CLINICAL AND MORPHOLOGICAL FEATURES OF LUMINAL A SUBTYPE OF INVASIVE DUCTAL BREAST CANCER

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Summary

The aim of this article was to study clinical and morphological features of luminal A subtype of breast cancer to assess its relationship with disease progression. Methods: This study included 79 patients with luminal A subtype of breast cancer who treatment in 2017 at the Lviv State Oncological Regional Treatment and Diagnostic Center. The Luminal A subtype was identified by immunohistochemistry (IHC) as ER+, PR+/-, HER2- and Ki-67 less than 20 percent on surgically resected breast cancer tissue. Results: The mean age of patients was 60,41±12,25 (range, 32–85 years), 26 (32,9%) were under 55 years. Nottingham Histologic Grade distribution was as follows: G1 – 10 (12,66%), G2 – 56 (70,88%), and G3 – 13 (16,46%) cases. Clinical stage II – 35 (44,3%) and III – 31 (39,24%) was observed. Menopausal status was in 67,1% of cases. Morphological analysis of the tumor tissue showed that except alveolar structures, there were trabecular, solid, tubular structures and separately located groups of tumor cells. The stromal component of the tumor was weak or moderate, most tumors showed minimal or marked inflammatory infiltration and low proliferative activity. Conclusions: To predict the probability of lymphogenic metastasis should be considered: menstrual function, histologic grade, the presence of alveolar structures in the infiltrative component, the different types of structures in the infiltrative component, hyalinosis in the stroma of the tumor node and inflammatory infiltration of tumor.

Keywords: clinical features, morphological structure, luminal A breast cancer, disease progression

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1. Introduction

Breast cancer is the most common malignancy in the female population worldwide. It is the most commonly diagnosed cancer among women in 140 of 184 countries. According to the WHO data, published in 2018, the number of deaths from breast cancer in Ukraine reached 8,983, or 1,49% of total deaths. With age-related mortality 20,93 per 100,000 population, Ukraine ranks 36th pace in the world. Early diagnostic and treatment of this pathology is not only an important medical, but also a social task *(Bulletin, 2020).*

To mark International Women's Day 8 of March 2021, "WHO is launching a new Global Breast Cancer Initiative, to reduce mortality from breast cancer by 2,5% every year until 2040, saving 2,5 million lives" *(WHO, 2021).*

Breast cancer is a morphologically heterogeneous group of tumors that differ in clinical course and sensitivity to treatment. Characteristics of breast cancer are presented in the World Health Organization's classification of breast tumors *(Tavassoli and Devilee, 2003).* It is known that tumors that belong to the same histological type may have different clinical course. The most numerous group is ductal breast cancer and this type of cancer has the highest heterogeneity.

Previously, pathological diagnosis was the "gold standard" in determining the histological subtype and assessing the degree of differentiation. It was further established that breast tumors with similar histological pattern can have different clinical manifestations, aggressive course, treatment outcome, overall and recurrence-free survival.

Currently, to determine adequate treatment tactics used molecular-genetic classification of breast cancer, proposed in 2000 by Perou CM. and co-authors *(Perou CM, 2000).* This approach is based on patterns of expression of so-called native genes, which show a greater difference in expression between tumors than within a single tumor *(Perou et al., 2000; Strehl et al., 2011).* The molecular subtype identifies subgroups with different biological properties and response to treatment.

The most well-known molecular subtypes of breast cancer include luminal, with positive expression of HER-2 /neu human epidermal growth factor receptors and triple-negative tumors *(Guarneri V., Conte PF., 2009).* In addition, there is a well-known division of the luminal subtype into luminal A and luminal B. Basal breast cancer is also being actively studied today because it is overlapping on the triple negative subtype, but is not synonymous with it.

Luminal A subtype, according to various authors, amount up to 60% of cases of breast cancer and is characterized by positive receptors for hormones (estrogen and / or progesterone), negative HER-2 / neu receptor and low levels of Ki-67 protein. This group, compared with others, is characterized by low recurrence rates and a high level of overall survival, a high sensitivity to hormone therapy (e.g. tamoxifen, aromatase inhibitors) *(Parker J.S., 2009, Zaha et al., 2010; Yanagawa M. et al., 2012).*

Most genes found in luminal A subtype of breast cancer are usually expressed in the luminal ductal epithelium *(Raica et al., 2009).* However, despite the rather favorable biological characteristics of luminal type A breast cancer, patients in this group may develop both lymphogenic and hematogenous dissemination and have different disease outcomes. The search for additional clinical and morphological criteria will help to individualize the prognosis in patients with breast cancer.

The aim of this article was to study clinical and morphological features of luminal A subtype of breast cancer to assess its relationship with disease progression.

2. Material and methods of research

Current study included patients with luminal A type of breast cancer stages T1-3N0-3M0, who were treated in 2017 at the Lviv Regional Oncological Treatment and Diagnostic Center. Patients who received neoadjuvant chemotherapy or were diagnosed with recurrent breast cancer or cancer without invasive component were excluded from this study. A total of 79 consecutive cases meeting the criteria above were included in this study. Medical histories, outpatient medical records were analyzed in order to identify clinical and treatment data.

Morphological and immunohistochemical examination of the surgical material of all patients was performed at the Western Ukrainian Histological Laboratory, Lviv. The study was approved by the Ethics Committee of Danylo Halytskyi Lviv National Medical University.

General morphological data included tumor size, assessment of tumor location in the surgical sample, tumor color, tumor edges and affected lymph nodes. For microscopic examination, tumor tissue, tissue from lines of surgical resection, breast tissue outside the evident tumor, all identified lymph nodes were presented.

Samples of primary tumor tissue after macroscopic examination were fixed in neutral buffered 10% formalin, carried out the conductance of pieces of biological material in solutions of alcohols of ascending concentration, prepared in paraffin blocks. On a *Microtome Manual* Microm *HM325* serial standard sections were made with a thickness of 5 ± 1 μm, which were placed on ordinary slides for histological staining or Thermo Scientific™ *SuperFrost Plus*™ *Adhesion slides* for immunohistochemical studies.

Histological examination was performed on deparaffined sections of 5 ± 1 μm, which were stained with hematoxylin and eosin according to standard methods. Stained slides were examined under microscope Leica DM 750 (Leica Microsystems GmbH, Germany) to determine the type of tumor, the differentiation grade, the presence of secondary changes such as necrosis, inflammation, sclerosis, peritumoral lymphatic infiltration and invasion.

Tumors were diagnosed according to the WHO classification of breast tumors *(Tavassoli and Devilee, 2003, Lakhani SR, 2012).* The characteristics of the parenchymal component of the tumor (formation of various morphological structures, cell polymorphism, mitosis, tumor invasion beyond the basal membrane), the microenvironment of the tumor were evaluated. Tumors were classified according to grade of differentiation based on the classification of the Scarff – Bloom – Richardson, modified by Elston and Ellis (1991), which takes into account the ability of neoplasia to form tubular and glandular structures, the degree of nuclear polymorphism and the number of mitoses: G1 – well differentiated tumor, G2 – moderately differentiated tumor and G3 – poorly differentiated tumor. TNM stages were determined according to the 7th edition of the AJCC Cancer Staging Manual *(Edge et al., 2010).*

Based on ER, PR, HER2 / neu and Ki-67 expression status, breast cancers were categorized into molecular subtypes in accordance with St. Gallen 2013 consensus surrogate definitions of the molecular subtypes *(Harbeck N., 2013).* The Luminal A subtype was identified by immunohistochemistry (IHC): ER +, PR +/-, HER2- and Ki-67 less than 20 percent on surgically resected breast cancer tissue.

Histological sections of 5 ± 1 μm were subjected to standard deparaffinization and dehydration in xylene and alcohols in increasing concentrations. After dewaxing and rehydration of the sections, Tris-EDTA Buffer for Heat Induced Epitope Recovery, pH 9.0, inhibiting the activity of endogenous peroxidase with 3% hydrogen peroxide solution and applying blocking serum. Incubation with primary antibodies was performed according to the instructions of the manufacturers, visualization of the IGH reaction was performed using the detection system DAKO EnVision + System with diaminobenzidine (Dako). The sections were stained with Mayer's hematoxylin and enclosed in Canadian balm.

In our study we used an antibody panel (Dako, Denmark) to determine the expression of ERα, PgR sex hormones – monoclonal rabbit antibodies to estrogen receptor) (Clone ER1, dilution 1: 1, Dako Flex) and progesterone receptor (Clone PgR 636, dilution 1: 1, Dako, Flex).

Evaluation of ER and PR expression was performed according to the recommendations of D.C. Allred taking into account the proportion of stained nuclei and the intensity of their staining. It was considered a negative reaction when the sum of points was 0-2, weakly positive – 3-4 points, positive – 5-6 points and strongly positive – 7-8 points *(Allred D.C., 2010).* A total score of 3 on this scale corresponds to 1-10% of stained cells and is the minimum positive result.

Membrane staining was evaluated for HER-2 / neu (Clone SP3, dilution 1: 1, Thermo scientific) according to HercepTestTM as follows: 0 – no staining is observed or membrane staining is observed in less than 10% of tumor cells; 1 – weak or barely noticeable staining of the membrane is found in more than 10% of tumor cells, the cells are stained only in part of their membrane; 2 – weak and moderate complete staining of the membrane is observed in more than 10% of tumor cells; 3 – strong complete staining of the membrane is observed in more than 30% of tumor cells. HercepTest is interpreted as negative for HER2 protein expression (staining intensities 0 and 1+), weakly positive (2+ staining intensities) and strongly positive (3+ staining intensities) according to Dako HercepTestTM, 16th edition. At the level of expression 2+, a FISH study was required.

To study the proliferative activity of tumor cells we used rabbit moloclonal antibodies to the protein Ki-67 (Clone MIB-1, dilution 1: 1, Dako, Flex). According to the classification of St. Gallen Consensus (2013) considered the level of Ki-67 to be less than 20% as the index of proliferative activity for Luminal A breast cancer.

Routine microscopy, photographing of micropreparations, evaluation of immunohistochemical staining was performed on a light optical universal laboratory microscope Leica DM 750 (Leica Microsystems GmbH, Germany) with a digital video camera Leica ICC50 HD.

All calculations were performed using the statistical software package Statistica® for Windows 13.0 (StatSoft Inc., license №JPZ804I382130ARCN10-J). The results were represented by the interval M ± m. Significance of differences was assessed by Student's t-test. Survival rates were assessed by Kaplan-Meyer analysis. The difference parameters were considered statistically significant at $p < 0,05$.

3. Results of the research and their discussion

The Luminal A subtype was identified by immunohistochemistry (IHC) and *immunohistochemical profile was:* ER+, PR +, HER2-negative, and Ki-67 less than 20 percent (Fig. 1).

The mean age of patients was 60,41±12,25 years (range, 32–85 years), 26 (32,9%) were under 55 years. Clinical stage II – 35 (44,3%) and III – 31 (39,24%) was observed. Menopausal status was in 67,1% of cases. G1 – 10 (12,66%), G2 – 56 (70,88%), and G3 – 13 (16,46%) cases. In 42 (53%) cases, the tumors were localized in the left and in 37 (47%) – in the right breast. All patients received combination treatment in the form of surgery in the amount of radical mastectomy or radical resection and hormone therapy (aromatase inhibitors or tamoxifen). Clinicopathological characteristics of Luminal A subtype of invasive ductal breast cancer are shown in Table 1.

According to the results of morphological examination of the surgical material, metastases to the axillary lymph nodes were diagnosed in 39 (49,37%) patients. Morphological analysis showed that tumor involvement of the lymph nodes was found more often with a large variety of infiltrative component of the primary tumor node and the presence of alveolar structures. Alveolar structures represent as clusters of tumor cells either rounded or slightly irregular, resembling a rounded shape. The morphology of the cells forming this type of structures varied from small with moderate cytoplasm and rounded nuclei, to large with hyperchromic, irregularly shaped nuclei and abundant cytoplasm (Fig. 2). Simultaneously, we diagnosed trabecular, solid, tubular structures and separately located groups of tumor cells and single tumor cells.

An important practical morphological characteristic feature of alveolar complexes in invasive ductal breast cancer is the absence of myoepithelial cells on the periphery. At immunohistochemical typing single myoepithelial cells can be found in the central departments of a complex.

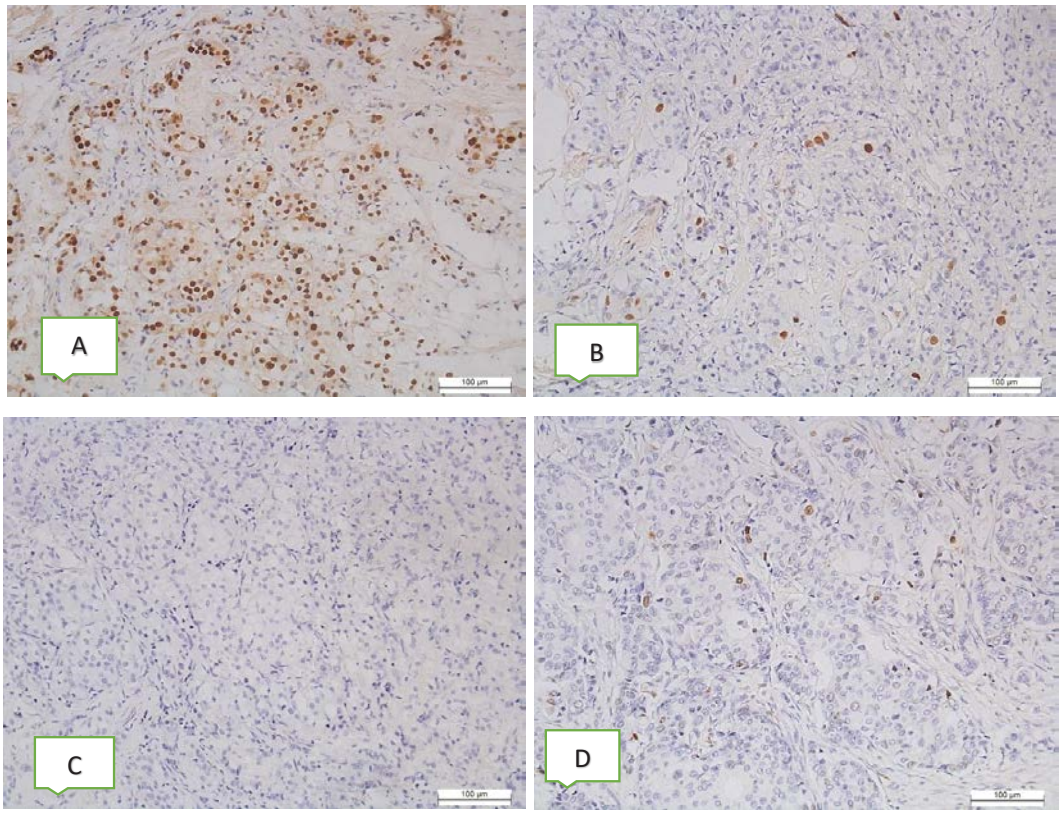

Fig. 1. Invasive ductal carcinoma of the breast. Luminal A subtype. IHC. A – Positive nuclear expression of ER (Clone EP1, Dako Flex). B – Positive nuclear expression of PgR (Clone PgR 636, Dako, Flex). C – Negative membrane expression of receptors for c-erbB-2 (negative HER-2 / neu status, Clone SP3, Thermo scientific). D – Positive nuclear expression of Ki-67 in the tissue of invasive carcinoma (Clone MIB-1, dilution 1: 1, Dako, Flex). x200.

Table 1

Clinicopathological characteristics of Luminal A subtype of invasive ductal breast cancer

Variable	Luminal A n=79
Age Mean ± SD (years)	60,41 ± 12,25 (Range, 32–85 years)
Menopausal status	
Premenopause	26 (32,91%)
Postmenopause	53 (67,09%)
pT1	25 (31,64%)
pT2	39 (49,37%)
pT3	7 (8,86%)
pT4	8 (10,13%)

Table 1 (Continued)

pN0	36 (45,57%)
pN1	23 (29,11%)
pN2	13 (16,46%)
pN3	3 (3,8%)
Nx	4 (5,06%)
G1	10 (12,66%)
G2	56 (70,88%)
G3	13 (16,46%)
Positive ER status	79 (100%)
Negative ER status	0 (0%)
Positive PR status	72 (91,14%)
Negative PR status	7 (8,86%)
Low Ki-67	79 (100%)
High Ki-67	0 (0%)
Negative HER2 status	79 (100%)

Trabecular structures were short, formed by one line of small monomorphic cells, or long, consisting of 2-3 lines of medium-sized cells with moderate cytoplasm, rounded normochromic or hyperchromic nuclei (Fig. 3). Tubular structures were formed by 1-2 lines of monomorphic cells with normochromic rounded nuclei and had the form of thin channels (Fig. 4). Solid structures were represented as fields of different size and shape, consisting of small cells with moderate cytoplasm and monomorphic nuclei or of large cells with abundant cytoplasm and polymorphic nuclei (Fig. 5). Separate groups of cells were clusters of 1-4 cells of variable morphology (Fig. 6). Most often, the infiltrative component had a mixed structure (Fig. 7). Microscopic examination in each case indicated the number of different types of structures in the infiltrative component.

The stromal component of the tumor was weak or moderate. In most tumors, there was minimal (Fig. 8) or moderate inflammatory infiltration (Fig. 9). Neoplasms were characterized by low proliferative activity.

The study of the infiltrative component of Luminal A subtype of invasive ductal carcinoma of the breast showed the presence of different types of morphological structure, such as alveolar, solid, trabecular, tubular and separately located groups of tumor cells. The frequency of detection of different structures is presented in table 2.

Invasive ductal carcinoma is the most common morphological type of breast cancer. In our study, almost all cases of luminal A subtype of ductal cancer were diagnosed at stage pT1 and pT2, when the tumor had the largest diameter up to 5 cm. Metastases to the axillary lymph nodes were diagnosed in 39 (49,37%) patients. Among the tumors which were smaller than 2 cm in the largest diameter (pT1), lymph node metastases are absent.

In pT2 cancer, the distribution of pN was different: metastases were not detected in 11 (28,21%) cases, 1-3 positive lymph nodes were detected in 23 (58,97%) cases, and 4-9 metastases to axillary lymph nodes were detected in 5 (12,82%). Larger tumors were associated with more aggressive spread, as pT4 cases had ≥10 metastases in 37,5% of cases.

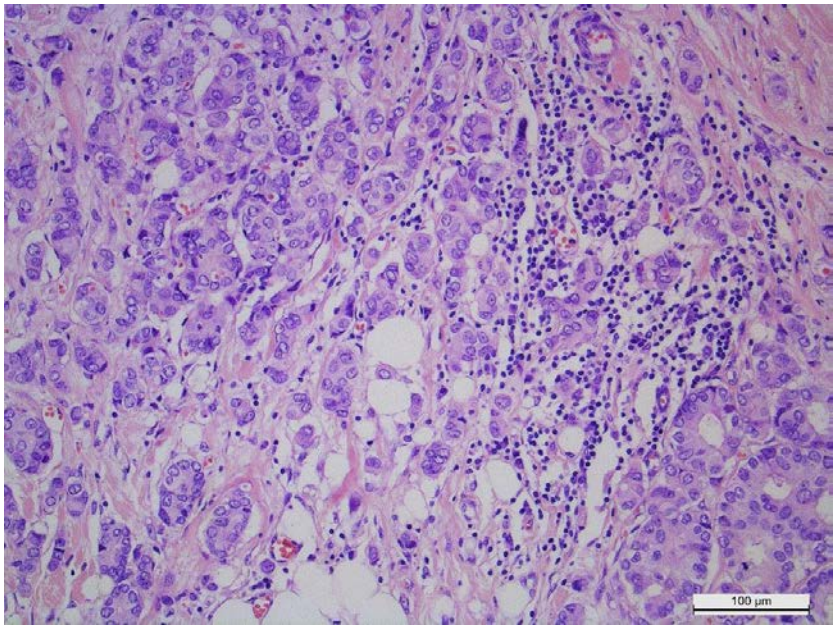

Fig. 2. Clusters of tumor cells of round or oval shape forming alveolar structures in the invasive component of ductal cancer. H&E stain, × 200

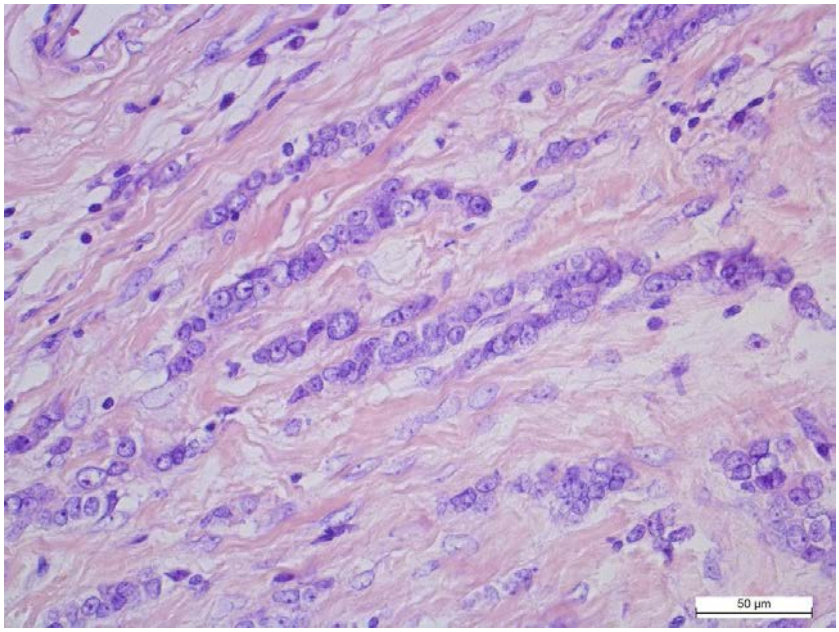

Fig. 3. Trabecular structure in the infiltrative component of invasive ductal carcinoma of the breast. H&E stain, × 400

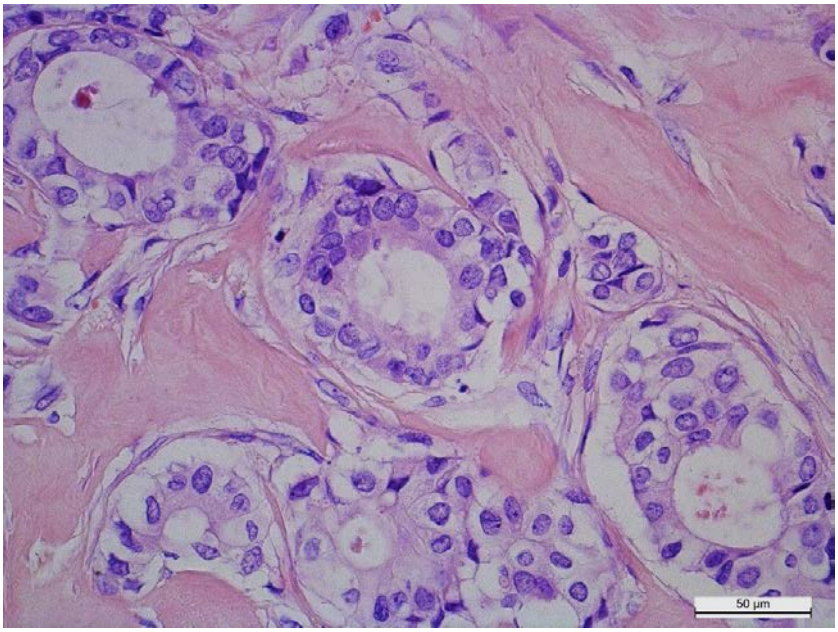

Fig. 4. Typical tubular structures in the infiltrative component of invasive ductal carcinoma of the breast. H&E stain, × 400

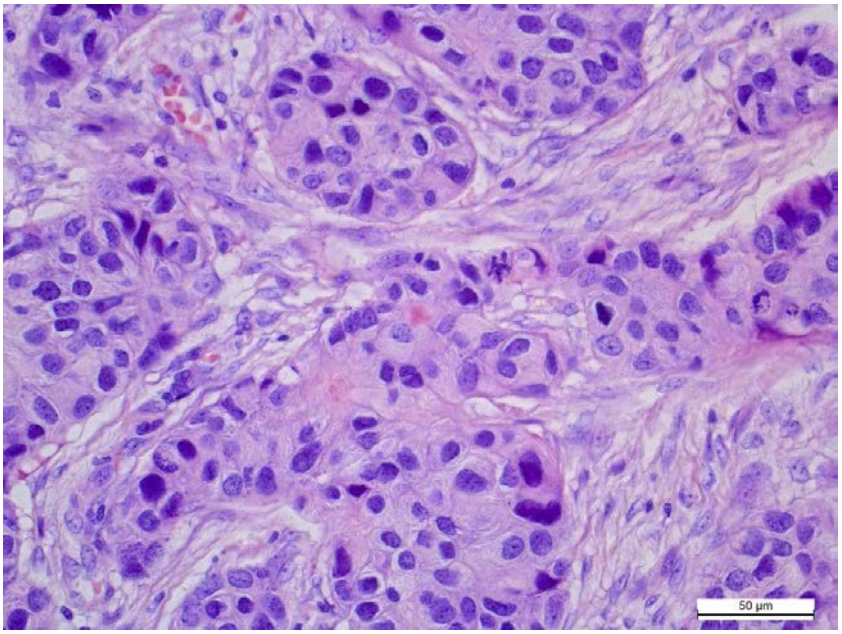

Fig. 5. The presence of solid structures in the infiltrative component of invasive ductal carcinoma of the breast. H&E stain, × 400

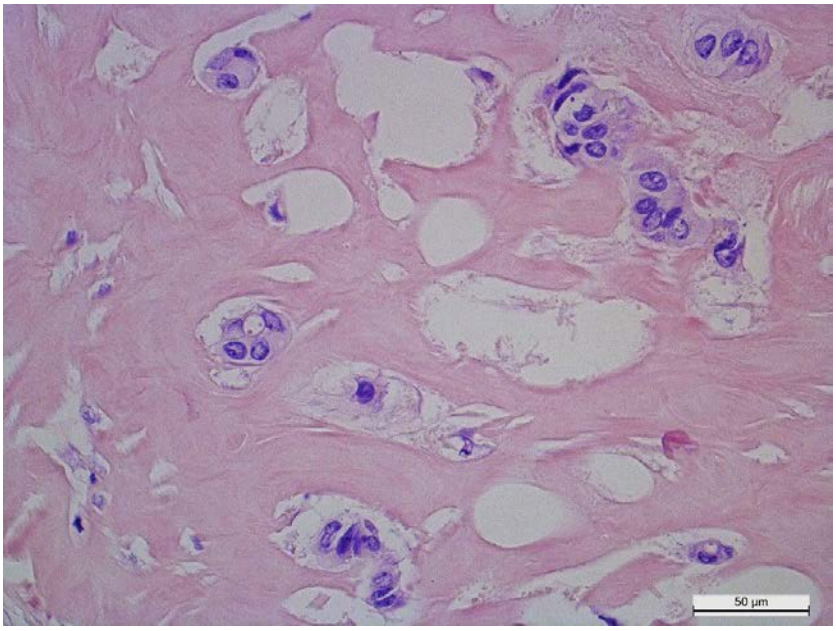

Fig. 6. The presence of individual tumor cells in the infiltrative component of invasive ductal carcinoma of the breast. H&E stain, × 400

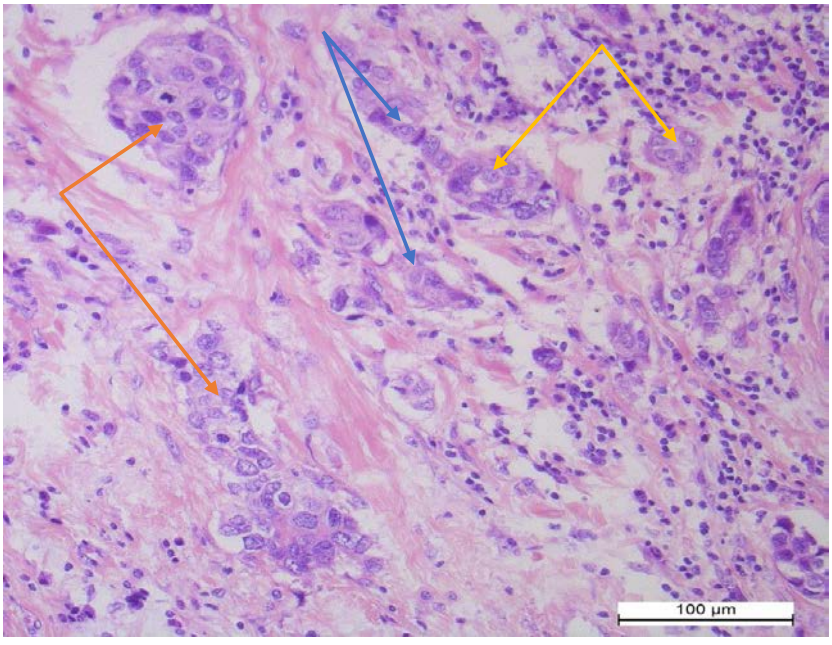

Fig. 7. The infiltrative component of invasive ductal carcinoma of the breast is represented by solid (orange arrow), trabecular (blue arrow) and alveolar (yellow arrow) structures. H&E stain, × 200

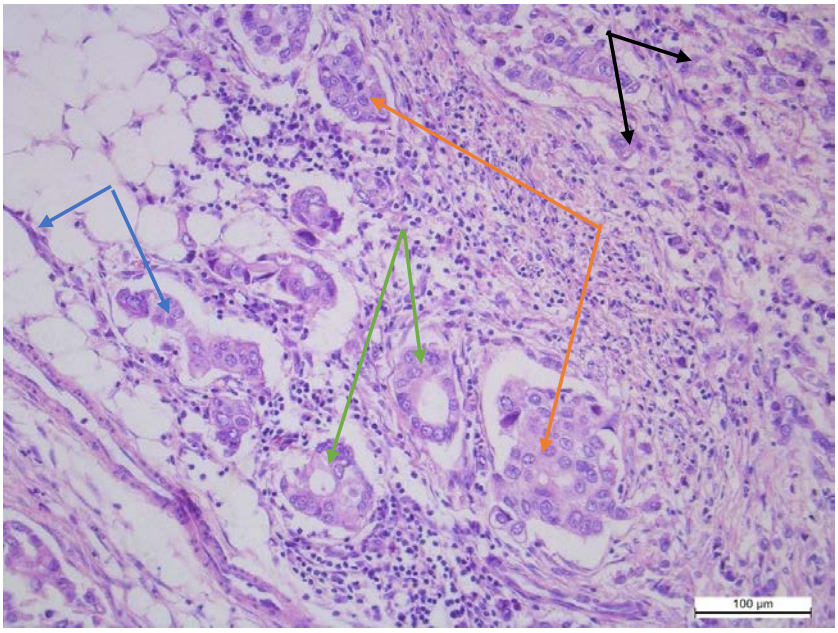

Fig. 8. Infiltrative component of invasive ductal carcinoma of the breast of mixed structure, represented by tubular (green arrow), solid (orange arrow), trabecular (blue arrow) structures and individual groups of tumor cells (black arrow). Weak inflammatory infiltration of the stroma. H&E stain, × 200

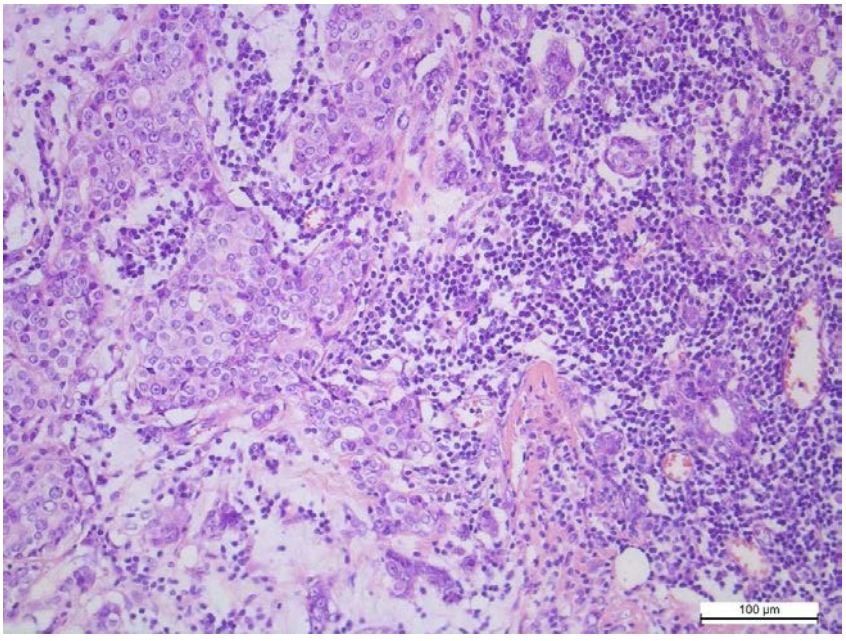

Fig. 9. Abundant inflammatory infiltration of the stroma of invasive ductal carcinoma of the breast. H&E stain, × 200

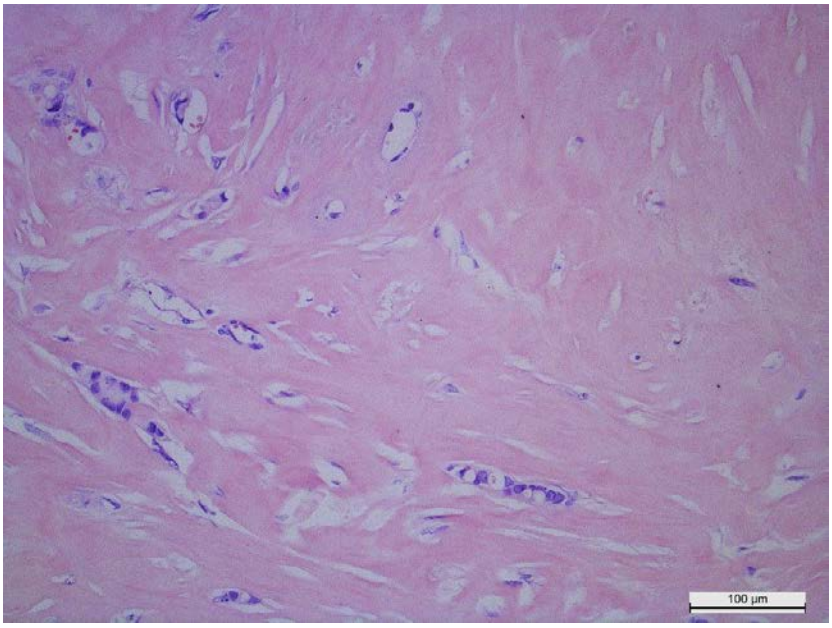

Fig. 10. Severe hyalinosis of the stroma of invasive ductal carcinoma of the breast. The infiltrative component is represented by separate small groups of tumor cells. H&E stain, × 200

Table 2

Frequency of detection of different types of morphological structures in the infiltrative component of Luminal A subtype of invasive ductal carcinoma of the breast

Types of morphological structures in the infiltrative component	Luminal A subtype n=79
Alveolar (in the form of glandular structures)	56 (70,89%)
Trabecular (in the form of chains or cords)	61 (77,22%)
Tubular (in the form of tubes)	35 (44,30%)
Solid (solid sheets as nests)	32 (40,51%)
Individual single cells	53 (67,09%)

Evaluating negative and positive cases of lymph node involvement, pT1 tumors predominated in the pN0 group. In the pN1 group with 1-3 positive lymph nodes, pT2 was the most common finding, accounting for 58,97%. Similarly, pN2 (4-9 positive lymph nodes) was dominated by pT2, which was 12,82%. There were statistically significant differences (P <0,0001). Among the cases showing peritumoros invasion of lymphatic vessels, cases of pT2 were predominant, which is consistent with studies by other authors *(Metzger-Filho O., 2013).*

In our study, patients with Luminal A subtype had a total three-year survival rate of 100%, and one-, two-, and three-year recurrence-free survival was 91,7%. Molecular luminal A subtype is generally associated with an extremely favorable prognosis *(Tsoutsou PG et al., 2017)* and usually exhibits less frequent and less extensive lymph node involvement *(Sanpaolo P et al., 2011, García Fernández A et al., 2014)*. This subtype tends to develop more slowly over time than other molecular subtypes *(Jatoi I et al., 2011).* In addition, the positive

status of hormone receptors is a favorable prognostic factor and also provides a response to endocrine therapy *(van der Leij F. Et al., 2012, Haffty BG., 2002)*. Several retrospective studies have shown similar results with a percentage ranging from 0,8 to 8% *(Millar EKA et al., 2009; Voduc KD. Et al., 2010; Arvold ND et al., 2011; Albert JM et al., 2010 Nguyen PL et al., 2008)*.

As breast cancer is a heterogeneous group of tumors with variable biological and clinical characteristics, the detection of prognostic markers is clinically important. ER and PR, determined immunohistochemically, are widely used as prognostic markers for hormone therapy, and as prognostic factors *(Elizabeth M. H. 2010)*.

According to the histological evaluation (G), all cases in presented study were classified as following: G1 – 10 (12,66%), G2 – 56 (70,88%), and G3 – 13 (16,46%) cases. Onitilo et al. (2009) analyzed the histological parameters of breast cancer. Their study group included G3 tumors (35,9%), G2 tumors (38,4%), and a relatively small proportion of G1 tumors (21,2%). Luminal A subtype group included almost half of the cases (44,9%) of the disease with G2.

High proliferative activity of the tumor with a high level of Ki-67 expression is associated with worse prognosis. The Ki-67 proliferation marker should be included in routine clinical trials, as the Ki-67 index is crucial for distinguishing between luminal A and luminal B (negative HER-2 / neu) molecular subtypes. The value of the Ki-67 index is being studied by many researchers and important recommendations for this test are still being developed. Ki-67 values <14% were found for differentiation with luminal B subtype and this means that tumors with high Ki-67 values have a worse prognosis *(Cheang et al., 2009; Goldhirsch et al., 2011)*. According to the latest recommendations of St. Gallen Consensus (2013) the Ki-67 level of less than 20% is considered to be the index of proliferative activity for Luminal A breast cancer. According to our results, this study showed an association between luminal A subtype and low Ki-67 proliferation index.

4. Conclusions

Molecular classification of breast cancer has important prognostic value. Luminal A subtype is associated with good prognosis and less aggressive behavior.

Luminal A subtype of breast cancer was characterized by small tumor nodules not exceeding 2 cm in diameter and stage I of the process in 31,64% of cases, which is consistent with well-known data.

Luminal A subtype of breast cancer is diverse in the morphological structure of the tumor and lymphogenic metastasis is associated with a variety of structures of the infiltrative component, including the presence of alveolar, solid, trabecular, tubular structures and separate groups of tumor cells. Survival is significantly affected by pT, pN, age, menopausal status, molecular subtype and structure of the infiltrative component.

Molecular subtypes should be determined using immunohistochemistry as a cost-effective surrogate method and a significant factor associated with survival or locoregional recurrence *(Gabos Z, 2010)*.

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