; in the ductal-invasive variant, a predominance of stromal remodeling (47.31%), a predominance of excretory ducts (33.38%), a decrease in lobes (13.65%) and a decrease in the vascular component (5.66%) reflected a deficit of the parenchyma reserve and a predominance of the fibrous component. In the inflammatory variant, the vascular-inflammatory profile was leading, the proportion of blood vessels increased to 10.43%, inflammatory infiltration (10.38%) and interstitial edema (6.13%) sharply changed the tissue architecture.

In all diffuse variants, a decrease in the nuclear-cytoplasmic index (0.61-0.69) correlated with aggressive biological behavior, indicating an increase in cellular dedifferentiation. In this regard, a morphometric panel, including YAS, parenchymal-stromal ratios, and vascular component, is recommended as a set of reliable biomarkers for differentiating diffuse phenotypes, assessing the potential for invasion, and the degree of angiogenesis.

Clinically, the obtained indicators justify the integration of targeted approaches to treatment tactics: stroma-oriented strategies in ductal variants with stroma predominance, antiangiogenic components in lobar variants with parenchyma/angiogenesis predominance, and immunomodulatory and anti-inflammatory therapy in inflammatory variants.

The standardized digital approach in this work provides a basis for the development of morphometric norms for diffuse carcinomas; in the future, it is recommended to validate with a larger sample, molecular profiling, and multicenter correlation analysis with clinical results.

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