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IMPACT OF CD44 EXPRESSION ON THE EFFECTIVENESS OF TREATMENT OF LOCALLY ADVANCED PRIMARY INOPERABLE BREAST CANCER PATIENTS

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The study included 157 breast cancer patients aged from 27 to 82 years with IIIA–IIIC stages of the disease, who had no positive response to 6 courses of anthracyclines and/or taxanes-based neo-adjuvant polychemotherapy (AC, FAC, AT). Main group included 74 patients who underwent a course of radiotherapy (RT) under radical program in traditional fractionation mode against the background of daily administration of the cytostatic fluoropyrimidine series drug. Tegafur was used at a dose of 750 mg/m² daily throughout the radiotherapy course for the purpose of radiomodification. Comparison group included 83 patients, who underwent radiotherapy alone in traditional fractionation mode. When using RT in conjunction with radiomodifier, we managed to achieve a better response to treatment in our study patients with CD44+ expression, namely to increase the number of partial response by 41.64 % (p=0.02), resectable cases by 17.28 % (p=0.016), to improve the grade of therapeutic pathomorphosis intensity, including through increasing the percentage of reaching pathomorphological complete response by 4.08 % (p=0.03), improving the overall 5-year survival rate by 28.51 % (p=0.01) and progressive-free survival rate by 37.72 % (p<0.001).

Key words: breast cancer, radiotherapy, fluoropyrimidine radioimodifier, CD44, tumor response, overall survival, recurrence-free survival.

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ВПЛИВ ЕКСПРЕСІЇ CD44 НА ЕФЕКТИВНІСТЬ ЛІКУВАННЯ ХВОРИХ НА МІСЦЕВО ПОШИРЕНИЙ ПЕРВИННО НЕОПЕРАБЕЛЬНИЙ РАК ГРУДНОЇ ЗАЛОЗИ

У дослідження залучено 157 хворих на рак грудної залози віком від 27 до 82 років з IIIA–IIIC стадіями захворювання, у яких не досягнуто позитивного ефекту після проведення 6-ти курсів неоад'ювантної поліхіміотерапії на основі антрациклінів та/або таксанів (АС, FAC, АТ). 74 пацієнткам основної групи проводили курс дистанційної променевої терапії за радикальною програмою в режимі класичного фракціонування на тлі щоденного прийому цитостатичного препарату фторпіримідинового ряду (тегафур в дозі 750 мг/м² на добу щоденно впродовж всього курсу променевої терапії) з метою радіомодифікації. У групу порівняння увійшло 83 хворих, котрим була проведена лише дистанційна променева терапія в режимі класичного фракціонування. При використанні променевої терапії на тлі радіомодифікатора у хворих з експресією CD44+ у нашому дослідженні вдалося досягти кращої відповіді на лікування, а саме, збільшити кількість часткових регресій на 41.64 % (p=0.02), радикально резектабельних випадків на 17.28 % (p=0.016), покращити ступінь вираженості лікувального патоморфозу, у тому числі, збільшивши відсоток досягнення повної патоморфологічної відповіді на 4.08 % (p=0.03), покращити показник 5-річної загальної на 28.51 % (p=0.01) та безпрогресійної виживаності на 37.72 % (p<0.001).

Ключові слова: рак грудної залози, променева терапія, CD44, радіомодифікатор, регресія пухлини, загальна виживаність, безпрогресійна виживаність.

The work is a fragment of the research project "Development of new methods for prevention and treatment of breast cancer recurrence, aimed at improving the efficacy of treatment and quality of life", state registration No. 0121U110085.

One of the most pressing problems of modern oncology is breast cancer disease (BCD), which ranks first in the structure of cancer incidence among women in most countries. According to the WHO, about 2 million new cases of BCD are registered in the world every year, which is more than 11 % of all new cases of malignant neoplasms [10]. In Ukraine, BCD ranks first in the structure of morbidity and mortality – 20.3 %. Although during the period 2002–2020 the proportion of sick women with stage III disease decreased from 19.8 to 16.0 %, and with stage IV – from 10.2 to 10.1 %, the rate of neglect remains high, and the percentage of women who received special treatment, 82.8 %, which still indicates problems in providing highly qualified specialized care [9].

Despite progress in the comprehensive treatment of BCD, distant metastases can develop in more than 30 % of patients with primary BCD, even at its early stages. Some authors explain this by the theory of stem tumor cells (STC), according to which cancer can arise and develop from a small part of the stem cells that can cause tumor growth. A number of studies indicate the possible role of STC in the formation of BCD resistance to treatment due to preservation of their viability after chemotherapy, radio- and/or hormone therapy [3, 6-8].

In 2008, B. Morrison et al. published a list of markers, the presence of which on the membranes of BCD cells allows them to be attributed to BCD stem cells. ALDH1+ and CD44+CD24 phenotypes have been found to be associated with an aggressive molecular subtype – basal-like BCD, and are more common in tumors with BRCA1 mutations. It has been shown that CD44 isoforms can be expressed differently in

different subgroups of BCD, and it has been suggested that the CD44 molecule may be part of a tumor progression program that leads to development of individual molecular subtypes [5, 12].

Today, scientists are actively studying the role of STC in tumor progression, studying the causes and mechanisms of their therapeutic resistance. Most authors dealing with the problem of heterogeneity of tumor cells from the standpoint of the concept of STC, conclude that higher radioresistance of STC compared to the rest of the mass of tumor cells, the reasons for which may be: the state of proliferative rest of STC, high efficiency in these cells, as well as hyperactivation of signaling pathways that ensure cell survival after radiation exposure [13, 15].

The presence of a correlation between the number of BCD stem cells in the primary tumor, the course of the disease and the efficacy of its treatment suggests that BCD STC play a key role in the biology of BCD, require further study and development of new treatments to eliminate these cells by effecting their cell cycle, membrane markers, changes in their microenvironment functions, etc. [11, 14].

The purpose of our work was to study the efficacy of neoadjuvant radiation therapy against the background of the radiomodifier tegafur in the complex treatment of patients with locally advanced primary inoperable stage III breast cancer, taking into account the molecular biological characteristics of the tumor.

Materials and methods. The National Cancer Institute monitored 157 patients with BCD aged 27 to 82 years with IIIA–IIIC stages of the disease, in which no positive effect was recorded after 6 courses of neoadjuvant polychemotherapy (PChT) based on anthracyclines and/or taxanes (AS, FAC, AT).

According to the objectives of the study, all patients were blindly randomized into two groups. In the main group (74 patients) a course of remote radiation therapy (RT) was carried out according to the radical program in the mode of classical fractionation against the background of daily intake of cytostatic fluoropyrimidine series drug. Tegafur was used at the dose of 750 mg/m² per day daily throughout the course of PT (dividing the daily dose into two doses) for radiomodification. In the comparison group (83 patients) remote PT in the mode of classical fractionation was only performed.

3D conformal PT was performed on a Clinac 2100 CD (Varian Medical Systems) linear electron accelerator model with integrated multi-petal collimator diaphragm Millenium 120, with built-in X-ray systems of portal imaging. The radiation effect on the breast was carried out using photon radiation with the energy of 6 MeV. The course of remote PT according to the radical program on the area of the breast was performed with a single total radiation dose (TRD) 2 Gy, to the total radiation dose (TRD) 60 Gy. The radiation dose was applied to the axillary, parasternal and supraclavicular LV areas up to 40–46 Gy.

The general characteristics of the patients included in the study are presented in table 1.

Table 1

Characteristics of patients included in the study

Index	Group of patients		p
	Main	Control	
Mean age, years (27–82)	56.24±1.38	53.37±1.13	0.8
Disease stage (NCCN)			
IIIA	35 (47.3±5.8)	43 (51.81±5.48)	$\chi^2=0.50$; p=0.78
IIIB	35 (47.3±5.8)	37 (44.58±5.46)	
IIIC	4 (5.41±2.63)	3 (3.61±2.05)	
Distribution by histological structure (ICD–O–3)			
Adenocarcinoma	72 (97.30±1.89)	82 (98.80±1.20)	$\chi^2=0.47$; p=0.49
Mucosal carcinoma	2 (2.70±1.89)	1 (1.20±1.20)	
Distribution by molecular subtype			
Luminal A	8 (10.81±3.61)	7 (8.43±3.05)	$\chi^2=1.43$; p=0.15
Luminal B Her 2-negative	38 (51.35±5.81)	44 (53.01±5.48)	
Luminal B Her 2-positive	5 (6.76±2.92)	8 (9.64±3.24)	
Her 2- positive	12 (16.22±4.28)	15 (18.07±4.22)	
Triple negative	11 (14.86±4.14)	14 (16.87±4.11)	

In the pathology department of the National Cancer Institute, all patients included in the study underwent pathomorphological and immunohistochemical (IHC) examination of biopsy and postoperative material.

Using the IHC method, in addition to the standard determination of the expression of estrogen receptors (ER), progesterone (PR), the Her2/neu gene and the proliferative index Ki-67, the expression of the CD44 marker on tumor cells was determined. The reaction was performed with monoclonal murine antibodies against the human CD44 receptor (Clone 156-3C11, DBS, USA) using the detection system En

Vision TMFLEX (Dako, Denmark) according to the manufacturer's instructions. Sections were stained with hematoxylin Gill.

Statistical processing of the obtained results included: calculation of primary statistical indices; identification of differences between groups on statistical grounds; establishing the correlation between variables using parametric and nonparametric correlation analysis. The Kaplan-Meier method was used to study survival. To compare the two survival curves in general, in addition to visual graphical analysis, we used statistical nonparametric criteria: Gehan-Wilcoxon (Breslau-Wilcoxon), Cox-Mantel, logarithmic-rank (lograng, log-rank) [1].

Results of the study and their discussion. The study included female patients. The age of patients ranged from 27 to 82 years. The groups were homogeneous in age ($\chi^2=2.32$; $p=0.80$) and at the stages of the main process ($\chi^2=0.50$; $p=0.78$). In the main group histological diagnosis of infiltrating breast adenocarcinoma 72 patients had (97.30–1.89) %, in the comparison group – 82 patients (98.80 – 1.20) %, mucosal carcinoma - in 2 patients of the main study group (2.70–1.89)% and in 1 – comparison groups (1.20–1.20) %. No significant differences in histological type of tumor between groups were found ($\chi^2=0.47$; $p=0.49$).

In the vast majority of patients there was a moderate degree of G2 malignancy, namely in 58 (78.38±4.79) % in the main group and in 64 (77.11±4.61 %) in the comparison group. Adenocarcinomas with a high degree of G3 malignancy in the main group were found in 16 patients (21.62±4.79) % and in 19 (22.89±4.61) % in the comparison group. Tumors with a low degree of malignancy were not recorded in both groups ($rS=0.015$; $p=0.85$). Thus, differences in the histological structure of tumors are not statistically significant.

Based on the assessment of IHC study of tumor tissue obtained by trepan biopsy, biological subtypes of BCD were identified before neoadjuvant treatment.

The division of patients into subtypes was carried out according to the following criteria:

– luminal (Lum) A: ER+/PR+/HER2/neu-, low (G1) or moderate (G2) degree of malignancy, Ki-67≤20 %;

– luminal B (HER2-negative): ER+and/or PR+/HER2/neu-, high degree of malignancy (G3), Ki-67>20 %;

– luminal B (HER2- positive): ER+/PR+/HER2 (3+); HER2+ hER2/neu overexpression (3+) or HER2 gene amplification (FISH), ER- / PR-;

– triple negative BCD: ER-/PR-, HER2-.

Both study groups of patients were homogeneous in immunohistochemical characteristics of tumors ($rS=0.03$; $p=0.63$). Luminal B and aggressive Her2+ and triple negative subtypes predominated in both the main and the comparison group.

The expression of CD44 in RGZ cells of patients of both groups was determined using the IHC method of research. CD44 expression was assessed by the severity of the membrane-cytoplasmic staining and the percentage of positive tumor cells: – response to 10 % of tumor cells;

“- / +” reaction of 10-50 % of tumor cells; “+/-” reaction of 50-90 % of tumor cells; “+” Reaction > 90 % of tumor cells.

When assessing the expression of CD44 in BCD cells of patients in both groups, there was a pronounced expression of this marker. In the analysis of the studied groups, significant differences in the presence of tumors with CD44 expression were not detected. Positive expression of CD44 was recorded in 49 (66.22 %) patients of the main group and in 47 (56.63 %) – comparison group, no expression of CD44 marker was detected in tumor cells of 25 (33.78 %) patients of the main group and in 36 (43.37 %) patients of the comparison group, ($rS=-0.09$; $p=0.22$) (fig. 1).

The conjugation tables confirmed the negative correlation of CD44+ expression with ER+ ($rS=0.15$; $p=0.05$), (OR=2.0; 1.29–2.72; $p<0.05$) and PR+ ($rS=0.18$; $p=0.02$), (OR=2.29; 1.57–2.99; $p<0.05$). Thus, we can conclude that in tumors with hormone-positive status, the expression of CD44+ is much less common. The correlation between the degree of G differentiation and the presence of the CD44 marker expression ($rS=0.21$; $p=0.009$), (OR=3.18; 2.27–4.07; $p<0.05$). Therefore, tumors with a higher degree of malignancy predominate among tumors with CD44 expression.

Subsequent analysis revealed that the presence of CD44 expression negatively affects the severity of pathomorphosis ($rS=0.21$; $p=0.01$), overall survival of patients ($rS=0.4$; $p<0.001$), (OR=8.79; 7.86 Subsequent analysis revealed that the presence of CD44 expression negatively affects the severity of pathomorphosis ($rS = -0.21$; $p=0.01$), overall survival of patients ($rS = -0.4$; $p<0.001$), (OR = 8.79; 7.86–9.72; $p<0.05$) and progression-free survival ($r=0.509$; $p<0.001$).

The effect of CD44 expression on the overall and improgressive survival of patients in both groups was analyzed. As a result of the analysis, the adverse effect of CD44+ expression level on BCD tumor cells on the overall ($p<0.001$) and non-progressive ($p=0.01$) survival of patients was proved.

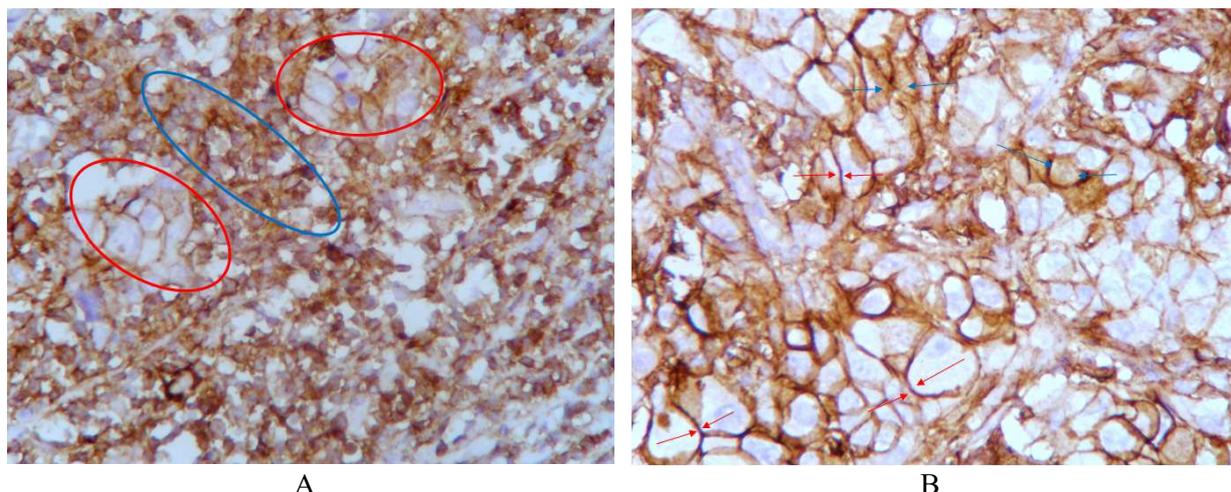


Fig. 1. CD44. Membrane-cytoplasmic staining. Photomicrograph. Staining with hematoxylin-eosin, ob. x40, oc. x10: A - positive reaction in tumor cells (red circle), positive reaction to lymphoid infiltrate (blue circle), expression +; B - between red arrows – membrane reaction, between blue arrows – cytoplasmic reaction, reaction >90 % of tumor cells, expression +.

The overall 5-year survival of patients with CD44 marker expression was 47.92 %, with negative expression – 83.61 % ($p<0.0001$). 5-year progression-free survival of patients with CD44 marker expression was 30.1 %, with negative expression – 77.05 % ($p=0.01$).

A comparison of the treatment efficacy in patients of both groups was performed, taking into account the expression of CD44. Among the patients of the main group, the expression of CD44 was detected in 49 women (66.22 ± 5.50 %), and in the comparison group – in 47 patients (56.63 ± 5.44 % ($p=0.22$)).

Response to treatment in patients of the main group: according to the criteria of RECIST 1.1 stabilization was observed in 12 patients (24.49 ± 6.14 %), partial regression - in 35 (71.43 ± 6.45 %), disease progression – in 2 (4.08 ± 2.83 %).

46 patients of the main group (93.88 ± 3.42 %) reached the operable state, 3 patients (6.12 ± 3.42 %) were not operated. In the analysis of the surgical material signs of pathomorphosis of the first degree were not detected; II degree pathomorphosis was recorded in 9 patients (18.37 ± 5.53 %); III – in 24 patients of the main group (48.98 ± 7.4 %); IV – in 11 (22.45 ± 5.96 %) and complete morphological response was achieved in 2 (4.08 ± 2.83 %) of patients. OCHZHPT in the main group of patients made 37.43 %.

In the comparison group, stabilization in response to treatment was recorded in 32 patients (68.09 ± 6.80 %), partial regression – in 14 (29.79 ± 6.67 %), progression – in 1 (2.13 ± 2.10 %). It was not possible to reach an operable state in 11 patients of this group (23.40 ± 6.18 %). In the analysis of surgical material pathomorphosis of the first degree was detected in 1 patient (2.13 ± 2.10 %); II degree was recorded in 19 patients (40.43 ± 7.16 %); III – in 17 (36.17 ± 7.01 %) of patients; IV degree – in 4 patients (8.51 ± 4.07 %) and no case of complete morphological response was recorded. OCHZHPT in the comparison group – 53.69 %.

As a result of the analysis, a reliable difference was obtained in the frequency of radical surgical interventions ($p=0.016$), the degree of regression ($p<0.001$), pathomorphosis ($p=0.03$) and OCHZHPT ($t=2.86$; $p=0.005$), which indicates the better efficacy of patients' treatment carried out according to the developed technique with use of PT against a radio modifier (tab. 2, fig. 2, tab. 3, fig. 3).

Table 2

Objective response to treatment in patients with locally advanced primary inoperable BCDwith CD44 expression

Regression degree	Groups of patients, n (%)		p
	main (n=49)	comparison (n=47)	
Partial regression	35 (71.43±6.45)	14 (29.79±6.67)	<0.001
Complete regression	–	–	–
Stabilization	12 (24.49±6.14)	32 (68.09±6.80)	<0.001
Progression	2 (4.08±2.83)	1 (2.13±2.10)	0.58

Therapeutic pathomorphosis in patients with locally advanced primary inoperable BCD with CD44 expression after neoadjuvant CPT

Pathomorphosis degree	Groups of patients, n (%)		p
	main (n=49)	comparison (n=47)	
I	–	1 (2.13±2.10)	–
II	9 (18.37±5.53)	19 (40.43±7.16)	0.017
III	24 (48.98±7.14)	17 (36.17±7.01)	0.20
IV	11 (22.45±5.96)	4 (8.51±4.07)	0.05
V	2 (4.08±2.83)	–	–

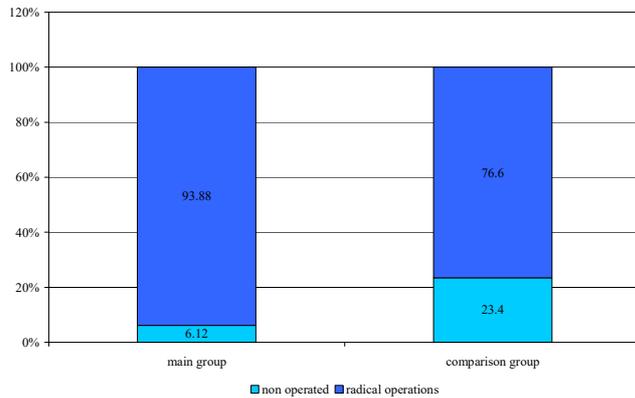


Fig. 2. Assessment of the frequency of radical surgery in patients with locally widespread primary inoperable BCD with CD44 expression.

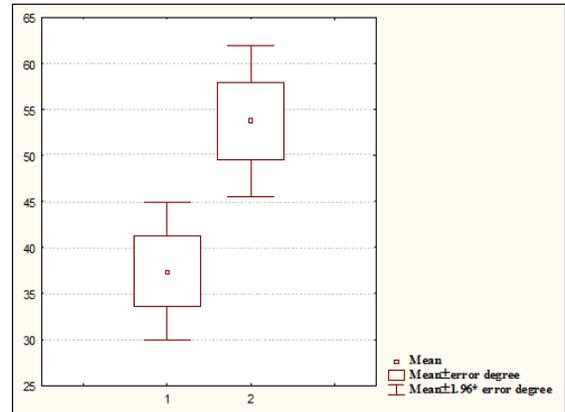


Fig. 3. Diagram of the VPVTT extent in patients with locally widespread primary inoperable BCD with CD44 expression after neoadjuvant CRT.

Assessing the 5-year overall survival (fig. 4A), we see that its rate in the main group was (59.76±7.70) %, and in the comparison group – (31.25±7.97) %. The median overall survival in the main group was not achieved, in the comparison group its rate was 42 months (p=0.01). 5-year non-progressive survival (fig. 4B) in the main group was (45.74±7.70)%, in the comparison group – (8.02±4.45) %. The median progressive survival in the main study group was by 36 months longer (in the main group it was 54 months, in the comparison group – 18 months, respectively).

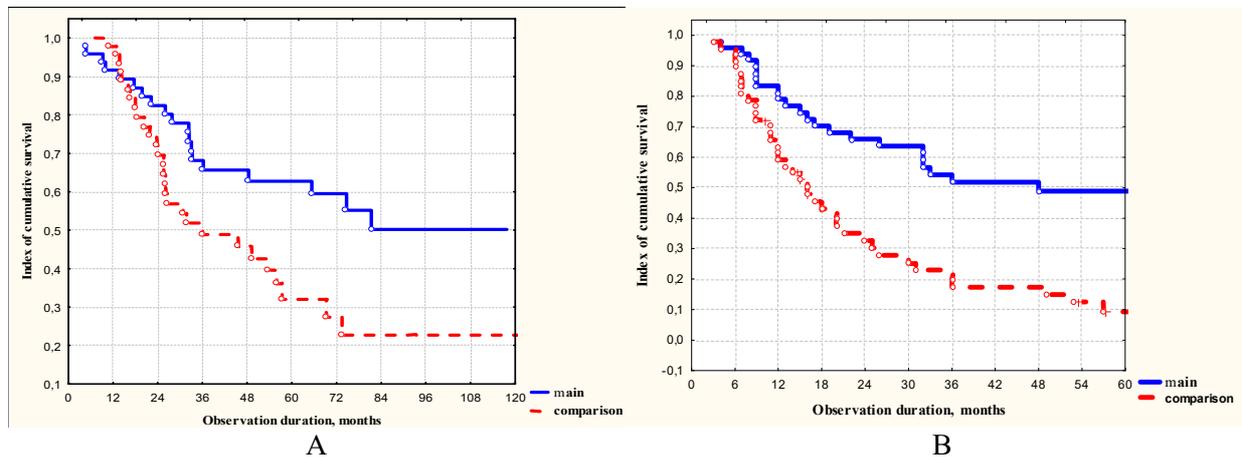


Fig. 4. 5-year survival of patients with locally advanced initially inoperable BCD with CD44 expression. Lograng criterion: A - total, p=0.01; B - non-progressive, p=0.0001.

Thus, the use of radiation treatment (RT) against the background of the radio modifier improved the 5-year overall survival rate by 28.51 % (p=0.01) and non-progression survival by 37.72 % (p<0.001).

The study confirmed the negative correlation of CD44+ expression with ER+(rS=–0.15; p=0.05), (OR=2.0; 1.29–2.72; p<0.05) and PR+ (rS=–0.18; p=0.02), (OR=2.29; 1.57–2.99; p<0.05). Thus, we can conclude that in tumors with hormone-positive status, the expression of CD44+ is much less common and more characteristic of aggressive forms of BCD.

The correlation was noted between the G differentiation degree and the presence of the CD44 marker expression (rS=0.21; p=0.009), (OR=3.18; 2.27–4.07; p<0.05). Therefore, tumors with a higher degree of malignancy predominate among tumors with CD44 expression.

Subsequent analysis revealed that the presence of CD44 expression negatively affects the severity of pathomorphosis ($rS=-0.21$; $p=0.01$), overall survival of patients ($rS=-0.4$; $p<0.001$), (OR=8.79; 7.86–9., 72; $p<0.05$) and progression-free survival ($r=-0.509$; $p<0.001$).

According to the results of the study, it can be stated that the presence of CD44+ expression in BCD tumor cells has an adverse effect on the overall ($p<0.001$) and progressive ($p=0.01$) survival of patients with locally advanced primary inoperable breast cancer. This correlates with current global studies suggesting that CD44 expression promotes tumor progression, which is characteristic of more aggressive molecular subtypes, and enhances therapeutic and especially radioresistance [5, 12].

Potential of radiation therapy using a radiomodifier improved the efficacy of comprehensive treatment of patients with locally advanced primary inoperable breast cancer, increased the percentage of partial regressions by 41.64 % ($p=0.02$), radically resectable cases – by 17.28 % ($p<0.001$), from pathomorphological response 4 by 4.08 % ($p=0.03$), to improve the 5-year overall survival rate by 28.51 % ($p=0.01$) and progression-free survival by 37.2 % ($p<0.001$).

Conclusions

1. The expression level of CD44+ has an adverse effect on the overall ($p<0.001$) and progressive ($p=0.01$) survival of patients with locally advanced initially inoperable breast cancer.

2. In the absence of tumor response to treatment and prolongation of the disease after systemic neoadjuvant chemotherapy in patients with CD44 expression, the use of radiation therapy against the background of radiomodifier can improve the efficacy of comprehensive treatment in patients with locally advanced primary inoperable breast cancer increasing the partial regression percentage by 41.64 % ($p=0.02$), radically resectable cases – by 17.28 % ($p<0.001$), the percentage of complete pathomorphological response – by 4.08 % ($p=0.03$).

3. The developed method of treatment significantly improves the indices of 5-year overall survival by 28.51 % ($p=0.01$) and non-progression survival by 37.72 % ($p<0.001$).

Prospects for further research are that the work opens new horizons for further study of molecular genetic markers to personalize approaches and improve treatment outcomes in patients with locally advanced breast cancer. The search for reliable predictive markers of sensitivity and resistance to therapy, as well as development of new techniques to enhance the tumor response to treatment and overcome resistance is the basis for further research to accumulate clinical material and obtain statistically reliable results.

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