ORIGINAL ARTICLE

CONTENTS

Prognostic factors for breast cancer progression

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ABSTRACT

Aim: To investigate the clinical and laboratory features of breast cancer with the progression of the tumour process, after complex treatment, depending on the stage of the disease and the molecular type of the tumour, and to determine the prognostic value of each factor.

Materials and Methods: A retrospective analysis of 701 outpatient records of patients with breast cancer in the long term, after complex treatment, was performed.

Patients, depending on the presence of verified breast cancer progression, were divided into two groups - 472 (67.3%) patients 'without tumour progression' and 229 (32.7%) patients 'with tumour progression'.

The informativeness of the studied indicators and diagnostic coefficients was determined using the Kullback method. The results were statistically processed using Microsoft Excel spreadsheets and the PAST statistical processing software package.

Results: Breast cancer progression occurs more often at stage III of the disease, in Lum.-B, Her/2new+, and Triple-negative tumour types. The progression of breast cancer is characterized by a relatively more extended history of the disease, a larger size of the primary tumour, and a higher percentage of comorbidities. The study of the informativeness of the studied indicators and diagnostic coefficients made it possible to form a table of prognosis of possible progression of breast cancer after complex treatment.

Conclusions: The prognostic model of breast cancer progression enables to obtain the prediction of the absence of tumour progression, uncertain prognosis, and the appearance of the latter, with the sensitivity (Se=75%) and specificity (Sp=75%) of this model.

KEY WORDS: breast cancer, progression of the tumour process, breast cancer metastases

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INTRODUCTION

Despite the development of modern oncology, breast cancer (BC) remains an extremely urgent problem, as it is one of the most common forms of malignant tumours among women in the vast majority of developed countries [1].

According to the National Cancer Registry, more than 12,000 cases of breast cancer are diagnosed in Ukraine every year. Even though breast cancer is curable at an early stage in 95% of women, every fourth woman in Ukraine learns of the diagnosis at the III-IV stages, when more expensive and long-term treatment is required, and the effectiveness of the latter is significantly reduced [2].

Treatment of breast cancer is complex and involves a combination of local methods, systemic antitumour, and supportive treatment, which is carried out in different sequences and combinations, depending on the patient's condition, tumour morphology, stage of the disease, etc [3].

The effectiveness of breast cancer treatment is directly related not only to the early detection of this disease but also to the absence of progression of the tumour process, i.e. the time before metastases appear.

At present, the main prognostic guideline for the prognosis of the disease and, accordingly, the effectiveness of breast cancer treatment is the stage of the disease and the division of carcinomas into molecular types [4-6].

To date, there is a fairly large number of scientific papers in which the authors use the patient's anthropometric data, tumour size, location, presence of metastases, etc. to predict the metastatic spread of breast cancer [7-9].

However, there are no clear criteria or algorithms for predicting the progression of the tumour process, nor their prognostic value.

The present study aims to address these issues by studying the peculiarities of breast cancer progression, namely the appearance of metastases, depending on the stage of the disease, and the molecular type of the tumour, and identifying relevant prognostic and predictive factors.

AIM

The aim of the study was to investigate the clinical and laboratory features of breast cancer with the progression of the tumour process, after complex treatment, depending on the stage of the disease and the molecular type of the tumour, and to determine the prognostic value of each factor.

MATERIALS AND METHODS

A retrospective analysis of 701 outpatient records of patients with breast cancer who were treated in healthcare facilities in Ukraine from 2017 to 2021 was conducted.

Patients, depending on the presence of verified breast cancer progression after complex treatment, were divided into two groups - 472 (67.3%) patients 'without breast cancer progression' and 229 (32.7%) patients 'with breast cancer progression'.

The TNM classification of the 8th edition (2016) was used to determine the stage of breast cancer. In our studies, 54 (7.7%) patients had stage I, 227 (32.4%) had stage II A, 181 (25.8%) had stage II B, 93 (13.3%) had stage III A, 81 (11.6%) had stage III B, and 65 (9.3%) had stage III C.

Immunohistochemical classification of molecular types of breast cancer was also used []. Thus, 350 (49.9%) patients were diagnosed with Luminal-A tumour type, 127 (18.1%) with Luminal-B tumour type, 78 (11.2%) with Her/2new+ tumour type, and 146 (20.8%) with triple-negative tumour type.

The most common histological type of breast cancer was invasive ductal carcinoma (642 (91.6%)). In addition, cases of mucinous carcinoma were detected in 31 (4.4%) patients, lobular carcinoma - in 22 (3.1%) patients, and medullary carcinoma - in 6 (0.9%) patients.

The informativeness of the studied indicators and diagnostic coefficients were determined by the Kullback method.

The diagnostic coefficient was calculated by the formula:

$$DC\ (x_{ij}) = 10 \cdot \lg \frac{P(x_{ij}/G_+)}{P(x_{ij}/G_-)}$$

where G_+ - the presence of metastases in the patient, G_- - the absence of metastases, $x_=$ - j th range of the prognostic criterion $x_i, i = \overline{1,m}$, $P(x_{ij}/G_+)$ - the conditional probability of a patient with metastases falling into the j -th range of the *i*-th prognostic criterion, $P(x_{ij}/G_-)$ - the conditional probability of a patient without metastases falling into the j -th range of the *i*-th prognostic criterion.

To determine the contribution of this prognostic criterion to the approach to the correct diagnostic threshold, the informativeness of the criteria was calculated using the formula.

$$(x_i/G_+, x_i/G_-) = \sum_{j=1}^{n_i} 10 \cdot \lg \frac{P(x_{ij}/G_+)}{P(x_{ij}/G_-)} \times 0{,}5[P(x_{ij}/G_+) - P(x_{ij}/G_-)]$$

where x_i is the prognostic criterion, n_i is the number of ranges of the prognostic criterion x_i

Statistical processing of the obtained research results was carried out on a personal computer using Microsoft Excel spreadsheets and the PAST statistical processing software package. The correctness of the data distribution in the samples was checked by applying the Shapiro-Wilk criteria. In the case of normal distribution of independent groups, the Student's t-test was used. In the case of non-normal distribution of continuous variables, the Mann-Whitney test (U-test) was used. Fisher's tests were used to assess the significance of the difference between the percentage shares of the two samples. The differences in the results obtained were considered statistically significant at $p<0.05$, which is generally accepted in biomedical research.

ETHICS

The work is written in accordance with the ethical standards of the industry.

RESULTS

The results of the study presented in Table 1 indicate a significantly lower number of people in the main group with stages I, II A, and II B of the disease and a higher number with stages III A, III B and III C.

Analyzing the results of the study, Table 2 shows a significantly lower number of patients in the main group with Lum-A tumour type and a higher number with Lum-B, Her/2new+, and Triple-A tumour types.

It should be noted that there was no significant difference in the percentage of patients with right and left breast lesions in each study group.

Analysing the results of the study of the average age of patients, it should be noted that there was no significant difference in both study groups at all stages of the disease, with the exception of stage II A, where the indicators of the comparison group significantly prevail.

Regarding the difference in the average age of individuals, depending on the molecular type of tumour, it should be noted that women with Lum.-B and Her/2new+ tumour types are significantly older.

The results of the study presented in Table 3 indicate a significant prevalence of the average duration of the disease history in women in the main group, with the exception of stage I, where this difference is not significant. In both study groups, there was a significant increase in the average duration of the disease history in parallel with the increase in stage, except that the indicators of the main group were not significant in stage II B.

Table 1. Distribution of breast cancer patients, depending on the stage of the disease, abs., %

Stage of the disease	Comparison group		Main group		Difference between both groups
	Abs.	%	Abs.	%	
I	46	9.7	8	3.5	p=0,0007
II A	182	38.6	45	19.7	p=0,0
II B	132	28.0	49	21.4	p=0,029
III A	52	11.0	41	17.9	p=0,0072
III B	39	8.3	42	18.3	p=0,0001
III C	21	4.4	44	19.2	p=0,0
Total	472	100	229	100	p=0,0

Source: compiled by the authors of this study

Table 2. Distribution of breast cancer patients, depending on the molecular type of the tumour, abs., %

Molecular type of the tumour	Comparison group		Main group		Difference between both groups
	Abs.	%	Abs.	%	
Lum. A	296	62.7	54	23.6	p=0,0
Lum. B	72	15.2	55	24.0	p=0,029
Her/2new+	31	6.6	47	20.5	p=0,0
Triple-	73	15.5	73	31.9	p=0,0
Total	472	100	229	100	p=0,0

Source: compiled by the authors of this study

Table 3. The average duration of the disease history of patients with breast cancer, depending on the stage of the disease, months (M±m)

Stage	Comparison group	Main group
I	2.5 ± 0.14 n=46	3.1 ± 0.4 n=8 p=0.175
II A	3.0 ± 0.09 n=182 p_1=0.0383	3.6 ± 0.23 n=45 p=0.0131; p_1=0.4741
II B	3.2 ± 0.09 n=132 p_1=0.0309	3.6 ± 0.16 n=49 p=0.0322; p_1=0.7668
III A	3.5 ± 0.15 n=52 p_1=0.0315	4.1 ± 0.15 n=41 p=0.0104; p_1=0.0109
III B	4.0 ± 0.17 n=39 p_1=0.0355	4.6 ± 0.17 n=42 p=0.0241; p_1=0.0375
III C	4.7 ± 0.21 n=21 p_1=0.0262	5.4 ± 0.21 n=44 p=0.0485; p_1=0.0114

Notes.
n - the number of people;
p - the difference between the two respective study groups;
p_1 - the difference about the next stage of the disease in the corresponding study group
Source: compiled by the authors of this study

When studying the average duration of the disease history, depending on the molecular type of the tumour, it should be noted that the main group is significantly more likely to have the highest rates in all types of tumours. If we compare the indicators in the average comparison groups, there is a significant difference in the Her/2new+ tumour type versus all other types. In the main group, there is a significant difference between the Her/2new+ and Triplets types, but no difference between all other types.

The results of the study presented in Table 4 indicate a predominance of malignant tumour size in patients of the main group, except that this difference is significant only at stages II A and III A of the disease.

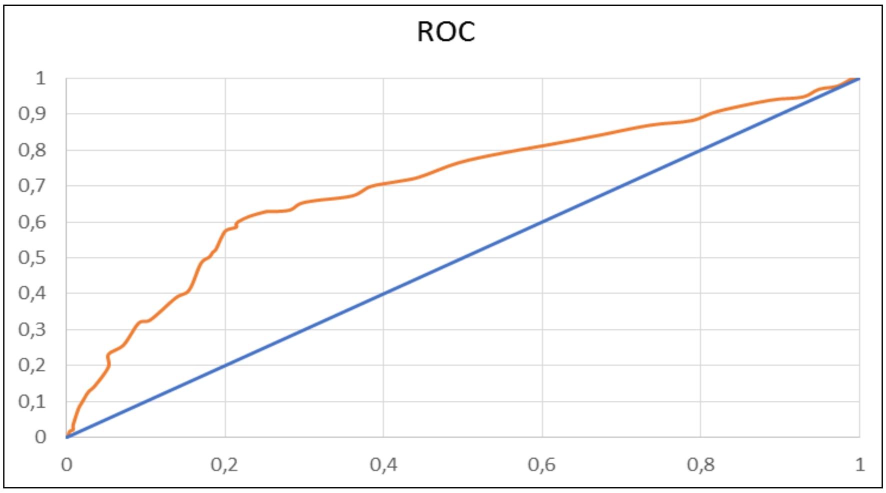

Fig. 1. ROC-curve. Area under the ROC curve AUC=0.69
Picture taken by the authors

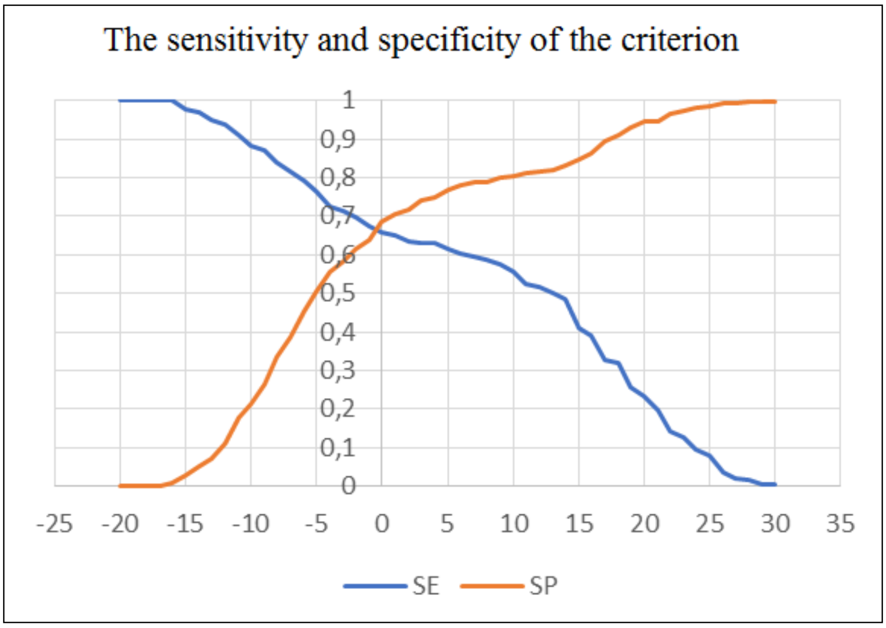

Fig. 2. Graph of sensitivity and specificity of the criterion for predicting breast cancer progression after complex treatment
Picture taken by the authors

When studying the size of the tumour, depending on its molecular type, it is necessary to note the probable predominance of the main group in all types of tumour.

When studying the frequency of concomitant pathology in patients with breast cancer, a significant difference in the total percentage of indicators between both study groups should be noted. At stages I and II of the disease, there is a significant predominance of the percentage of patients in the comparison group. At stage III of the disease, the percentage of women in the main group with concomitant pathology is significantly higher.

In patients of the main group, there is a significant prevalence of metabolic pathology in stages III A and III C of the disease. At stage III B, cardiovascular, respiratory, metabolic, and gynaecological pathology is likely to predominate in patients of the main group.

It should be noted that there is a significant predominance of the number of comparison group patients with concomitant pathology in the Lum-A tumour type, but in all other tumour types, the rates of women in the main group prevail, except for the difference in Triple tumour type. In the main group of patients with Triple tumour type, there is a significant prevalence of patients with respiratory system pathology and a significantly lower percentage of patients with metabolic diseases.

When assessing the degree of differentiation of the malignant neoplasm, it should be noted that there is no significant difference in the percentage of moderately differentiated and low-differentiated tumours between both study groups, at stages I and II A of the disease. At all other stages of the disease, the percentage of G_3 in patients of the main group and G_2 in the comparison group significantly prevails.

In the Lum-A tumour type, the percentage of G_3 tumours in women of the comparison group and G_2 tumours in the main group significantly prevails. There was no significant difference in the percentage of patients with G_2 and G_3 tumours between the two study groups. In both Her/2new+ and Triple-negative groups, there were no patients with G_2 tumours.

Table 4. Size of malignant neoplasm in breast cancer progression, depending on the stage of the disease, (M±m), cm

Stage of the disease	Comparison group	Main group
I	1.3 ± 0.06 n=46	1.6 ± 0.09 p=0.0634 n=8
II A	3.2 ± 0.08 n=182	3.5 ± 0.17 p=0.0345 n=45
II B	4.7 ± 0.15 n=132	5.0 ± 0.14 p=0.0543 n=49
III A	4.0 ± 0.26 n=52	5.1 ± 0.31 p=0.0069 n=41
III B	5.8 ± 0.26 n=39	6.3 ± 0.31 p=0.2787 n=42
III C	5.5 ± 0.34 n=21	6.2 ± 0.55 p=0.0581 n=44
Total	3.8 ± 0.09 n=472	5.1 ± 0.13 p=0.0001 n=229

Notes:
n - the number of people;
p - the difference between the two study groups
Source: compiled by the authors of this study

It should be noted that the longest time for breast cancer progression is likely to be observed in stage I of the disease and the shortest in stage III C, which is logically explained by the aggression of the tumour process. With the increase in the stage of the oncological process, there is a significant increase in the time to breast cancer progression, with the exception of stages III A and III B, where this difference is not significant.

The longest time to breast cancer progression is observed in Lum-A and Lum-B tumour types and is probably the shortest in Her/2new+. Although the time to breast cancer progression in the Triple type is shorter than in the Lum-A and Lum-B types, this difference is not significant.

In the analysis of metastatic lesions, depending on the stage of the cancer process, it is necessary to note a significantly lower number of metastases at stage I.

If we consider the spread of metastatic lesions, depending on the molecular type of the tumour, we should note a significantly higher number of metastases in the T3 tumour type compared to other types.

Patients in stage I of the disease, in both study groups, underwent only organ-preserving operations.

At stage II A of the disease, the number of organ-preserving operations performed in each study group was significantly higher.

At stages II B and III A of the disease, in the comparison group, there is no significant difference between the number of organ-preserving and radical surgical interventions, while in the main group, the number of organ-preserving operations significantly prevails.

In both study groups, organ-preserving surgical interventions were not performed at stages III B and III C of the disease.

In the Lum-A tumour type, in the comparison group, there is a significant predominance of the number of patients who underwent organ-preserving surgery, but in the main group, this difference is not significant. The number of organ-preserving and radical surgical interventions performed between the two study groups of women is not significant.

In the case of Lum-B tumours, in both study groups, there is a significant predominance of the number of patients who underwent organ-preserving operations.

In Her/2new+ and Triple-negative tumour types, in both study groups, there is a significant predominance of the number of patients who underwent radical surgery, but this difference is not significant.

Analysing the results presented in Table 5, it should be noted that all of the above indicators are arranged in the appropriate sequence, from the most informative in predicting breast cancer progression - the proliferative activity of tumour cells (Ki 67) (1.793) to the least informative - metastatic regional lymph node involvement (N3) (0.014), according to the TNM classification (2016).

For female patients, the sum of points is calculated according to this table. The higher the score, the worse the prognosis for breast cancer, i.e. the occurrence of metastatic spread of the cancer process.

The ROC curve for the proposed prognostic table is shown in Fig. 1.

To determine the threshold point for the purpose of forecasting, a graph of the sensitivity and specificity of the criterion is used, as shown in Fig. 2.

So, according to the graph, the optimal point of separation is 0 points. Patients with a score less than zero are predicted to have no metastatic spread of breast cancer, and those with a score less than zero are predicted to have metastases. The sensitivity of the test was Se=66% and the specificity was Sp=69%.

The threshold can be shifted to increase the sensitivity or specificity of the model.

The following predictive model should be considered:

- with a score of <-5 - predicting the absence of metastases;
- with a score between -5 and 5 - an uncertain prognosis;
- with a score of >5 - prediction of metastases.

For this model, Se=75%, Sp=75%.

Table 5. Predicting the metastatic spread of breast cancer

Sign (informative value)	Interval	The number of points
Ki 67 % (1.793)	[0;30]	-6
	[30;70]	3
	[70;100]	8
Duration of disease history (1.248)	0-2	3
	3-4	1
	5-6	-3
	>6	-6
PR % (0.963)	[0;25]	3
	[25;75]	0
	[75;100]	-3
SIZE P (0.884)	<2	-3
	2-5	-2
	>5	3
	Skin changes	5
ER % (0.858)	[0;25]	3
	[25;75]	0
	[75;100]	-3
Her2/new+ % (0.716)	[0;25]	3
	[25;75]	0
	[75;100]	-3
Lymph nodes (N2) (0.536)	axillary (4-9)	3
	Absent	-1
Lymph nodes (N1) (0.393)	Axillary (1-3)	2
	Absent	-2
Concomitant diseases (0.142)	Metabolic	2
	Respiratory	2
	Gynecological	0
	Cardiovascular	0
	Other	0
	Absent	-1
Histological type of tumour (0.136)	Lobular	5
	Mucinous	1
	Ductal	0
	Medullary	-1
Degree of tumour differentiation (0.112)	Low differentiation	1
	Intermediate	-2
Operation volume (0.101)	Sector	-1
	Mastectomy	1
Lymph nodes (N3) (0.014)	Axillary (10), connect	1
	Axillary (10), intrathoracic	-1

Source: compiled by the authors of this study

DISCUSSION

Summing up the results of the study, it should be noted that metastatic spread of breast cancer occurs more often in stage III of the disease, Lum.-B, Her/2new+, and Triple-neg. tumor types, which coincides with the literature data and proves a significant prevalence of the percentage of individuals with the above-mentioned signs [7, 9].

The average age of women cannot be useful for predicting metastatic spread of breast cancer, since the difference in indicators in most cases is unreliable, and the dynamics by stage of the disease and molecular type of tumor are opposite.

In our studies, more than half of the women (53.4%) were of elderly and senile age, which explains the lack of a significant difference in age indicators and the inability to use this sign.

The average duration of the disease history is of leading importance, since with metastatic spread of breast cancer, the latter is probably longer. This feature has a logical explanation, since the longer progression of the disease before the start of complex treatment contributes to the generalization of the oncological process, which directly affects the stage of the disease and, accordingly, the metastatic spread of breast cancer, which was proven by our studies, as well as by literature data [3, 11].

In our studies, the average size of the primary malignant neoplasm in women with metastatic spread of breast cancer significantly prevails, for all molecular types of the tumor, which also has significance in the prognosis of the occurrence of this complication. This is explained by the fact that the stage of the oncological process directly depends on the size of the primary tumor, especially in breast cancer. Additionally, the prognostic value of tumor size has been repeatedly emphasized in studies by other authors [2, 3].

According to the calculations of the informativeness of the criteria for predicting metastatic spread of breast cancer, the results were obtained, namely: active proliferation marker Ki 67, duration of the disease history, expression of PR receptors, size of the primary neoplasm, expression of ER receptors, epidermal growth factor Her/2new, regional lymph nodes (N2, N1), concomitant diseases, histological type of tumor, degree of tumor differentiation, volume of the performed surgical intervention (organ-preserving or radical), as well as regional lymph nodes (N3), which have the lowest prognostic value, which is explained by the generalization of the oncological process, where treatment is the least effective [2, 10].

Thus, this expert system for predicting the metastatic spread of breast cancer allows for obtaining information with a fairly high specificity and sensitivity (Se = 69.0% and Sp = 69.0%), which in the future will enable increasing the effectiveness of its treatment.

CONCLUSIONS

1. The stage of the oncological process most informatively determines the prognosis of breast cancer after complex treatment.
2. The age of the woman, the location of the tumour in the right or left breast, and its quadrants do not affect the progression of this cancer.
3. Marker of active proliferation Ki 67, duration of disease history, expression of PR receptors, size of the primary tumour, expression of ER receptors, epidermal growth factor Her/2new, regional lymph nodes (N_2, N_1), comorbidities, the volume of surgical intervention, histological type of tumour, and degree of differentiation are prognostic factors that can be used to formulate a clear and objective prognosis of breast cancer progression after complex treatment.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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