

Histopathological Prognostic Factors Evaluation in Invasive Mammary Carcinoma

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ABSTRACT The most frequent tumor on women is mammary carcinoma. The present study included 182 cases of invasive mammary carcinoma. We analyzed the clinical and morphological factors with prognostic value in the specialty literature. The surgical resection pieces were analyzed using the usual histopathologic technique by paraffin embedding and staining HE. One of the most important prognostic factors analyzed in this study was the axillary lymph node status. Half of the patients presented negative lymph nodes. The tumor size is one of the recognized prognostic factors, the most frequent tumors having 2-5 cm. The histopathological examination revealed that the most frequent invasive mammary carcinoma was infiltrative ductal tumours. Using the Nottingham grading system we found that the most frequent types of tumor was GIII.

KEY WORDS prognostic factors, invasive mammary carcinoma

Introduction

Mammary carcinoma is the most frequent malignant tumor on women and the second cause of mortality by cancer on them. The disease occurs mostly on women, men being rarely affected, lower than 1% from the cases of mammary carcinoma (1).

The incidence of this type of cancer is variable by geographic area. So, in the developed countries is more frequent, including North America, West Europe and Scandinavia. In Japan the incidence is 20% from that of United States of America. These indicate that are important genetic factors, cultural and environment involved in the development of this disease. (11)

The incidence of mammary carcinoma is variable depending on age, being rarely below 50 years and very rare below 25 years, the incidence increases especially after 50 years (12) and to men is more frequently in 7-decays (15).

Currently, are known morphological factors which are considered to have prognostic value. The factors which are correlated with the prognostic are: presence of distant metastasis or lymph nodes metastasis, and in the absence of the distant metastasis or lymph nodes metastases the tumor size is the factor most strongly associated with the clinic evolution (10). Other factors with prognostic value are the histological grading, the morphological type of carcinoma, the vascular

invasion, tumor multicentricity, the age, the perineural invasion and necrosis.

In this study we evaluate the histopathologic factors with prognostic value on a lot of patients diagnosed with invasive mammary carcinoma in the Pathology Laboratory of Emergency County Hospital of Craiova.

Material and Methods

In this study were included 182 of cases diagnosed with invasive mammary carcinoma on a period of 2 years. The samples have been prelevated from patients committed on Emergency County Hospital of Craiova. The pieces of surgical resection were described and were accomplished serial section interspaced at 0.5 cm. The description of the tumors comprised: number of formations, sizes, location, distance against tegument and against the resection margins, delimitation, form, consistence, presence of the necrosis. For the evaluation of the axillary lymph nodes, there were prelevated all the lymph nodes included in the piece of surgical resection.

The tissue was analyzed using the usual histopathologic technique by paraffin embedding and staining HE.

The histological grading of mammary carcinoma was evaluated using the Nottingham grading system (table 1) which combines nuclear grade, tubule formation and mitotic rate for each

element is given a score of 1 to 3. The total score is formed by the sum of this 3 parameters individual score. The lowest possible score is 3 and the highest possible score is 9 being graded as follows: 3-5 = grad I, 6-7=grad II, 8-9=grad III.

Table 1. Nottingham Grading System

INDIVIDUAL SCORE	TUBULE FORMATION	NUCLEAR GRADE	MITOTIC RATE
1	> de 75% from tumor	Regular uniform nuclei	0-9 mitosis/10 HPF
2pct	10-75% % from tumor	Moderate nuclear variation	10-19 mitosis/10 HPF
3pct	<10% % from tumor	Marked nuclear variation	>20 mitosis/10 HPF

Results

For the analyze of the 182 cases taken in consideration there were evaluated a series of clinical and morphological parameters relevant for the prognostic.

The most important clinical parameters for this study were age and **gender distribution** of the patients.

The analyzed cases with invasive mammary carcinoma were encountered both in women and men. So the gender distribution between the patients of the 182 analyzed cases were 2 men (1%) and 180 women (99%).

This pathology was encountered in patients with age between 30 and 81 years. The distribution evaluation of the age groups was realized differently on women and men. Hence, the women distribution of the age groups was the following: in the risk interval (<35 years) there were only 2% from the patients, between 35-50 years were 13% from the patients and the majority of them (85%) were over 50 years. The men patients were between 60 and 70 years old.

The morphological parameters analyzed in this study included macroscopic parameters like tumor size and multicentricity and histopathological parameters like: lymph nodes metastases, histopathological type and the histological grad.

The most of the tumors had sizes between 2 cm and 5 cm included (44%), the rest being distributed as follows: 38% had the size smaller or equal to 2 cm and the rest of 18% were bigger then 5 cm. The grow of the tumors size was associated with increasing number of the metastasis lymph nodes like: the tumors smaller or equal to 2 cm in 35% of cases, the ones between 2-5 cm in 40% of cases and the tumors bigger then

5 cm were associated with lymph nodes metastasis in 60% of cases.

On the macroscopic exam of the surgical resection specimen was important the fact that 7,14% of the tumors included in this study were multicentric.

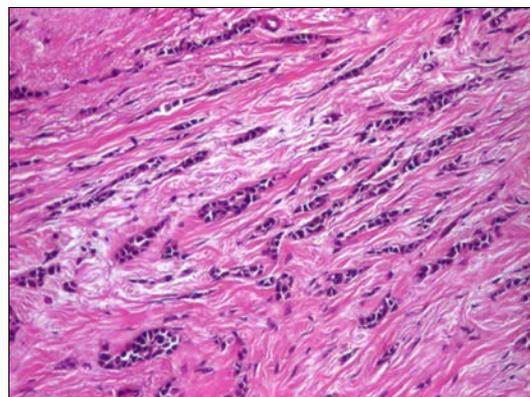


Fig.1: Lobular invasive carcinoma classical type, Ob.x100, HE stain;

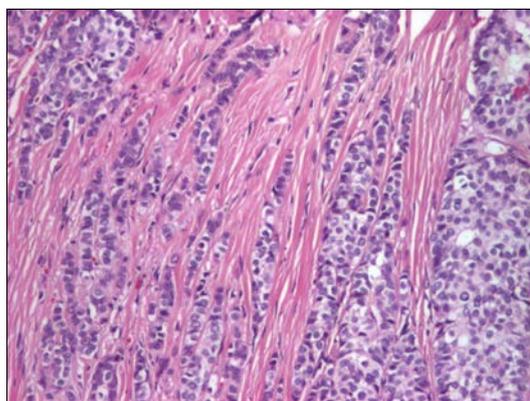


Fig.2: Invasive mixed ductal-lobular carcinoma, Ob.x100, HE stain;

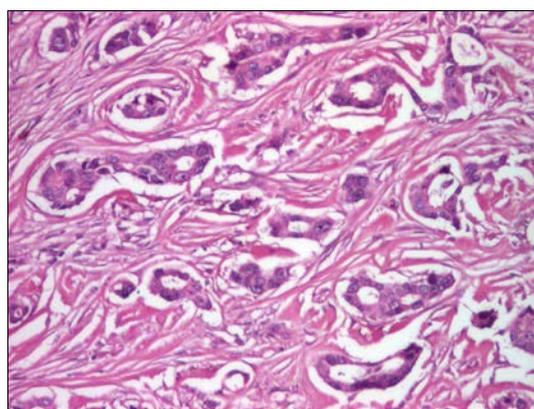


Fig.3: Tubular carcinoma, Ob.x100, HE stain;

From histophological point of view, the most frequently encountered was the classical type of ductal invasive carcinoma (83%), being followed in order by the classical type of lobular invasive

carcinoma (6%), invasive mixed ductal-lobular carcinoma (4%), invasive papillary carcinoma (3%), mucinous carcinoma (2%), tubular carcinoma (1%) and invasive cribriform carcinoma (1%).

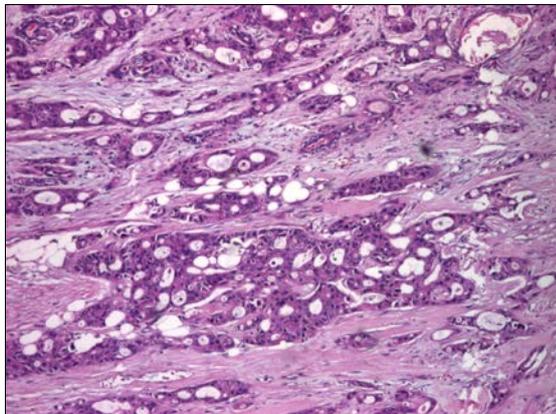


Fig.4: Invasive cribriform carcinoma, Ob.x40, HE stain;

The excision of the axillary lymph nodes was performed on 139 patients from whom 67 (48%) patients haven't had lymph nodes metastasis, 38 (27%) patients have had lymph nodes metastasis in ≤ 3 ggl, 34 patients (25%) have had metastasis in more than 3 lymph nodes.

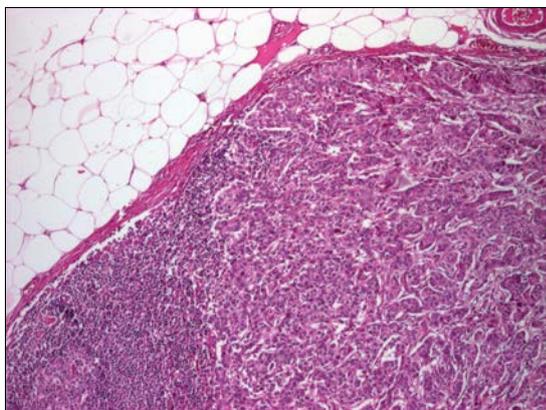


Fig.5: Lymph nodes metastasis, Ob.x40, HE stain;

In what concerns the histological grading assessed using the Nottingham grading system, the majority of the cases (78%) were G III tumors, the less of the cases (3%) were G I and G II in 19% of cases.

Others investigated histopathological parameters were: vascular invasion, perineural invasion and tumor necrosis. Hence, vascular invasion was encountered in 25% of cases, perineural invasion in 40% of cases, and tumor necrosis was encountered in 41% of the analyzed cases.

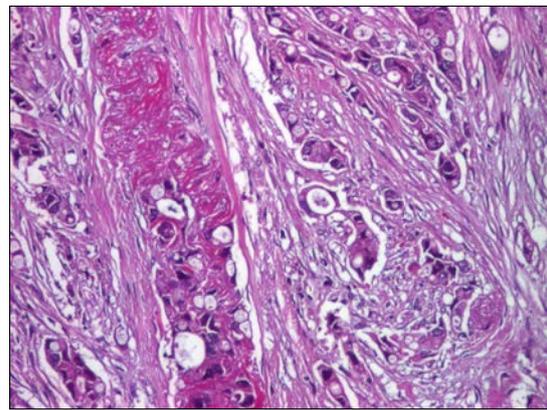


Fig.6: Perineural invasion, Ob.x100, HE stain;

Discussions

The cases we studied revealed that this pathology is especially a disease of women, the **report woman: man** being around 90:1. Thus the probability of male breast carcinoma is slightly increased reported to the data found in specialty literature which mentions a report of 135:1 (w: m) (1).

The distribution of mammary carcinoma cases by **age groups** respects entirely the one mentioned in the specialty literature both for women and men. Regarding women, the most frequent cases were discovered over the age of 50 (85%), and the most rare under the age of 35 (2%), and between those two age limits the occurrence was of 13%. The evolution of this disease in women under 35 years is known to be very aggressive, being associated with the decrees of the overall survival, also the occurrence of early metastasis with a high risk of local recurrence and being also associated with lymph nodes metastasis. This age interval is considered to have an unfavorable prognosis value (3). Men were aged between 60 and 70 years, similar range to the one mentioned in the specialized literature.

The survival and the response to the therapy it is generally accepted that are lower with the increasing of the **tumor size**. The relationship between the increasing of the tumor size and the worsening prognosis was observed also by Crile. He reported that survival at 5 and 10 years decreased at the same time as increasing the tumor size and was associated with the increased number of lymph nodes with metastasis (4). Regarding this, the analyzed tumors with the unfavorable prognosis (over 5 cm) were the fewest (18%), those with the most favorable prognosis were 38% of the total number of cases and the remaining 44% were ranged between these two extremes. Also in our study the increasing of the tumor size was associated with the increasing of the number

of lymph nodes with metastasis. Tumors larger than 5 cm were associated with lymph nodes metastasis in 60% of the cases, those between 2-5 cm corresponding to 40% of the cases and those smaller or equal to 2 cm in 35%, this association showing the correlation of the two prognostic factors, increasing the unfavorable effect on the subsequent evolution of the disease.

Histopathological type of carcinoma is a recognized prognostic factor significantly correlated with the evolution of the patients. Ellis IO and colleagues (6) found in a study on 1621 subjects that there are forms that have an excellent prognosis: tubular carcinoma, invasive cribriform and mucinous carcinoma. Lobular carcinoma has variable prognostic depending on the subtypes. Thus, the classical variant the tubulo-lobular, and the mixed types of invasive lobular carcinoma and also the invasive papillary carcinoma (9) are associated with a better prognosis than classic ductal carcinoma. Meanwhile, the solid form of lobular carcinoma, classic form of infiltrating ductal carcinoma and invasive mixed ductal-lobular carcinoma, present an unfavorable prognosis. From this point of view the vast majority of woman patients had unfavorable prognosis: 83% of cases were diagnosed with classical form of invasive ductal carcinoma and 4% with invasive mixed ductal-lobular carcinoma. Some of the patients were diagnosed with types that have a favorable prognosis such as classical lobular carcinoma (6%) and invasive papillary carcinoma (3%) while the rest of cases were diagnosed with forms that are associated with an excellent prognosis - 2% carcinoma mucinous, 1% tubular carcinoma, 1% invasive cribriform carcinoma.

The histological grading is significantly correlated with the prognosis, patients with G I tumors showing a significantly increased survival comparing to patients with tumors of G II or G III tumors (7). Thus, Bassler R. (2) reported in 1984 the following correlation between this and 10 years survival: G I degree - 45%, G II degree - 27% and G III degree - 18%. In our study, the most of the cases (78%) had an unfavorable prognosis, with the G III degree, while the less cases (3%) had a favorable prognosis, with G I degree, while the remaining of 19% of the cases had G II degree and are associated with a more favorable evolution than those of G III degree.

The lymph nodes status was considered by some authors like being the only significantly prognostic factor regarding the survival and the free period of illness (5). An argument for this is the fact that patients without lymph nodes

metastasis present a rate of 10 years survival of 75%, but the once with lymph nodes metastasis presents a rate of survival of only 25-30% (18). In our study half of the patients did not present lymph nodes metastasis having a favorable prognostic. Many studies mention the fact that the survival is strongly correlated with the number of lymph nodes metastasis. Hence, the tumors with an invasion in 1-3 lymph nodes involved will have a favorable evolution compared to the ones with invasion of more than 3 lymph nodes the 5 years survival decreasing with the number growth of the lymph nodes metastasis (14). From the analyzed cases the proportion of the ones with invasion in 1-3 lymph nodes and more than 3 lymph nodes was the same, respectively 25% from the patients. In the specialized literature, the mammary carcinoma at patients under 35 years old is associated in general with lymph nodes metastasis (3) but, in our study we did not find that fact. From the analyzed tumors at patients under 35 years, 66% did not present lymph nodes metastasis, the proportion overcoming the one from the general population (48%).

In 7,5% from the analyzed cases, the tumors were multicentric. The influence of the multicentric tumors on the prognostic attracted the attention of many researchers, this kind of studies concluding in the end the fact that this is correlated with other known prognostic factors (the lymph nodes status was, tumor size, histological grading), but it does not represent a factor of independent prognostic (16). It was established instead that it is correlated with the period free of illness (13).

The tumoral vascular invasion evaluated on routine staining was evaluated like a prognostic factor in a study on 1704 women by Pinder SE and collaborators (17). Those ones concluded the fact that is a prognostic fact independent both for the survival and for the local recurrences. In our study this was encountered on 25% of patients.

In the invasive mammary carcinoma, **perineural invasion** is associated with more expressed invasive capacity (18) and it was encountered in 40% from the analyzed cases.

The tumor necrosis is correlated with the shortening of the survival period and indicates the therapeutic failure (8). In our study this was encountered in 41% of cases (indicating an unfavorable prognostic for the patients).

Conclusions

The complete histopathological result that includes all the macroscopic and microscopic

feature of the mammary tumor can offer useful data for the prognostic evaluation.

The majority of the women patients were >50 years old. From the analyzed cases, the majority of the tumors had sizes between 2 cm and 5 cm, 18% of them having sizes more than 5 cm which is associated with an unfavorable evolution. The histopathological type of mammary carcinoma that was the most frequently encountered was the classical type of ductal invasive mammary carcinoma which is associated with an unfavorable evolution. In the case of patients on which there was performed axillary lymph nodes excision, approximately half of them did not present lymph nodes metastasis, what is correlated with a favorable evolution.

The resection pieces must be thoroughly analyzed to identify the multicentric tumors, especially when there are not clinical suspicions, because this fact influences the patients' evolution.

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