

## Clinical-Morphological and Immunohistochemical Characteristics of Primary Disseminated Breast Cancer with Skeletal Bone Lesions

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**Annotation:** Primary disseminated breast cancer (PDBC) with skeletal metastases is one of the most aggressive forms of breast cancer, associated with an unfavorable prognosis and high mortality. Despite advancements in early diagnosis and treatment of breast cancer, the survival rate of patients with PDBC remains significantly low, especially in cases with bone metastases, which are observed in 60-70% of patients with metastatic breast cancer.

The article presents a modern approach to treating PDBC. According to the presented statistical data, on average, 10% of diagnosed breast cancer cases worldwide are PDBC (stage IV). In most cases, these are patients with stage T3-4N1-3M1 and metastases in regional lymph nodes. In primary disseminated breast cancer, metastases typically develop in the skeletal bones, lungs, liver, and several other organs. To date, standardized treatment protocols have not been developed, and various opinions are expressed regarding treatment strategies. The article presents the results of a study on clinical and morphological features and survival rates depending on these factors, as well as treatment methods and clinical recommendations for primary disseminated breast cancer and their outcomes, with significant attention paid to the biological features of the tumor.

**Keywords:** primary-disseminated breast cancer, bone metastases, cumulative survival rate, median survival rate, radical mastectomy, breast resection, chemotherapy, hormone therapy, radiation therapy.

**The aim of the study** is to analyze the clinical, morphological, and immunohistochemical characteristics of CRP with bone metastases to identify prognostic factors influencing treatment outcomes.

### **Introduction:**

Breast cancer (BS) is one of the most common malignant neoplasms (16.7%) in the world. If in the world (according to the WHO, 2018) about 18 million new cases of various forms of malignant neoplasms are registered annually, of which 2,03 million (11,3%) are SCC. Unfortunately, the number of patients with this disease is increasing every year, and according to WHO forecasts, by 2030, the number of registered patients may increase to 2.5 million. This is due to the fact that screening studies are widely conducted in many countries of the world (5)

In recent decades, there has been a significant improvement in the early diagnosis and treatment of breast cancer. However, despite the successes achieved in treating early stages of the disease, metastatic cancer, especially with bone damage, remains a serious clinical problem associated with high mortality rates.

Primary-disseminated breast cancer (PMDR) is characterized by metastases at the time of diagnosis, making it one of the most aggressive forms of the disease. In such patients, the prognosis is significantly worse, especially in cases of skeletal bone damage, which is found in 60-70% of patients

with metastatic CKD (Garcia et al., 2020). Bone metastases lead to serious complications such as pathological fractures, hypercalcemia, and severe pain, which worsen the quality of life of patients and limit treatment options (Lobo et al., 2019).

The importance of studying CRP with bone metastases is also due to the fact that this disease requires a multidisciplinary approach to treatment, including systemic therapy, radiological treatment, and palliative methods to improve the patient's condition. The survival rate of patients with Cerebral Palsy varies significantly depending on a number of factors, such as the histological structure of the tumor, the degree of its malignancy, and the expression of various immunohistochemical markers, including estrogen, progesterone, and HER2/neu receptors (Thornton et al., 2018).

According to some data, chemotherapy and hormonal therapy are the main treatment methods for advanced breast cancer, allowing for significantly extending the patient's life and improving its quality. In 10-25% of women with disseminated breast cancer, it is possible to achieve a complete response to the tumor with a long non-recurrent period. Anthraciclines or taxa are the most effective treatment regimen for line 1. In cases of hyperexpression of HER2/PE, the use of herceptin increases the effectiveness of treatment by 42-60%.

The relevance of this research is determined by the need for in-depth study of the clinical, morphological, and immunohistochemical characteristics of CPR, which will allow for a more accurate prediction of the outcome of the disease and optimize treatment approaches.

### **Materials and methods of research.**

We observed 128 patients with primary-disseminated breast cancer with skeletal bone damage who were treated from 2010 to 2023 at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Ministry of Health of the Republic of Uzbekistan. The patients' ages ranged from 23 to 76 years, averaging 49.4 years. Patients under 30 years old comprised 3 patients (2.3%), 30-40 years old - 13 (10.1%), 41-50 years old - 37 (28.9%), 51-60 years old - 41 (32%), 61-70 years old - 25 (19.5%) and over 70 years old - 9 (7%). The majority of patients (60.9%) were in the age group of 40-60 years.

The duration of the history ranged from 1 month to 5 years from the onset of the first symptoms of the disease. Of the 128 patients, 37 (28.9%) sought medical attention for up to 6 months, 41 (32%) for 6 months to 12 months, and 50 (39.1%) for more than 12 months.

Of the 128 patients, 5 (3.9%) had a history of breast pain, 52 (40.6%) had a history of pain and tumor. Of these, 21 (16.4%) had tumors, 39 (30.4%) had skeletal pain, 4 (3.1%) had chest pain, 6 (4.6%) had back pain, and 1 (0.7%) had frequent headaches and vision impairment.

Anamnestic data revealed that 26 (20.3%) patients had a burdened family history. Clinical examination revealed lesions of the right mammary gland in 59 (46.0%), the left mammary gland in 63 (49.2%), and both mammary glands in 6 (4.6%).

Of the 128 patients, 56 (43.7%) had tumor localization in the upper non-external segment, 29 (22.6%) in the upper internal segment, 22 (17.1%) in the central zone, 12 (9.3%) in the lower-external quadrant, 4 (3.1%) in the lower-internal quadrant, and 7 (3.9%) in the total breast area.

In 14 (10.9%) cases, there was hyperemia of the skin, in 25 (19.5%) cases - infiltration of the skin, in 3 (2.3%) - swelling, in 5 (3.9%) - ulceration of the skin, in 15 (11.7%) - symptom of the lemon peel, in 1 (0.7%) - symptom of the area, in 18 (14.0%) - symptom of invasion of the nipple, in 11 (8.5%) - tumor decay, in 2 (1.5%) - skin decay and ulceration and in 19 (14.8%) - infiltration and ul No skin changes were observed in 15 (11.6%) cases.

Clinical examination revealed that in 108 (84.3%) observations, the breast tumor was dense, in 6 (4.6%) - stony, in 5 (3.9%) - calcined, and in 9 (7.0%) - soft. Clinical examination revealed that 67 (52.1%) patients had a more mobile tumor, 42 (32.8%) had a less mobile tumor, 15 (11.7%) had a fixed tumor, 3 (2.3%) had a punctured tumor, and 1 (0.7%) had a single conglomerate.

Clinically, nodular forms were identified in 22 (17.1%) patients - 2 (1.5%) - rosette-like, in 77 (60.1%) - edematous-infiltrative, in 11 (8.5%) - decomposing tumor, in 1 (0.7%) - pancreatic form, in 13 (10.1%) - diffuse breast disease and in 2 (1.5%) - Pajet cancer.

Cytological examination revealed atypical cancer cells in 103 (80.41%) patients, malignant tumor cells in 20 (15.6%), some atypical cells in 2 (1.5%), and an inflammatory process in 3 (2.3%) patients.

The histological structure of the tumor in 16 (12.5%) patients consisted of in situ cancer, 89 (69.5%) - infiltrative carcinoma, 13 (10.1%) - infiltrative lobular cancer, 4 (3.1%) - tubular cancer, 4 (3.1%) - papillary cancer, 1 (0.7%) - adenokistotic cancer and 1 (0.7%) - Pejet cancer.

Analysis of malignancy levels showed that 56 (43.7%) patients had highly differentiated, 40 (31.2%) had moderately differentiated, 18 (14.0%) had low differentiated, and 14 (10.9%) had undifferentiated adenocarcinoma. Overall, 24.9% of patients had low-differentiated and undifferentiated malignancy levels.

Of the 128 patients, 75 (58.6%) underwent immunohistochemical examination. At the same time, 25 (33.3%) patients had luminal type A, 43 (57.3%) had luminal type B, and 7 (9.3%) had triple negative type. Meanwhile, 54 (72.0%) patients had positive estrogen receptors, while 44 (58.7%) patients had positive progesterone receptors. Ki-67 levels were up to 20% in 22 (17.1%) patients and 20% to 60% in 53 (82.9%) patients. Her-2 was positive in 29 (38.7%) patients and negative in 46 (61.3%).

The presented data indicates that the mitotic activity (Ki-67) was high in most patients.

Analysis of the localization of metastases revealed that in most cases - 81 (63.2%) metastases in the skeletal bones were multiple in nature, relatively rarely spinal column - 31 (24.2%), and rarely solitary skull - 3 (2.3%), pelvic - 6 (2.2%), shoulder - 1 (1.07%), hips - 4 (3.1%), peroneal - 1 (0.7%), and chest - 1 (0.7%).

All patients underwent comprehensive examination using clinical-laboratory, radiological, ultrasound, morphological (cytological, histological), immunohistochemical studies, as well as MRI, MSCT of the entire body and radioisotopic studies of skeletal bones.

Metastases in the skeletal bones of 98 (76.4%) patients were detected during radioisotopic examination (scanning) of the skeleton bones by the radioisotope Te99. In addition, metastases were detected during follow-up MRI in 7 (5.3%), MSCT in 6 (4.6%), X-ray in 1 (0.7%) and WHOLE BODY in 2 (1.5%) and PET/CT in 12 (9.3%). In 91 (71%) patients, metastases in skeletal bones were detected using several radiological research methods (MRI, MSCT).

Of the 128 patients, 117 (91.4%) were diagnosed with stage IV on admission to the oncology facility. Subsequently, during chemotherapy, hormone therapy, and radiation therapy for breast cancer in 9 (8.6%) patients, metastases were detected in the skeletal bones of stage I in 5 (3.9%) - stage II and in 4 (3.1%) - stage III.

A study of the distribution of breast cancer patients in the skeleton revealed that 12 (9.3%) patients had T1N1M1, 2 (1.5%) had T2N0M1, 1 (0.75%) had T2N2M1, 6 (4.6%) had T3N1M1, 30 (23.4%) had T2N1M1, 2 (1.5%) had T3N2M1, 3 (2.3%) had T3N3M1 and 50 (39.0%) had T4N2M1.

Of the 128 patients, 45 (35.2%) had a T1, T2 stage of primary lesions, while the remaining cases (64.8%) had a T3, T4 stage. It should be noted that in 128 patients with COPD, regional lymph node involvement was noted in 126 (98.5%) patients, respectively, N1, N2 and N3 (98 patients, 12 and 15).

Of the 128 patients with breast cancer, systemic chemotherapy was initiated using the CAF scheme (one-day scheme) in 23 (17.9%), (8-day scheme) - 62 (48.4%), AS - 21 (16.4%), dotatsaxel and admiramicin - 1 (0.7%), cisplatin + adriamicin + cyclophosphanthan - 12 (19.3%), paclitaxel and adriamicin - 2 (1.5%) and hertin - 2 (1.5%). Five (3.9%) patients underwent symptomatic treatment, ranging from 8 to 12 courses. Of the 128 patients, 34 (26.6%) received radiation therapy in combination with other methods in different regimens. Of these, 1 (0.75%) patient received preoperative, 4 (3.1%) patients - postoperative, 1 (0.75%) patient - preoperative and postoperative, 25

(19.5%) patients - postoperative radiation therapy and chemotherapy, 2 (1.5%) patients - non-adjuvant chemotherapy, after radiation therapy and chemotherapy, and 1 (0.75%) patient - non-adjuvant chemotherapy and postoperative radiation therapy.

Of the 128 patients, 64 (50%) underwent surgery on the primary lesion site. At the same time, 1 (0.75%) patient underwent Blochin radical resection, 2 (1.5%) patients underwent Veronesi radical suture resection, 2 (1.5%) patients underwent sectoral resection, 47 (36.6%) patients underwent palliative-radical mastectomy according to Madden, 3 (2.3%) patients underwent palliative-radical mastectomy according to Peiti, and 9 (7.0%) patients underwent palliative-simple mastectomy. The surgical intervention was performed after 8 to 12 courses of chemotherapy in case of tumor decay and bleeding.

## Results and discussion.

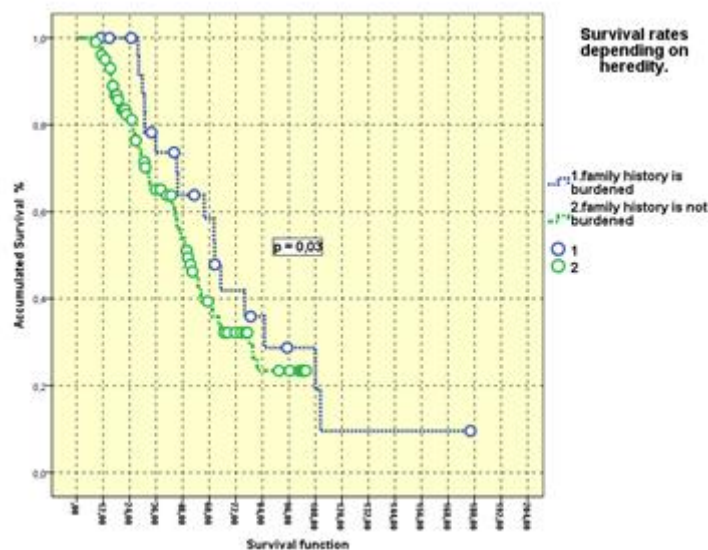
In our observations, patients with CKD were observed from 1 to 8 years. With a systemic approach to treatment, 89 (69.5%) patients showed tumor stabilization, 21 (16.4%) showed partial effect, 5 (3.9%) showed progression, and only 5 (3.9%) showed complete tumor regression. The remaining 8 (6.2%) patients underwent symptomatic treatment.

Of the 128 patients, 24 (18.7%) had tumor recurrence and 117 (91.4%) had further progression of the tumor process. Meanwhile, 15 (11.7%) metastases were subsequently detected in the liver, 2 (1.5%) in the brain, and 35 (27.3%) in the lungs.

Between 1 and 8 years of observation, 71 (55.5%) died and 57 (44.5%) lived with tumor metastases.

In addition, we conducted an analysis of survival rates depending on various clinical, morphological factors and treatment methods.

In our observations, out of 128 patients, 26 (20.3%) had a hereditary tumor process. In the history of survival rates depending on the hereditary severity of primary breast cancer, it was established that the cumulative survival rate in the presence of hereditary severity was -  $74.6 \pm 10.5\%$ , and in the absence of this trait -  $56.1 \pm 3.7\%$ , and the median survival rate was -  $62.5 \pm 5.0$  months and  $49.9 \pm 4.0$  months ( $\chi^2 = 2.93$ ,  $p \leq 0.02$ ). In this case, the 3-year and 5-year survival rates among patients with chronic non-alcoholic fatty liver disease with a hereditary severity of the tumor process were - 76.9% and 65.3%, and among patients with the opposite feature - 69.6% and 53.9%, respectively (Fig. 1).

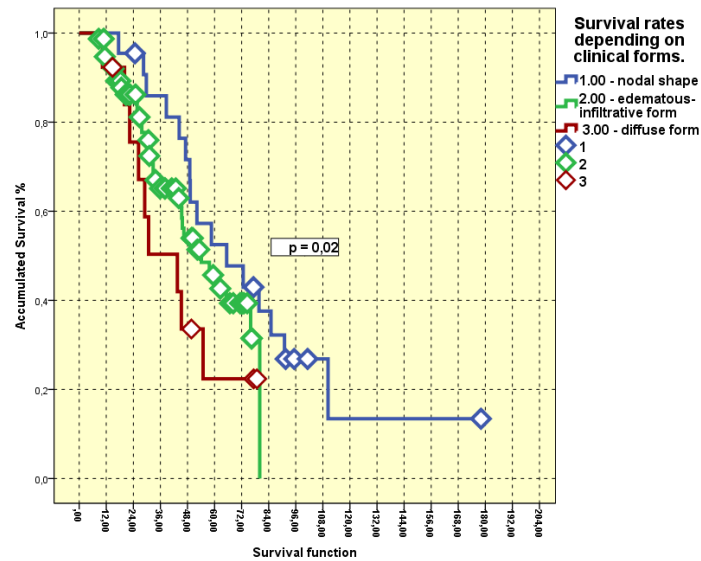


**Picture 1. Survival rates depending on heredity.**

A study of survival rates depending on the clinical form of primary-disseminated breast cancer revealed that cumulative survival in the nodular form of breast cancer was -  $78.7 \pm 11.5\%$ , in the edematous-infiltrative form -  $52.9 \pm 3.3\%$  and in the diffuse form -  $42.8 \pm 6.6\%$ . The median survival rate

in the clinical forms was  $65.3 \pm 15.6\%$  months,  $51.1 \pm 8.3\%$  months, and  $43.6 \pm 12.2\%$  months. ( $\chi^2 = 4.575$ ,  $p < 0.002$ ).

The 3-year and 5-year survival rates for the nodular form were - 86.3% and 54.5%, for the edematous-infiltrative form - 71.4% and 61.0%, and for the diffuse form - 53.8% and 30.8%, respectively (Fig. 2).



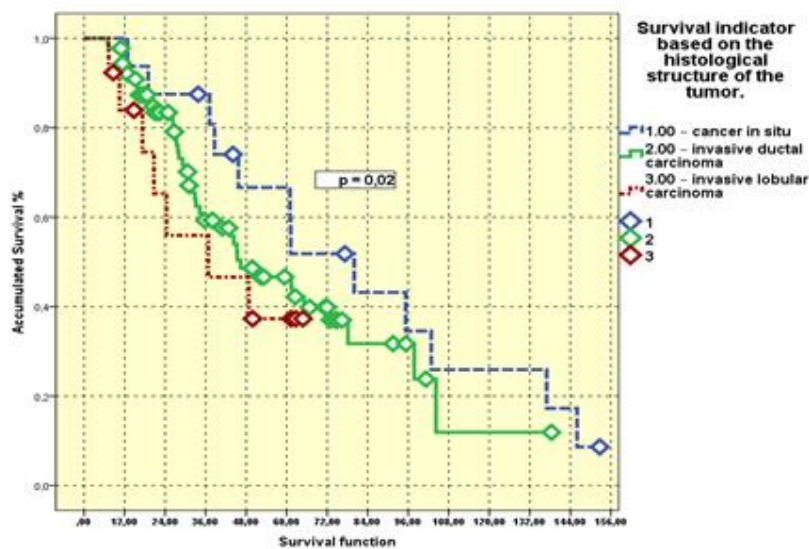
**Picture 2. Survival rates depending on clinical forms.**

In addition, we studied survival rates depending on the histological structure and immunohistochemical markers of the tumor.

Histological examination of 16 patients revealed in situ cancer of the primary focus of the disease. Meanwhile, the cumulative survival rate among patients with CKD was  $81.17 \pm 12.16\%$ , while in patients with infiltrative-ductal cancer it was  $62.36 \pm 6.17\%$ , and in patients with infiltrative-granular cancer it was  $39.41 \pm 6.64\%$ .

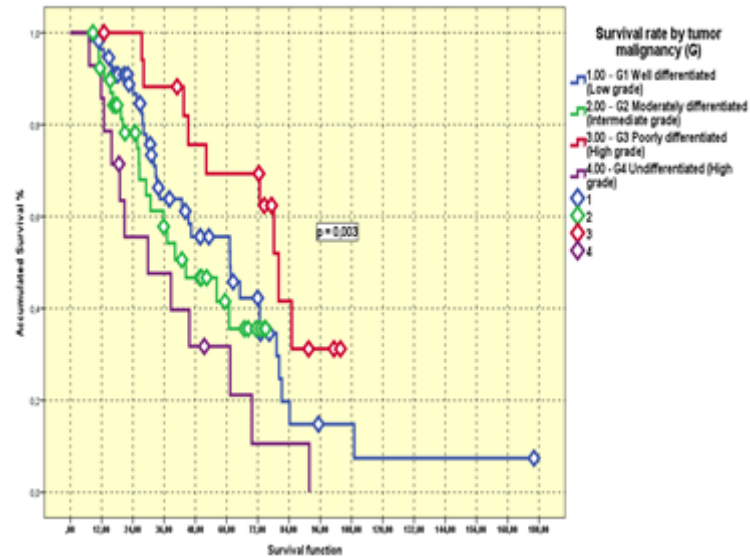
When analyzing the median, the median survival rate was  $80.0 \pm 16.10$  months,  $46.40 \pm 9.78$  months, and  $36.80 \pm 19.72$  months, respectively ( $\chi^2=3.318$ ,  $p<0.019$ ).

The 3-year and 5-year survival rates for these histological types were 87.5% and 46.2% respectively (Fig. 3).



**Picture 3. Survival rates depending on histological type of tumor.**

Analysis of survival rates depending on the histological degree of malignancy (G) revealed that in the highly differentiated form of breast cancer, cumulative survival was -  $63.93 \pm 7.8\%$ , moderately differentiated form -  $46.87 \pm 4.37\%$ , low-differentiated form (G3) -  $39.21 \pm 7.87\%$ , and the median survival rate was -  $61.33 \pm 11.25$  months,  $44.0 \pm 11.55$  months, and  $29.80 \pm 11.55$  months ( $\chi^2 = 12.14$ ,  $p < 0.003$ ).

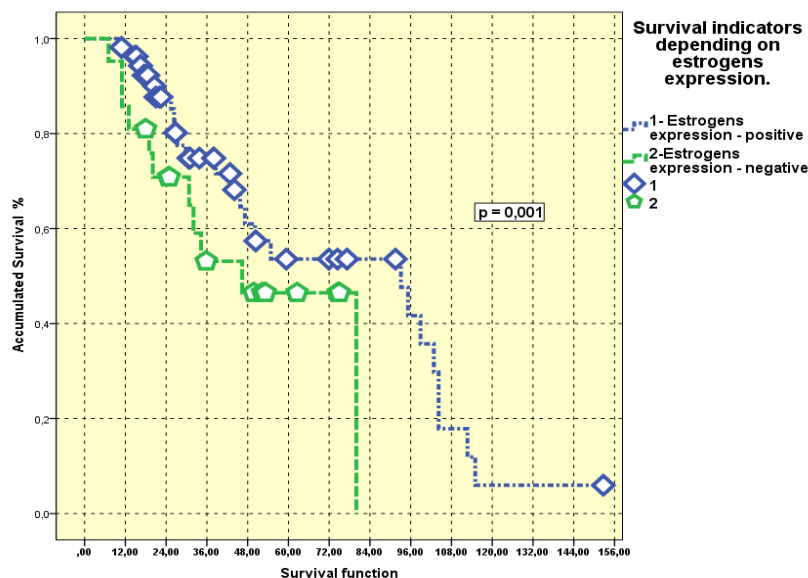


**Picture 4. Survival rates depending on histological type of tumor.**

The 3-year and 5-year survival rates were 69.7% and 64.3%, 65.0% and 55.0%, 88.8% and 72.3%, and 50.0% and 35.8% respectively (Figure 4).

An immunohistochemical study of estrogen receptor parameters revealed a positive response to this hormone in tumor cells, cumulative survival was  $73.73 \pm 7.15\%$ , and in the absence of this hormone receptor, it was  $49.98 \pm 7.10\%$ . The median survival rate was  $93.10 \pm 27.0$  months with positive estrogen receptors and  $46.40 \pm 9.68$  months without estrogen receptors ( $\chi^2 = 2.587$ ,  $p < 0.04$ ).

The 3-year and 5-year survival rates were 79.7% and 68.5% with a positive estrogen receptor, and 57.2% and 52.4% without estrogen receptor expression, respectively (Fig. 5).



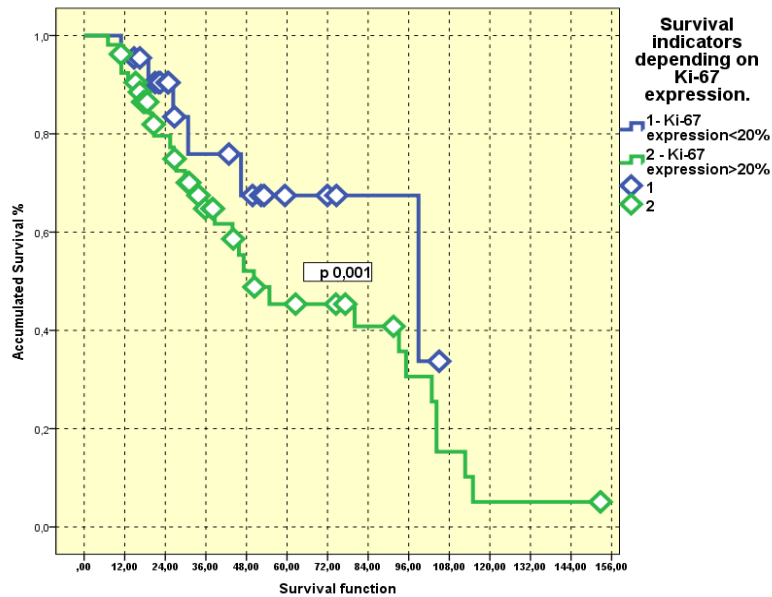
**Picture 5. Survival rates depending on Estrogens.**

Studying the mitotic activity of the tumor is of great importance in determining the treatment tactics and prognosis of the disease.

In our studies, the activity indicators (Ki-67) were determined by the amount of expression in breast tumors and were conventionally divided into two groups up to 20% and more (20-60%).

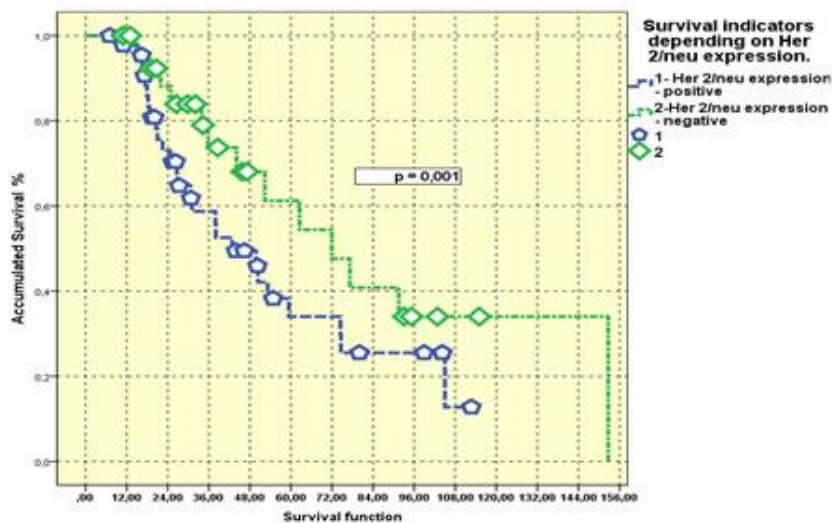
Of the 75 patients, 22 (29.33%) had Ki-67 expression up to 20% and 53 (70.67%) had more than 20%. Analysis showed that cumulative survival at expression up to 20% was -  $78.30 \pm 9.05\%$ , and at  $>20\%$  -  $50.20 \pm 19.43$  months. ( $x_2 = 1.560$ ,  $p < 0.001$ ).

Three-year and five-year survival rates with expression  $<20\%$  were 81.8% and 77.3%, respectively, with  $>20\%$  - 69.8% and 58.3% (Fig. 6).



**Picture 6. Survival rates depending on Ki-67 expression.**

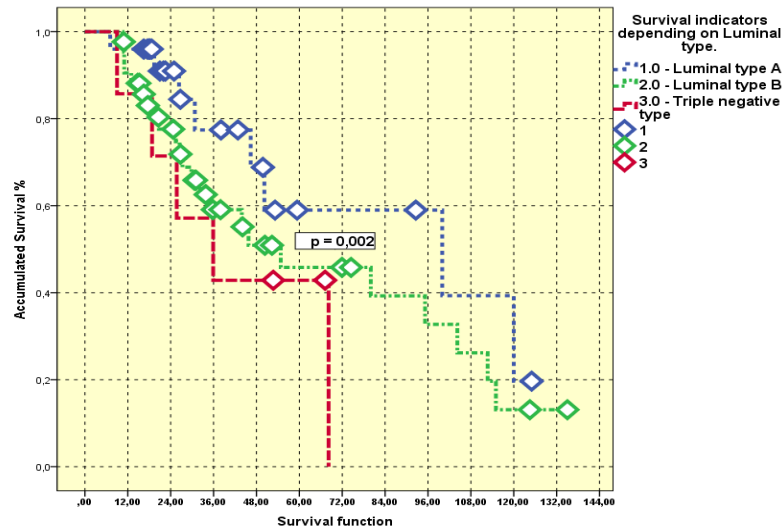
Analysis of survival rates revealed that with high HER 2/neu expression, cumulative survival was  $7.97 \pm 9.94\%$ , while with negative expression it was  $67.73 \pm 7.31\%$ . But the median survival rate was very different. With positive indicators, it was  $93.10 \pm 38.44$  months, and without expression -  $80.0 \pm 23.97$  months.



**Picture 7. Survival rates depending on Her2/neu expression.**

The 3-year and 5-year survival rates corresponded to 68.9% and 58.7% with positive indicators and 76.1% and 67.3% with negative indicators (Fig. 7).

Analysis of survival rates in patients with primary-disseminated breast cancer showed that in luminal subtype A, cumulative survival rates were significantly higher -  $81.89 \pm 11.45\%$ , compared to other subtypes - luminal B -  $66.07 \pm 8.2$  and triple-negative type -  $42.0 \pm 10.08\%$ . Accordingly, the median survival rate was high in luminal A subtype -  $100.0 \pm 46.93$  months, while in other subtypes -  $54.80 \pm 21.40$  months and  $3590, \pm 13.355$  months, respectively ( $\chi^2 = 3.084$ ,  $p < 0.04$ ).



**Picture 8. Survival rates depending on Luminal type.**

The 3-year and 5-year survival rates were 84.0% and 76.0%, 65.1% and 58.1%, 71.5% and 28.6%, respectively (Fig. 8).

**Conclusions:** Thus, the results of the analysis showed that in case of primary-disseminated breast cancer with skeletal bone metastases, cumulative and median survival rates, prognosis of the disease were significantly influenced by clinical and morphological features, such as the hereditary severity of the tumor, clinical forms, histological structure and its malignancy level, Ki-67 and HER 2/neu indicators, and the luminal type of tumor. This should be taken into account when determining treatment tactics for primary breast cancer.

### Discussion:

Primary-disseminated breast cancer (PMDR) with skeletal bone metastases is a complex clinical problem requiring individualized treatment and prognostic evaluation. Our study identified important clinical-morphological and immunohistochemical factors that play a key role in predicting outcomes in this category of patients. These data are consistent with the results of international studies, which emphasize the importance of comprehensive assessment of the tumor process.

One of the main factors influencing the prognosis is the histological structure of the tumor and its malignancy. In our research, as in the work of Miller and co-authors. (2017) showed that patients with low-differentiated tumor forms exhibit a more aggressive course of the disease and significantly lower survival rates compared to patients with high-differentiated tumors. We found that 24.9% of patients had a low level of differentiation, which correlated with worse prognosis. According to Elston and Ellis (2018), the level of tumor differentiation is one of the most significant prognostic markers, and its significance should be taken into account when determining treatment tactics.

Another important aspect is the immunohistochemical profile of the tumor. As our research and data by Thornton and co-authors have shown. (2018), Ki-67 proliferation marker expression is an indicator of tumor growth aggression. In our study, Ki-67 levels exceeded 20% in 82.9% of patients, indicating



high proliferative activity and an unfavorable prognosis. This agrees with Goldhirsch and co-authors' work. (2017) showed a correlation between high Ki-67 levels and rapid disease progression, especially in patients with triple-negative breast cancer.

The expression of hormonal receptors, particularly estrogen (ER) and progesterone receptors (PR), also plays an important role in the prognosis and treatment of patients with CVD. In our study, 72% of patients exhibited positive ER expression, which correlated with better survival rates, as in Harris and co-authors' studies. (2019), where patients with positive hormonal receptors showed better response to hormone therapy and had a longer period of remission. Positive ER and PR expression confirms the possibility of using anti-hormonal therapy, which improves long-term treatment outcomes, especially in patients with luminal A subtype cancer, which demonstrated the highest survival rates.

The expression of HER2/neu deserves special attention. In our study, 38.7% of patients had a positive HER2 expression, which agrees with Smith and co-authors. (2020), where it is also noted that a positive HER2 status is associated with a more aggressive course of the disease, however, the use of targeted therapy, such as trastuzumab (Herceptin), significantly improves the prognosis in this group of patients. Our data shows that patients with high HER2 expression, despite the more aggressive nature of the disease, have the opportunity to receive more effective treatment, which is confirmed by the best survival rates in this group when using targeted drugs.

An important aspect of our research was the study of skeletal bone metastatic lesions, which is a characteristic feature of CVD. As our data and research shows, Garcia and co-authors. (2020), bone metastases significantly worsen the prognosis and require special attention when choosing treatment regimens. In our study, 76.4% of patients had multiple metastases in the bone, which highlights the high aggressiveness of CPR. Lobo and colleagues. (2019) also emphasize that the presence of bone metastases is associated with a high risk of pathological fractures and hypercalcemia, which requires the appointment of bisphosphonates or denosumab in complex therapy to prevent complications.

Thus, the results of our study confirm the importance of a multifactorial approach to the treatment of primarily disseminated breast cancer. The prognosis and treatment strategy depend on the histological structure of the tumor, the degree of differentiation, immunohistochemical indicators such as Ki-67, ER, PR, and HER2/neu, as well as the presence of metastases in the bones. These factors should be taken into account when developing individualized treatment regimens and assessing prognosis in patients with PDBC.

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