MONITORING AND PERSONALIZATION IN TREATMENT OF BREAST CANCER PATIENTS WITH METASTATIC BONE LESIONS

Volodymyr Konovalenko

Oleg Drobovat
Bogomolets National Medical University
13 Shevchenko blvd., Kyiv, Ukraine, 01601

Nikolai Ternovsky

Sergii Konovalenko
servlakon@ukr.net

Oksana Garashchenko
State Organization Kyiv City Oncology Center
69 Verkhovynna str., Kyiv, Ukraine, 03115

1R. E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology,
National Academy of Sciences of Ukraine
45 Vasylivska str., Kyiv, Ukraine, 03022

Abstract

The aim. To increase the efficiency of treatment of BC patients with metastatic lesions of long tubular bones by using, Multidetector computed tomography (MDCT) and bone marrow markers for diagnostics and monitoring the clinical course of the oncologic process, accompanied by surgical intervention with endoprosthetics along with the treatment of polymorbid pathology in a specific patient.

Materials and methods. Authors provide systemic personification including visualization of the tumor site and its vascularization; printing out the 3D model; surgical planning, including optimal surgical access to the tumor site considering the volume and topographic and anatomical location and dissemination of the tumor, the convenience of intraoperative tasks (removal of the tumor, bone grafting or endoprosthetics), preoperative planning of bone resection lines with maximum preservation of intact bone tissue.

Results. Personalization of the treatment of breast cancer patients with metastatic bone lesions contributes to a significant reduction in postoperative complications of endoprosthetic replacement of large joints (up to 15.2 %) and increases the overall three-year survival rate (up to 40.6 %), as well as significantly improves their quality of life.

Conclusions. The personalization of treatment of patients with tumor lesions of the skeletons contributes to a significant decrease in the indicator of postoperative complications of endoprosthetics of great joints and to an increase in the total three-year survival rate, as well as to the improvement of the quality of life after the conducted treatment.

Keywords: breast cancer, bone metastases, bone resorption, osteogenesis, endoprosthetics, personalized treatment.

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1. Introduction

Breast cancer (BC) is the most common malignancy and the leading cause of cancer deaths among women worldwide [1, 2]. In the United States, the number of new cases and deaths as of 2020 was 276,480 and 42,170, respectively. In Europe, despite the increase in morbidity recorded in recent decades, the mortality rate was assumed to fall from 17.9/100,000 in 2002 to 13.4/100,000 in 2020, but these assumptions have not been confirmed [3, 4]. According to the National Cancer Registry of Ukraine, more than 15,000 women are diagnosed with breast cancer; the rate of 5-year overall survival in Ukraine is 60.6 % and varies from 47.7 % to 72.2 % [5, 6].

In a systematic analysis of the results of the treatment of cancer patients in large clinical samples, it was found that cancer patients require not only removing the primary tumor and
restoration of organ function, but also comprehensive monitoring of the quality of life with its possible deterioration in the presence of residual tumor disease, most notably tumor bone lesions [7, 8].

Bone metastases (BM) in cancer are an urgent clinical problem due to the complication of clinical course of the disease. Moreover, BM significantly impairs the quality of life and decreases the survival rate of patients with cancer [9, 10]. The research data suggest that bones are fertile ground for developing of metastases through the «vicious circle» of resorption/formation of bones and tumor growth [11, 12].

Currently, the principal methods for diagnosing the spread of a solid tumor on the skeletal system are plain radiography of the pain area, osteoscintigraphy with labeled 99mTe-phosphates, which has low specificity; computed tomography (CT), single-photon emission computed tomography in combination with CT (SPECT-CT), which includes functional and anatomical methods for assessing the condition of bone tissue and significantly streamlines the interpretation of pathological changes in the bones [13, 14].

An important factor in the clinical course of cancer is the presence of polymorbid pathology in cancer patients (several synchronously occurring diseases related or unrelated genetically or pathogenetically). Today, medicine is gradually moving from the era of «one chronic disease» to the era of «polymorbid medicine» [15, 16].

Malignant skeleton lesions have developed a pathological vascularized periphery. On the borders of the tumor, a vascular margin differs significantly from the surrounding healthy tissues, which are why the image of malignant neovascularization by perfusion indices allows identifying its margins. There is an acknowledged opinion [17, 18] that a high level of vascularization and perfusion could determine the metastatic potential of the tumor. Functional characteristics of the vascular system and perfusion have long attracted attention as markers of prognosis of tumor progression.

Personalization of treatment is one of the most actual problems of current medical practice. In a loose sense, personalization is understood as an individual assessment of the results of clinical examination and laboratory tests of each individual patient [19, 20].

The problem of monitoring the treatment of BC patients after per-protocol complex therapy according to national standards of one or another country remains relevant throughout the life of the treated patient. Resulting from the progression of residual tumor disease, pathological changes occur in various organs and systems of the patient’s body, which cause a significant deterioration in their quality of life and organ function leading to general disorders and pain, and in the case of spinal cord and brain damage – to paralysis and loss of consciousness [20, 21].

The need for monitoring the state of patients after special treatment is advocated by many researchers in the field of medicine and biology. The authors suggest the creation and functioning of interdisciplinary treatment teams including oncologists, biologists, radiologists, physicists, chemists, and others for the prevention and immediate detection of pathological changes in the body of the treated patient to prevent the development of clinical complications of the tumor process and to contribute to the preservation of the good quality of life, which is significantly impaired when the oncologic disease spreads to the bone system [22].

Similar to other malignant epithelial tumors, primary breast tumors could influence the metastatic process from the earliest stages of the disease. On the one hand, BC cells undergo epithelial-mesenchymal transition (EMT) to activate their migratory capacity and invasiveness, acquiring mesenchymal features (spindle-shaped; loss of intercellular connection; accumulation of N-cadherin, vimentin, fibronectin) or epithelial features (polarity of cells, tight cell-cell interaction, accumulation of cytokeratins).

In the majority of patients with breast cancer, malignant cells can pre-affect the colonization of the skeleton, which leads to the formation of bone metastases. In fact, while breast cancer cells undergo EMT to gain both migration and invasiveness, they also organize premetastatic niches, releasing cytokines, growth factors, and exosomes involving myeloid cells from the bone marrow.

Therefore, after the invasion into the surrounding tissues, BC cells invade the blood and lymphatic vessels to reach distant anatomical areas, to which they are attracted by the expression of specific receptors of chemokines and other molecules that are involved in the processes of bone metabolism. After their extravasation, BC cells could settle in the bone microenvironment,
competing with hemopoietic stem cells for niche control. On the other hand, primary BC organizes preparation of pre-metastatic niche by recruitment of myeloid cells from the bone marrow due to the release of cytokines, growth factors, and exosomes, i.e. vesicles of tumor cells that contain proteins, small fragments of nucleic acids, and other soluble factors [23, 24].

Despite the constant improvement of treatment methods, nowadays, the rate of breast cancer metastasis is 75 %. Therefore, monitoring the course of tumor disease during the life of patients with possible tissue damage is an actual problem of clinical oncology, both in terms of survival rate and the quality of life of treated patients [25, 26].

The aim of the study. To increase the efficiency of treatment of BC patients with metastatic lesions of long tubular bones by using, Multidetector computed tomography (MDCT) and bone marrow markers for diagnostics and monitoring the clinical course of the oncologic process, accompanied by surgical intervention with endoprosthetics along with the treatment of polymorbid pathology in a specific patient.

2. Materials and methods

We propose a systemic personification including visualization of the tumor site and its vascularization; printing out the 3D model; surgical planning, including optimal surgical access to the tumor site considering the volume and topographic and anatomical location and dissemination of the tumor, the convenience of intraoperative tasks (removal of the tumor, bone grafting or endoprosthetics), preoperative planning of bone resection lines with maximum preservation of intact bone tissue. It is also important to determine the phenotypic characteristics of the patient – the presence of cancer markers, biological and radiological markers of skeletal mineralization, bone metabolism, and reparative osteogenesis. A rather important factor is medication treatment depending on the concomitant pathology, which significantly impacts the approach to the treatment of the underlying disease (if the patient has concomitant diseases, it is necessary to use drugs with a wide range of pharmacological activity, effective against cancer and polymorbid diseases).

Printing out of 3D models contribute to rational planning of the surgical intervention scope, as the models anatomically correspond to the prototype in all dimensions: length of the arterial segment, caliber, and thickness of the vessel wall, accurately correspond to the structure of the organs of a particular patient, taking into account the peculiarities of the structure and syntopia of the surrounding organs which are unique to the patient. Visualized 3D models of tumor-affected bones are shown in Fig. 1, 2.

Clinical, radiological, and laboratory methods of biological fluids’ examination, pathological and statistical studies were used for diagnostics of metastatic bone affection. We studied the volume of blood perfusion in the area of the localization of the pathological lesion by multidetector computed tomography (MDCT), the content of markers of bone resorption and osteogenesis in blood and urine of the patients, and indicators of the overall survival and quality of life of the patients after treatment.

Statistical processing of the quantitative indicators was performed using nonparametric Mann-Whitney and Wilcoxon criteria, using variation statistical methods with «Statgraphics» version 3.0 (USA) and «Microsoft Excel» version 5.0 (USA). Changes at \( p < 0.05 \) were considered valid [27].

All patients undergo multidetector computed tomography (MDCT) to detect changes in blood flow in the area of pain localization and to determine the extent of bone damage. The baseline level of markers of bone resorption and osteogenesis is determined. Structural and functional changes caused by polymorbidity are diagnosed.

Biochemical markers of bone resorption (C-terminal telopeptide – CTT, deoxypyrididoline – DPD, tartrate-resistant acid phosphatase 5b – TRACP-5b) and osteosynthesis (bone alkaline phosphatase – BAP) and osteocalcin – OC were studied.

The concentration of CTT (ng/ml), and the activity of TRAP-5b (U/l), Dkk-1 (ng/ml), BAP (U/l), and osteocalcin (µg/l) in blood serum were determined by the appropriate test-systems: SerumCrossLaps (Osteometer), «Bone TRAP» (IDS), «Metra BAP» (QuidelCor.), Human Dkk-1 (AssayDesigns) and Osteocalcin «ELISA» (Nordicbioscience).
Determination of DPD in urine was performed by the kit «Metra DPD EIA Kit» (QuidelCor.). The following levels were taken as normal values of bone metabolism markers: CTT < 0.8 ng/ml, DPD < 8 nmol/mol of creatinine, TRAP-5b < 4.2 U/l, BAP < 45 U/l, osteocalcin < 11 µg/l.

Blood perfusion is pumping at the arterial inlet, passing through the vascular tree of the whole volume and circulation at the venous outlet. The main perfusion indices that are used for indication of the margins of femoral bone (FB) tumor are as follows: volumetric blood flow rate (VBFR) in ml/min/100 g, volumetric capillary blood flow rate (VCBFR) in ml/min/100 g, blood volume (BV) in ml/100 g, transit time (TT) in seconds that are determined by «accumulation-washout» curve, which could be registered by any transit indicator impulse. In MDCT-perfusion, this registration is conducted after the start of bolus X-ray contrast therapy (50 ml of X-ray contrast agent is injected automatically into the interstitial vein at a rate of 4 ml/s) by recording 300–400 digitized pixel scans of the volume of interest within one second.

In the process of post-processing of the acquired data we used Perfusion II program packages to obtain images of VBFR, BV, TT, graphs of the dependence of the X-ray intensity of arterial blood, venous blood, and tumor tissue on the time.

Methods of treatment of metastatic bone lesions included surgical intervention in the form of endoprosthetics or metal cement osteosynthesis with Biomin coating of endoprosthesis stem, depending on the local spread of the process and the degree of bone damage. The therapy also included the use of bisphosphonate Mebifon (disodium salt of methylenebisphosphonic acid: $\text{CH}_4\text{Na}_2\text{O}_6\text{P}_2\text{H}_2\text{O}$) and neuropeptide Dalargin in combination with drugs for treating polymorbid pathology present in a particular patient.

Mebifon has a strong antitumor effect and the ability to suppress the advanced tumor process. The drug combines antitumor action and suppression of bone destruction with the ability to correct
the oncogenic effects on bone tissue. Unlike cytostatics, bisphosphonates do not have a negative effect on the blood circulation system. The advantageous addition to their pharmacodynamics is the presence of a pronounced analgesic and certain antipyretic effects. Due to these properties, anti-recurrence, antimetastatic effects, and increased osteointegration of the implant is ensured. The degree of clinical effectiveness of Mebifon can be compared with clodronate. Both drugs work in close molar concentrations, their single dose is 300 mg daily five times intravenously, a total of 1500 mg. With this treatment regimen in patients with breast cancer with bone metastases in the studies reduced pain after a course of Mebifon in 72.6 versus 71.4 % of patients receiving clodronate. At the same time, the results of comparing the ability of both drugs to form complexes with calcium ions in vitro by the polarographic method showed greater tropism to these clodronate ions [28]. Therefore, the clinic recommends a slow intravenous administration of clodronate for 2–3 hours to prevent the formation of a large number of insoluble complexes and their negative effects on the kidneys. Mebifon can be administered in the same way in 30–40 minutes, which is less traumatic for the patient and more convenient for medical staff. Mebifon differs from the known and widely used BF (clodronate, pamidronate and bondronate) in its cytotoxic activity against tumors. The drug, like zolendronic acid, has high antitumor activity. In an experiment on 11 tumor strains, Mebifon caused inhibition of tumor growth by 70–90 % of patients receiving clodronate. These data were confirmed in phases I–II of clinical trials in patients with disseminated breast cancer (reduction of affected lymph nodes, fluid accumulation in metastatic pleurisy; in some patients there was a partial regression of metastatic foci in the liver) [29, 30].

Mebifon was used 2 days before and 3 days after surgery for 3 days in the standard dose. The choice of Dalargin neuropeptide use is conditioned by its multifunctionality and practically total absence of adverse effects, which are characteristic for all neuropeptides. Dalargin, like leynenkephalin, is a relatively selective ligand of delta-type opiate receptors. The selectivity of its action to a certain type of receptor depends on the dose. It appears only in small concentrations. Dalargin exhibits antihypoxic, antiischemic, immunomodulatory, antioxidant, organoprotective effects [31]. Experimental studies have shown that dalargin at a dose of 100 μg/kg exhibited an antitumor effect on models of transplanted tumors – Ehrlich’s ascites carcinoma, Pliss lymphosarcoma. The ability of dalargin to positively modify the radiosensitivity of cells was also found in patients with inoperable rectal cancer at a dose of 2 mg per day. An increase in the radio resistance of normal body tissues, a decrease in vegetative and local reactions to irradiation were noted [32].

Dalargin at a dose of 1 mg intravenously for 10 days by 5–6 months increased the duration of the relapse-free period in patients 12–14 months after radiation treatment of malignant tumors of the upper respiratory tract [33].

After intravenous administration in the body there is a quick breakdown into amino acids. Dalargin was administered on the second day in the standard dose for 10 days. Three-year overall survival rates were estimated using Kaplan-Meier method. The reliability of differences in the obtained indices was evaluated by the Log-rank criterion. The differences at \( P < 0.05 \) were considered statistically valid.

Long-term treatment outcomes were evaluated within the framework of the following classifications and systems:

– clinical and radiological treatment results according to ISOLS system;
– functional treatment efficacy in the distant period according to the system of evaluation of the function of the coxofemoral/knee joints according to Harris;
– the quality of life of patients with bone tumors according to the EORTC QLQC30 assessment (scale from 0 to 4), based on the WHO recommendations;
– causes of complications in the area of the implanted endoprosthesis that required the repeated surgical interventions, identified as periprosthetic, mechanical, and oncological according to a modified classification.

All complications were divided into 5 types according to their severity: Type I – complications of soft tissues (tendon rupture or fracture of wound edges) as well as cases of paraprosthetic fractures; Type II – aseptic instability of endoprosthesis; Type III – the destruction of endoprosthesis construction; Type IV – infectious complications; Type V – recurrence of the tumor.
The study included 192 patients aged 27–82 years, including 114 BC patients with metastatic lesions of the skeleton; the observation period was from 2001 to 2020. Of the 114 patients with skeletal metastases, the following biological subtypes of breast cancer were diagnosed: «luminal A» – 57, «luminal B» – 10, «HER2+» – 11, «triple negatives» – 36. During the course of the disease, depending on the biotype of the cancer, clinical presentation, determination of drug sensitivity, the patients received treatment according to internationally accepted guidelines: chemotherapy (according to CMF, FAC, TC, AC or a combination), endocrine therapy (tamoxifen, anostrozole, exemestane also in combination with chemotherapy), targeted therapy (trastuzumab). The authors confirm that this work was approved by the commission on bioethics of R. E. Kavetsky IEPOR NAS of Ukraine, record No. 3111/2003 and during the study all the necessary ethical standards were met in accordance with the guidelines of Declaration of Helsinki. Informed consent was obtained from all patients for inclusion in the study.

Taking into account the specificity of the clinical course of the tumor process, in the main group of patients, the dynamics of radiological changes in the skeleton and biological parameters of bone tissue were recorded once every three months.

The group of patients who underwent surgical treatment after detection of a femoral lesion was formed as follows: a single metastasis, threat or presence of a pathological fracture, informed consent of the patient to the proposed surgical intervention. The presence of metastases in other organs was not a contraindication for surgical intervention in case of bone fractures.

The control group (historical control) is patients who were treated in the clinic of the institute without using 3D modelling of pathological changes in the bone and without the use of Mebiphon and Dalargin.

To study the long-term results of treatment according to the indicators of overall survival, operated limb function, and quality of life of the treated patients two groups of patients were formed: the study group included 57 patients who were treated according to the methodology developed by the authors; the control group consisted of 57 patients who received treatment without surgical intervention – i.e., immobilization of the limb, anesthetics, radiation, and polychemotherapy. The control group is fully comparable with the study group by age and biological subtypes of BC.

To study the baseline status and dynamics of changes in the concentration of bone tissue metabolism markers, three control groups were formed, consisting of 37 patients with osteoporosis, 16 patients with benign skeletal tumors, and 25 patients with primary malignant skeletal tumors.

3. Results

When analyzing the results of CTT determination in the blood of patients with bone metastases a higher marker concentration was detected, compared with patients with primary malignant tumors of the bone, as evidenced by both median (0.92 and 0.41 ng/ml) and average values (1.12 and 0.43 ng/ml) of osteolysis marker, at that the found differences were valid \((P = 0.000001)\). At that, the maximum levels of CTT for the patients of the analyzed groups were significantly higher than the normal value (4.6 times for metastatic skeletal lesions and 1.5 times for no metastases). The observed excess of medians in both groups of patients with malignant skeletal lesions of the lower limbs compared with the control value is also valid \((P = 0.000001; \ p = 0.004)\). In the patients of the analyzed groups, the maximum DPD levels exceeded the corresponding indicator of the control group by 2.5 times in case of metastatic damage and 1.4 times – without metastases. Median DPD in patients with secondary tumor lesions of the lower limbs compared to the control group and patients with osteoporosis was approximately 1.2 times higher, the observed changes in the marker were valid \((P = 0.002 \ \text{and} \ \ p = 0.01, \ \text{respectively})\).

When analyzing the results of TRAP-5b activity determination in the blood of patients with bone metastatic lesions, it was found that their activity was increased compared with patients with primary malignant bone tumors, the difference in TRAP-5b medians (6.9 and 5.3 U/l, respectively) was valid \((P = 0.014)\). The maximum TRAP-5b levels in the patients of the analyzed groups were significantly higher than in the control group (2.3 times higher in metastatic lesions and 1.5 times higher in primary malignant tumors).
The values of bone metabolism markers in the blood and urine of the patients were determined in 10 days, 1, 3, 6, 9 months after the operation, and during stable remission or metastasis/recurrence. The results of the study of mineral metabolism indices in patients with tumors on the background of osteoporosis and those without osteoporosis are presented in Tables 1, 2.

Table 1
Dynamics of bone resorption and osteosynthesis in patients with primary malignant tumors after bone grafting and endoprosthetics with Biomin

| Before operation | Postoperative period, day, months |
|------------------|----------------------------------|
|                  | 10-th day | 1 month | 3 months | 6 months | 9 months | Sustained remission | Metastases, recurrences |
| **Bone resorption marker, CTT, ng/ml, blood serum** |          |         |          |          |          |                    |                           |
| 8.11 ± 0.19/    | 7.25 ± 0.18/ | 7.04 ± 0.17/ | 4.38 ± 0.18/ | 3.41 ± 0.17/ | 1.80 ± 0.16/ | 1.90 ± 0.18/ | 3.89 ± 0.20/ |
| 12.40 ± 0.33/   | 10.43 ± 0.34/ | 9.71 ± 0.31/ | 7.48 ± 0.31/ | 5.28 ± 0.29/ | 3.24 ± 0.26/ | 2.95 ± 0.24/ | 5.11 ± 0.38/ |
| **Bone resorption marker, DPD, nmol/mmol of creatinine, urine** |          |         |          |          |          |                    |                           |
| 9.34 ± 0.34/    | 8.57 ± 0.33/ | 7.85 ± 0.29/ | 6.21 ± 0.30/ | 5.36 ± 0.25/ | 4.04 ± 0.26/ | 3.92 ± 0.26/ | 7.83 ± 0.34/ |
| 13.54 ± 0.42/   | 13.08 ± 0.41/ | 10.84 ± 0.38/ | 8.87 ± 0.40/ | 6.95 ± 0.36/ | 6.18 ± 0.34/ | 6.39 ± 0.30/ | 9.76 ± 0.39/ |
| **Bone resorption marker, TRAP-5b, U/l, blood serum** |          |         |          |          |          |                    |                           |
| 6.01 ± 0.33/    | 5.80 ± 0.35/ | 4.97 ± 0.31/ | 4.61 ± 0.29/ | 3.80 ± 0.27/ | 3.25 ± 0.22/ | 4.09 ± 0.29/ | 5.24 ± 0.03/ |
| 8.87 ± 0.40/    | 8.15 ± 0.37/ | 7.61 ± 0.38/ | 5.94 ± 0.31/ | 5.22 ± 0.30/ | 4.88 ± 0.25/ | 4.61 ± 0.37/ | 6.89 ± 0.44/ |
| **Osteosynthesis marker, BAP, U/l, blood serum** |          |         |          |          |          |                    |                           |
| 59.73 ± 5.12/   | 50.08 ± 4.93/ | 48.21 ± 4.20/ | 46.31 ± 4.20/ | 41.82 ± 4.00/ | 35.24 ± 3.71/ | 30.85 ± 4.03/ | 44.27 ± 5.42/ |
| 84.44 ± 6.05    | 75.29 ± 5.71/ | 67.03 ± 5.08/ | 53.89 ± 4.51/ | 46.36 ± 4.52/ | 42.72 ± 4.04/ | 40.34 ± 4.80/ | 58.64 ± 6.19/ |
| **Osteosynthesis marker, osteocalcin, µg/l, blood serum** |          |         |          |          |          |                    |                           |
| 13.95 ± 0.89/   | 12.64 ± 0.62/ | 11.50 ± 0.57/ | 11.12 ± 0.48/ | 9.36 ± 0.47/ | 8.65 ± 0.44/ | 8.34 ± 0.60/ | 11.97 ± 0.93/ |
| 18.85 ± 0.84    | 16.37 ± 0.74/ | 15.21 ± 0.61/ | 12.82 ± 0.49/ | 11.08 ± 0.50/ | 11.25 ± 0.58/ | 11.37 ± 0.65/ | 13.71 ± 0.85/ |

Note: numeral – patients without osteoporosis, denominator – patients with osteoporosis

Table 2
Dynamics of bone resorption and osteosynthesis in patients with metastatic tumors after bone grafting and endoprosthetics with Biomin

| Before operation | Postoperative period, day, months |
|------------------|----------------------------------|
|                  | 10-th day | 1 month | 3 months | 6 months | 9 months | Sustained remission | Metastases, recurrences |
| **Bone resorption marker, CTT, ng/ml, blood serum** |          |         |          |          |          |                    |                           |
| 11.00 ± 0.21/    | 9.54 ± 0.23/ | 7.37 ± 0.25/ | 4.28 ± 0.22/ | 1.91 ± 0.15/ | 2.17 ± 0.12/ | 2.56 ± 0.11/ | 6.35 ± 0.36/ |
| 14.02 ± 0.45/    | 13.21 ± 0.38/ | 12.11 ± 0.34/ | 10.25 ± 0.36/ | 8.15 ± 0.30/ | 5.09 ± 0.24/ | 5.24 ± 0.27/ | 9.44 ± 0.38/ |
| **Bone resorption marker, DPD, nmol/mmol of creatinine, urine** |          |         |          |          |          |                    |                           |
| 8.80 ± 0.32/    | 7.50 ± 0.29/ | 7.10 ± 0.31/ | 5.35 ± 0.29/ | 4.28 ± 0.26/ | 4.49 ± 0.52/ | 4.89 ± 0.41/ | 7.49 ± 0.38/ |
| 11.94 ± 0.38/   | 11.00 ± 0.35/ | 10.80 ± 0.33/ | 8.89 ± 0.29/ | 7.51 ± 0.24/ | 6.74 ± 0.25/ | 6.85 ± 0.27/ | 9.83 ± 0.35/ |
| **Bone resorption marker, TRAP-5b, U/l, blood serum** |          |         |          |          |          |                    |                           |
| 5.62 ± 0.19/    | 5.04 ± 0.25/ | 4.24 ± 0.24/ | 2.65 ± 0.29/ | 2.69 ± 0.31/ | 2.50 ± 0.32/ | 2.79 ± 0.35/ | 4.06 ± 0.38/ |
| 7.22 ± 0.22/    | 6.61 ± 0.21/ | 6.14 ± 0.22/ | 5.64 ± 0.28/ | 4.88 ± 0.33/ | 4.07 ± 0.33/ | 3.96 ± 0.29/ | 4.99 ± 0.39/ |
| **Osteosynthesis marker, BAP, U/l, blood serum** |          |         |          |          |          |                    |                           |
| 48.80 ± 4.70/   | 39.71 ± 5.23/ | 28.46 ± 5.05/ | 15.04 ± 3.24/ | 14.32 ± 3.53/ | 15.41 ± 3.70/ | 17.21 ± 4.06/ | 41.77 ± 5.32/ |
| 79.22 ± 5.23    | 72.01 ± 6.65/ | 58.16 ± 6.95/ | 49.43 ± 6.13/ | 31.33 ± 3.07/ | 30.52 ± 4.33/ | 29.00 ± 4.24/ | 49.66 ± 6.31/ |
| **Osteosynthesis marker, osteocalcin, µg/l, blood serum** |          |         |          |          |          |                    |                           |
| 12.70 ± 0.73/   | 11.09 ± 0.74/ | 9.02 ± 0.82/ | 8.09 ± 0.84/ | 7.21 ± 0.65/ | 6.86 ± 0.55/ | 6.99 ± 0.61/ | 10.56 ± 0.84/ |
| 16.30 ± 0.82    | 14.50 ± 0.89/ | 13.33 ± 0.79/ | 10.72 ± 0.75/ | 8.99 ± 0.79/ | 9.08 ± 0.93/ | 8.75 ± 0.87/ | 12.36 ± 0.94/ |

Note: numeral – patients without osteoporosis, denominator – patients with osteoporosis

According to the data given in the tables, before the operation, the number of markers of bone resorption was significantly (p < 0.01) increased in comparison with the baseline value. On the 10th day after the operation, there was a tendency to decrease for the markers of bone resorption and osteosynthesis.
In further monitoring of the patients, the increase in markers of bone resorption and osteogenesis (for metastatic tumors: CTT > 0.72 ng/mL, DPD > 8.5 nmol/mol of creatinine, TRAP > 4.4 U/l, BAP > 47 U/l, osteocalcin > 10.20 µg/l; for primary malignant tumors: CTT > 0.82 ng/mL, DPD > 9.1 nmol/mol of creatinine, TRAP > 5.1 U/l, BAP > 54 U/l, osteocalcin > 11.80 µg/L) indicates the progression of the disease and is seen 3–6 months before clinical/radiological manifestation of recurrence and metastases.

MDCT perfusion imaging visualizes malignant, metastatic, or recurrent abnormally elevated/changed perfusion parameters (VBFR, VCBFR, BV, TT) zones in comparison with the surrounding intact tissues. The foci of increased angiogenesis in periprosthetic tissues are a symptom of recurrence or metastasis.

On the basis of the analysis of perfusionography results after endoprosthetics we performed MDCT with X-ray contrast, VBFR, VCBFR, BV, TT determination, according to which the recurrent or metastatic focus is determined on VBFR-weighed scans with values of not less than 13 ml/min/100 g, on weighed VCBFR scans with indication values not less than 23 ml/min/100 g, on valid BV scans with indication values – not less than 22 ml/100 g, on weighed TT scans with indication values – not less than 38 seconds.

Possible side effects (caused exclusively by the use of X-ray contrast media) were not observed in our studies.

According to our data, polymorbidity was observed in 40.9 % of patients with metastatic tumors of the bone at the age of 30+ and older, especially with pathological changes of the cardiovascular, nervous, respiratory systems, musculoskeletal apparatus, and gastrointestinal tract.

Optimization of surgical accesses allows shortening the term of surgical intervention by 1.5 times and contributes to less traumatization and blood loss (reduction of surgical intervention time from 3.5 to 2.5 hours, and the volume of blood loss of 1.0–1.5 l, to 0.7–1.0 l).

Type I postoperative complications occurred in 1 patient (through dislocation of the endoprosthesis head from a metal-polymer cup) – 1.9 %.
Type II complications (aseptic instability of endoprosthesis components) occurred in 3 patients (5.7 %).
Type III complications (endoprosthesis rupture) did not occur in the studies.
Type IV (infectious complications) occurred in 4 cases – 7.6 %.
Type V complications (recurrences) were not observed.

The endoprosthesis dislocation was repaired under anesthesia by a closed procedure. The suppuration of the postoperative wound occurred in 4 patients. In these cases, the wound was disinfected, and antibiotic therapy courses were administered. In 2 cases, the infectious process was successfully eliminated, and the endoprostheses were saved. In 2 cases, the endoprostheses were removed and orthoses were applied to eliminate the infection. In the future, repeated endoprosthetics was performed. There were no recurrences of tumor metastases in the early postoperative period.

In patients with instability of endoprosthesis components, repeated surgical treatment with correction of endoprosthesis fixation was performed.

Therefore, postoperative complications occurred in 8 (15.2 %) patients, which is much fewer than in our previous studies – 24.0 % and those, described in the literature – 26–40.0 % [34, 35].

All patients who received intravenous administration of Dalargin and Mebifon did not show any adverse events. In the control group of patients with metastatic bone lesions who received conservative treatment, none of the patients survived one year. In the study group, the overall three-year survival rate was 43.6 ± 9.4 %.

The results obtained according to the developed algorithm of treatment are comparable with the published results obtained by a number of researchers dealing with the problem of treatment of metastatic lesions of the femoral bone for the best direct and long-term results of treatment of the patients [36–38]. But it is important that the application of prophylactic bone stabilization to prevent the occurrence of a pathological fracture was definitely better compared with patients who received treatment after the occurrence of a pathological fracture [39].

Therefore, prevention of pathological fractures by performing stabilizing surgical interventions is the method of choice for preventing its occurrence in the affected bones.
When analyzing the functional results of treatment of patients with metastatic tumors of the femoral bone, the following indicators were obtained: excellent – 58.33 %, good – 41.67 %.

According to the results of the questionnaire, the physical state of the patients after endoprosthetics increased to 58.7 scores (with the baseline of 24.3 scores), the «emotional sphere» index increased from 40.5 to 63.3 scores, and the «cognitive function» index increased from 62.1 to 78 scores.

The «social activity» scores of patients increased from 19 to 58.9 scores. The patients’ self-reported «general state» changed from 21.9 to 38.6 scores. The data obtained indicate a significant improvement in the quality of life of the treated group of patients, which is confirmed by satisfactory results according to the ECOG scale: if before treatment out of 57 patients 4 points on the scale had 4 (7.01 %) patients, 3 points – 38 (66.66 %) patients, 2 points – 11 (19.29 %) patients, 1 point – 4 (7.01 %) patients, then after the complex therapy none of the patients had 4 points, 3 points had 19 patients (33.33 %) 2 points in 29 (50.87 %), 1 point – in 9 (15.78 %).

4. Discussion

In terms of the frequency of localization of metastatic lesions, the skeleton ranks third after the lungs and liver, and the symptoms of bone lesions (especially with pathological fractures) may be the first and only manifestation of a malignant tumor in the body [40, 41]. With the development of bone metastases, the quality of life deteriorates: the risk of pathological fractures is high, compression of the spinal cord with the development of neurological deficit is possible, hypercalcemia develops, and severe pain syndrome appears. Moreover, in some cases, the intensity of the pain syndrome does not correspond to extensive anatomical changes in the vertebrae. Mostly bone metastases occur in malignant epithelial tumors. Especially osteotropic should be considered breast cancer, prostate cancer, malignant tumors of the kidneys, malignant adenoma of the thyroid gland, lung cancer. The prevalence of metastatic tumors is determined to some extent by the location of the cancer. Breast cancer predominantly metastasizes to the spine, ribs, pelvic bones, skull, and proximal humerus [42, 43].

The high frequency of metastatic process in breast cancer is partly due to the wide prevalence of this type of tumor, as well as the relatively long course of the disease. In patients with advanced breast cancer, bone metastases are noted in 65–75 % of cases. Most of the bone lesions in patients with breast cancer are osteolytic, according to radiography, about a third of cases are mixed osteolytic and osteoblastic formations. The average time between surgical removal of the primary tumor and the appearance of bone metastases is 38 months, and the average life expectancy of patients with bone metastases ranges from 19 to 25 months [43, 44].

In this regard, it is important to conduct a thorough and complete examination of patients in order to establish the most accurate diagnosis and the subsequent choice of the optimal surgical tactics for each patient individually - that is, the implementation of the principles of personalized medicine. When choosing a method of surgical treatment, it is necessary to take into account a number of factors: the type of metastasis, its location and extent of bone damage, the presence of a pathological fracture, the prevalence of the metastatic process, damage to visceral organs, the presence or absence of the effect of previous systemic specific therapy, the duration of the relapse-free interval and the general somatic status of the patient. Thus, it is possible to determine the expected prognosis of the life of these patients and the degree of risk of surgical intervention. In the preoperative period, careful planning of the operation with the obligatory calculation of the tumor resection zone according to computed tomography with 3D reconstruction and angiography acquires a decisive role [45, 46].

Complex therapy of patients, as well as the ability to prevent pathological fractures in advance, predicting bone tissue destruction by determining special markers of bone resorption, is a timely and effective tool in onco-orthopedics to increase the life expectancy of patients and improve their quality of life.

Study limitations. Multimorbidity is common in patients with chronic diseases, and especially in older patients. In recent study we monitored patients with bone metastases, who could also have the following pathologies: coronary artery disease, chronic kidney disease, diabetes, heart failure, hypertension, osteoarthritis. Therefore, the main limitations for strict adherence to the planned diagnostic and treatment algorithm could be episodes of exacerbations of the above-mentioned diseases.

Prospects for further research. Treatments for metastasis to long bones include internal fixation, external fixation and prosthesis placement. One of the most important goals in the
Treatment of bone metastatic cancer is disease control. If a cancer is localized, surgery or radiation therapy is generally the first choice. Along with the use of bisphosphonates, the appointment of denosumab, a human monoclonal IgG2 antibody that acts by binding to both membrane bound and soluble RANKL with high affinity, seems promising. Considering the great importance of maintaining the functional capacity of bones through the timely prevention of pathological fractures, promising directions in future research can be identified as the search for new methods for preventing bone resorption in order to preserve the quality of life of patients.

5. Conclusions
The occurrence of pain syndrome in any skeletal area, especially in patients with breast cancer, necessitates a comprehensive radiological (osteoscintigraphy + multidetector computed tomography of the affected area) and biochemical examinations (the content of markers of bone resorption and osteogenesis in biological fluids of the body).

The monitoring of patients with cancer should necessarily include the examination of markers of bone resorption and osteogenesis, as their increased content in the blood and urine allows suspecting metastatic disease of the bone 3–6 months earlier than the clinical and radiological manifestation of the tumor process metastasizing to the bones. Since the assessment of the growth of biomarker expression raises suspicion of metastatic bone lesions and occurs much earlier than the clinical and radiological manifestation of the tumor process, we consider it necessary to monitor these parameters over time. It should be noted that in patients who did not have bone metastases, the indicators of osteosynthesis and osteoresorption remained within the normal range.

After the detection of the signs of a pathological bone fracture in the patients, or if it is present, surgical intervention by removing the pathological focus and replacing the defect with an endoprosthesis is required.

The special treatment of patients with metastatic bone affection should be supplemented with treatment measures aimed at the therapy of polymorbid pathology.

Visualization of the tumor bone lesion using 3D model, planning of surgical intervention – removal of the tumor and replacement of the defect with an adequate endoprosthesis, which ensures its reliable fixation, significantly shortens the surgical intervention duration, reduces the volume of blood loss, which positively influences the clinical course of the postoperative period and long-term outcomes of treatment.

The personalization of treatment of patients with tumor lesions of the skeletons contributes to a significant decrease in the indicator of postoperative complications of endoprosthetics of great joints and to an increase in the total three-year survival rate, as well as to the improvement of the quality of life after the conducted treatment.

Conflict of interests
The authors declare that they have no conflicts of interest.

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