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# Factors Associated With Revision Surgery in Long Bones Metastases

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***Background.*** Bones as an organ are one of the most common targets for tumor metastasis. Currently, the number of patients undergoing surgical treatment for metastatic bone lesions is steadily increasing. In most patients, after surgical treatment, the manifestation of clinical symptoms decreases, primarily pain syndrome, which improves their quality of life. However, it should be noted that the number of patients with bone metastases who underwent revision surgery is also increasing. This article retrospectively analyzes the factors leading to revision after surgical treatment of metastases in long bones.
***The aim of this study*** was to identify factors leading to revision after surgical treatment of patients with metastases in long bones.
***Methods.*** A retrospective medical records analysis of 247 patients who underwent surgical treatment for metastases in long bones in 2006–2020 was performed. Of these, 33 patients underwent revision surgery. The median age was 62 years. The localization of the primary tumor was as follows: breast cancer — 10 cases, kidney cancer — 13, lung cancer — 3, prostate cancer — 2, rectal cancer — 3, liver cancer and Ewing's sarcoma with bone metastases — 1 case each.
***Results.*** The following factors led to revision surgery: mistakes in preoperative diagnosis (3 patients); postoperative infectious complication (6 patients); dislocation of the endoprosthesis (4 patients); continued growth of solitary metastasis after osteosynthesis (5 cases); aseptic instability after intramedullary osteosynthesis (14 patients); traumatic fracture of the endoprosthesis stem (1 patient).
***Conclusions.*** Revision after surgical treatment of metastases in long bones, in addition to postoperative complications, lead to mistakes in diagnosis and incorrect choice of surgical treatment method. To reduce the risk of revision surgical interventions, a multidisciplinary approach is needed with the development of surgical treatment tactics in consultation and the use of specialized scales of oncological prognosis.

**Keywords:** metastasis, long bones, surgical treatment.

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# Факторы, приводящие к повторному хирургическому вмешательству при метастатическом поражении длинных костей

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***Актуальность.*** Кости как орган являются одной из наиболее распространенных мишеней для метастазирования опухолей. Число пациентов, подвергшихся хирургическому лечению по поводу метастатического поражения костей, неуклонно растет. Количество пациентов с метастазами в кости, которым проводили повторную операцию, также увеличивается.
***Цель*** — выявление факторов, приводящих к повторным операциям после хирургического лечения пациентов с метастазами в длинных костях.
***Материал и методы***. Выполнен ретроспективный анализ историй болезни 247 пациентов, которым на базе МНИОИ им. П.А. Герцена в 2006–2020 гг. было проведено хирургическое лечение по поводу метастазов в длинных костях. Из них у 33 пациентов выполнены повторные хирургические вмешательства. Средний возраст составил 62 года. Локализация первичной опухоли: рак молочной железы — 10 случаев, рак почки — 13, рак легких — 3, рак предстательной железы — 2, рак прямой кишки — 3, рак печени и саркома Юинга с метастазами в кости — по 1 случаю.
***Результаты.*** К повторной операции приводили следующие факторы: ошибки в предоперационной диагностике (3 пациента), послеоперационное инфекционное осложнение (6 больных), вывих эндопротеза (4 больных), продолженный рост солитарного метастаза после остеосинтеза (5 случаев), асептическая нестабильность после интрамедуллярного остеосинтеза (14 больных), травматический перелом ножки эндопротеза (1 пациент).
***Выводы.*** К повторным операциям после хирургического лечения метастазов в длинных костях, кроме послеоперационных осложнений, приводят ошибки в диагностике и некорректный выбор метода хирургического лечения. Для уменьшения риска повторных хирургических вмешательств необходим мультидисциплинарный подход с выработкой тактики хирургического лечения на консилиуме и использованием специализированных шкал онкологического прогноза.

**Ключевые слова:** метастазы в длинные кости, хирургическое лечение.

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## BACKGROUND

The improvement in diagnostics and of the techniques of surgical interventions and the development of drug therapy and radiation method of treatment have enabled to increase the life expectancy of cancer patients significantly. However, a significant proportion of patients has regional and/or distant metastases. Primary malignant tumors can metastasize to almost all body tissues, but some types of tumors, such as breast cancer, prostate cancer, lung cancer, thyroid cancer, and kidney cancer, metastasize preferentially to bones. According to the literature, the bone is the third most common site of metastasis after the lungs and liver [1, 2].

According to the American Cancer Society, more than 65% of breast and prostate cancers and 30–40% of lung, thyroid, and kidney cancers have bone metastases [3]. Metastases are most often localized in the femur and humerus among the long bones [3]. For most cancer patients, the emergence of metastases usually indicates an advanced stage of the disease and a poor prognosis. However, surgical treatment of patients with bone metastases improves the quality of life of patients and restores the function of the affected limb [4]. Along with the expansion of indications for surgical intervention, with metastatic lesions of long bones, there is an increase in the frequency of repeated surgeries due to the recurrence of the pain syndrome induced by various factors.

The study aimed to identify factors leading to revision surgeries after surgical treatment of patients with metastases in long bones.

## METHODS

### Study design

This is a retrospective analysis of the case histories of patients who underwent surgical treatment of metastases in long bones at the Hertsen Moscow Oncology Research Institute in 2006–2020. The study did not include patients in whom the identified metastatic focus was not surgically removed, as well as those who refused to undergo repeated surgical intervention.

### Patients

Out of 247 patients, 181 (73.3%) with metastatic lesions of long bones underwent removal of the metastatic focus with total joint replacement. Internal osteosynthesis was performed in 65 (26.3%) cases, and one patient (0.4%) underwent radiofrequency thermal ablation of the lytic femoral focus with osteoplasty.

In 33 (13.3%) patients, repeated surgical interventions were performed, including amputation in one patient, reduction of the endoprosthesis dislocation in four cases, one-staged or two-staged repeated endoprosthesis replacement in five patients, and segmental resection with endoprosthesis replacement was performed in 23 cases.

There were 15 men and 18 women. Their age ranged from 23 to 80 yr, with a mean age of 62 yr.

The primary tumor was as breast cancer in 10 patients, kidney cancer — in 13 patients, lung cancer — in three patients, prostate cancer — in two patients, rectal cancer — in three patients, liver cancer — in one patient and Ewing's sarcoma — in one patient.

Total joint replacement was performed in 11 (33.3%) patients as a primary surgery, intramedullary osteosynthesis in 21 (63.6%) patients, and radiofrequency thermal ablation of the femoral lytic focus with osteoplasty was performed in one patient (3%). At the same time, 20 (60.6%) patients had a pathological bone fracture, and seven (21.2%) patients had a risk of its occurrence. In five (15.2%) patients, the indication for surgery was the continued growth of solitary metastasis in the long bone.

The primary surgery in 11 patients was performed at the Hertsen Moscow Oncology Research Institute, and in 22 patients, it was performed in another clinic. During hospitalization 31 out of 33 patients had a pronounced pain syndrome, 17 patients had a limitation in the range of motion, and swelling of the affected extremities was registered in five patients.

### Evaluation of results

The visual analog scale (VAS) was used to assess the pain syndrome severity, and the Eastern Cooperative Oncology Group (ECOG)

and Karnofsky scales were used to assess the patients' quality of life before and after surgery [5].

## Statistical analysis

Statistical analysis of the data obtained was performed using the Solutions Statistical Package for the Social Sciences 22 (SPSS Statistics) program. Survival rate analysis was performed using the Kaplan-Meier method. Survival curves were compared using the log-rank test. Differences were considered statistically significant at $p<0.05$.

## RESULTS

The changes over time of pain syndrome according to VAS before and after repeated surgical intervention are presented in Table 1.

The follow-up revealed that 24 (72.7%) patients passed away as a result of repeated surgical interventions. Six of the 24 patients underwent total joint replacement during primary surgery, and 17 patients underwent intramedullary osteosynthesis. One patient underwent radiofrequency thermal ablation of the lytic lesion of the femur with osteoplasty. The median survival rate after repeated surgical interventions was 15 months (6–28 months). When studying the long-term results of treatment of patients after repeated surgical interventions, we revealed that the overall 1-year survival rate was 73%, and the 2- year survival rate was 24% (Figure 1).

The majority (226 [91.5%] patients) showed an improvement in the quality of life after surgery according to the Karnofsky and ECOG scales, and in 21 (8.5%) patients, the quality of life did not change. However, after repeated surgeries, all 33 patients showed an improvement in the quality of life, according to the Karnofsky and ECOG scales (Table 2).

*Table 1*

**Dynamics of pain syndrome according to VAS**

| Score | Number of patients | |
|---|---|---|
| | Before surgery | After surgery |
| 0–2 | 2 | 28 |
| 3–4 | 5 | 5 |
| 5–6 | 20 | 0 |
| 7–8 | 3 | 0 |
| 9–10 | 3 | 0 |
| Total | 33 | 33 |

Pearson's $\chi^2$ value is 48.533; $p < 0.001$.

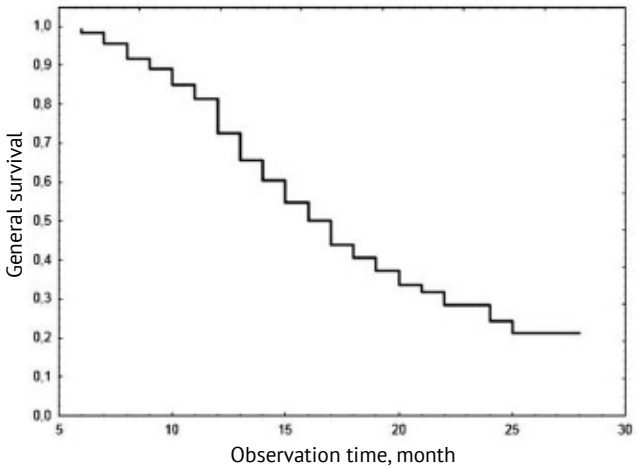


**Fig. 1.** Survival rate of patients after revision surgery

Indications for revision surgery were errors in preoperative diagnostics (three patients), postoperative infectious complication (six patients), endoprosthesis dislocation (four patients), continued growth of solitary metastasis after osteosynthesis (five patients), aseptic instability after intramedullary osteosynthesis (14 patients), and traumatic fracture of the endoprosthesis stem (one patient) (Table 3).

*Table 2*

**Changes in the level of quality of life after the initial surgery and repeated surgical interventions according to the ECOG and Karnofsky scales**

| Description | Karnofsky scores | ECOG scores | Number of patients (n = 247) | | Number of patients (n = 33) | |
|---|---|---|---|---|---|---|
| | | | Before the primary surgery | After the primary surgery | Before repeated surgical interventions | After repeated surgical interventions |
| The patient is fully active and is capable to perform activities as before the disease | 90–100 | 0 | 3 | 143 (3*) | 0 | 26 |
| The patient is unable to do heavy work but can do light or sedentary work (e.g., light housework or deskwork) | 70–80 | 1 | 12 | 50 (3*) | 2 | 7 |
| The patient is treated on outpatient basis, is capable of self-care but unable to work. He spends more than 50% of his waking time actively in an upright position | 50–60 | 2 | 18 | 28 (4*) | 8 | 0 |
| The patient is only capable of limited self-care and spends more than 50% of the time in a chair or bed | 30–40 | 3 | 64 | 19 (4*) | 17 | 0 |
| Disabled person, completely incapable of self-care, confined to a chair or bed | 10–20 | 4 | 150 | 7 (7*) | 6 | 0 |

* Number of patients whose quality of life has not changed after surgery; $p < 0.001$.

*Table 3*

**Causes of revision surgeries after treatment of metastases in long bones**

| Primary surgery | Number of patients | Complication | Revision surgery |
|---|---|---|---|
| Total arthroplasty | 4 | Dislocation | Revision arthroplasty |
| | 6 | Infection | Repeated endoprosthesis replacement |
| | 1 | Endoprosthesis fracture | |
| Osteosynthesis | 14 | Aseptic instability | Arthroplasty |
| | 4 | Continued growth of solitary metastasis | |
| | 1 | | Amputation |
| | 2 | Errors in preoperative diagnostics | Arthroplasty |
| Radiofrequency thermal ablation with osteoplasty | 1 | Errors in preoperative diagnostics | Arthroplasty |

## DISCUSSION

Currently, patients have higher demands on restoring the quality of life. Most of them hope for the fastest possible restoration of the affected limb function and the maximum reduction of pain after surgery. In order to remove metastatic foci and correct pathological fractures, surgical methods, such as intramedullary fixation, total joint replacement, and plate fixation, are used in clinical practice to restore the functional characteristics of the affected bone [6, 7]. An analysis of the literature shows that surgical treatment of metastases in long bones allows good immediate results and significantly improves the quality of life of this category of patients [8, 9, 10, 11].

Our study presents a retrospective analysis of data from 247 patients with long bone metastases, who underwent surgical treatment. The study of immediate results and data obtained during follow-up of patients in this group showed that the use of surgical interventions for the treatment of metastatic lesions of long bones is justified in most cases, since they provide good functional results and improve the quality of life of this category of patients (91%). However, at the same time, we concluded that due to the recurrence of pain syndrome and other clinical symptoms caused by various factors, the number of patients requiring repeated surgeries is increasing simultaneously.

Thus, according to the study results, the main factors of repeated surgical interventions were identified.

### 1. Errors in preoperative diagnostics

The above group of 33 patients included three patients with diagnostic errors. Two patients with suspected traumatic fracture were hospitalized in the trauma department of clinics, where intramedullary osteosynthesis was performed. One of the patients was diagnosed with osteosarcoma of the femoral metaphysis during the initial visit to a medical institution, and then radiofrequency thermal ablation in combination with osteoplasty was performed.

In clinical practice, bone metastases in patients can be asymptomatic and diagnosed incidentally during routine examinations or in case of a pathological fracture [12]. T. Sun et al. reported that 15 out of 121 patients (12.4%) with metastases to the femur did not have a clearly verified primary tumor during examination [13]. X.D. Tang et al. analyzed 125 cases of malignant tumors with bone metastases and revealed that 29.6% of patients did not receive diagnosis of metastases. At the same time, the frequency of positive results of physical examination was 9.6%, that of the study of specific tumor antigens was 43.2%, imaging study showed positive results in 60% of cases, and post-mortem examination showed positive results in 66.4% of cases [14].

According to research results, the bone microenvironment contributes to metastatic injury by changing the phenotype of tumor cells and plays a key role in the vicious circle of bone metastasis. The bone matrix is rich in many growth factors (e.g., TGF-α, IGF-I, and IGF-II), which are released because of osteolysis and stimulate simultaneously the proliferation of both bone and tumor cells. The physical factors of the bone matrix (e.g., acidic environment) create a favorable environment for tumor growth. Physical factors interact with growth factors, thereby contributing to the formation of a vicious circle of bone metastases development and accelerating the process of bone metastasis [11, 15, 16, 17, 18].

In our opinion, in most cases, diagnostic errors occur due to low oncological alertness of the general clinical health care unit, particularly among orthopedic surgeons. However, the progression of a malignant tumor is often associated to a greater extent with the development of metastases than with the growth of the primary focus, and even a small primary tumor can have obvious distant metastases.

### 2. Incorrect method of surgical treatment

In our study, aseptic instability developed in 19 patients after osteosynthesis of long bones for a verified metastatic lesion, and growth of a solitary tumor was recorded 6–12 months after the surgery, which subsequently required amputation in one patient, and segmental resection with joint replacement in the rest of the cases.

Functional results after segmental resection with joint replacement and osteosynthesis after 6 months were significantly different in favor of joint replacement due to tumor growth in

the affected bone segment after osteosynthesis and the development of aseptic instability. Due to the absence of tumor growth in the affected bone segment, the eradication of the tumor during segmental resection with joint replacement provides good functional results for a longer period. At the same time, it is noteworthy that there are no significant differences in the average duration of surgery, the volume of blood loss, and the terms of activation of patients after osteosynthesis and joint replacement [19].

The life expectancy of oncological patients has increased significantly in connection with the development of oncological science and the improvement of treatment methods, and this has led to an increase in the number of patients with bone metastases [20]. The complicated course of metastatic bone lesions affects significantly the quality of life of patients [21]. Indications for surgical treatment and methods of orthopedic management in patients with bone metastases can vary significantly in different countries. Thus, in the USA, 71% of patients with bone metastases undergo surgery due to the risk of pathological fractures, while it is performed only in 18% of cases in the Nordic countries [20, 22].

Predicting the life expectancy of patients with bone metastases is significant in the choice of treatment options, but the accuracy of such a prognosis is still insufficient. Over the past decades, there have been numerous attempts to develop new systems to assist in making decisions about the approach of treating patients with bone metastases [23, 24, 25, 26, 27]. Another important factor for determining the approach of surgical treatment is the metastatic lesion localization, as well as the presence or risk of a pathological fracture [12, 28, 29, 30]. Fracture risk is assessed using the Mirels scale; if there are more than 9 points, surgical treatment should be performed [31]. Currently, intramedullary osteosynthesis in the treatment of metastatic bone lesions has limited indications and is almost not used. Preference is given to oncological joint replacement [32, 33, 34, 35, 36].

For patients with long bone metastases associated with or at risk of pathological fractures, the optimal surgical method must be determined, taking into account the patient's life expectancy, fracture location, and many other factors. In breast cancer, prostate cancer, and other cancer sites with a long patient survival period, when the primary tumor has been removed or the tumor process manifests itself as a relatively slowly developing isolated bone metastasis, extensive tumor resection can be performed to reduce the incidence of local recurrences. However, the choice of surgical methods for restoring the affected limb function is focused on the pathological fracture area. If bone metastasis is located near the joints in combination with pathological fractures, total joint replacement may be the optimal treatment. This surgical method can replace a bone defect effectively during tumor removal and provide affected limb with sufficient functional performance and strength after surgery. Within a week after the surgery, functional exercises can be performed to avoid prolonged bed rest. If the pathological fracture is localized in the bone diaphysis, intramedullary osteosynthesis can be considered, since this method provides uniform tension and minor blood loss [32, 33]. Intramedullary osteosynthesis can also be used in the case when the tumor does not destroy strongly the bone tissue at the fracture site and the cortical bone is in good condition. The addition of bone cement to the site of a bone defect increases its stability and can destroy tumor cells and nerve endings in the lesion by increasing the temperature during the bone cement hardening. When the tumor destroys significantly the cortical bone at the fracture site or other methods of osteosynthesis are not effective, total joint replacement is preferred [34].

In our opinion, intramedullary osteosynthesis can prevent fractures of the proximal femur and femoral diaphysis. However, pathological fractures also occur in the greater or lesser trochanters of the bone, which is accompanied by severe damage to the cortical bone; in this case, arthroplasty should be used.

## 3. Postoperative complications

Infection and endoprosthesis dislocation are the most common postoperative complications in the surgical treatment of metastases to long bones; these situations were identified in 10 out of 33 patients.

### *3.1. Infection*

In this study, six patients underwent revision surgery due to postoperative infection of the endoprosthesis bed. At the same time, four patients underwent a two-staged revision athroplasty, and in two patients, after revision and debridment, a new endoprosthesis was immediately installed. There were no cases of amputation.

The most serious complication of oncological arthroplasty is postoperative infection. Infection can cause pain, severe joint function limitation, and, if not treated properly, can lead to limb amputation [37]. The probability of amputation due to suppuration has been reported to be 19–47% [38, 39]. It should be noted that the surgery is performed in a laminar flow operating room, bone cement with antibiotics is used, and patients take antibiotics before and after the surgery to prevent infection. However, postoperative infection is still a major concern for orthopedic oncologists. Literature data indicate that revision surgery enables to control the infection in most cases [37, 40]. Efficiency of revision surgeries in terms of stopping the infection can reach 70% [40].

Based on our experience and literature data, it can be assumed that postoperative infections leading to revision surgery may be associated with the following factors:

– adjuvant therapy reduces the patient's autoimmune resistance;

– intraoperative aseptic treatment is not performed carefully enough, which leads directly to intraoperative contamination;

– the tumor widely invades, and as a result, the local soft tissues become thin after resection of the tumor site, the ability to absorb exudate and combat infection decreases, and there is a predisposition to postoperative infection;

– poor drainage of the wound after surgery can lead to accumulation of fluid and blood;

– after the surgery, the surrounding soft tissues are not adjacent to the prosthesis, so a cavity can form around it, where fluid accumulates easily and infection develops;

– between the body and the prosthesis, a rejection reaction occurs, which manifests itself in the form of exudation of a brown liquid, while at first there is no growth of bacteria, however, a large amount of exudate over a long period of time creates conditions for the growth of bacteria, and repeated dressings can easily induce the wound contamination;

– soft tissues do not close the wound well; after an extensive marginal tissue resection, wound closing with tissues is often complicated, poor healing of the incision and even necrosis of the skin edge are noted, which can lead to secondary infection.

### *3.2. Dislocation*

Dislocation is a serious complication after total hip replacement and usually requires revision surgery. According to the literature, the incidence of dislocations after shoulder joint replacement is 12% to 54.5% [41]. Research by C.U. Gwam et al. showed that joint dislocation after hip arthroplasty is the main cause for revision surgery (17.3%) and is more common than infection and aseptic instability [42].

In our study, four patients underwent revision surgery for dislocation. In two patients, dislocation occurred 15 and 45 days after total joint replacement of the shoulder joint, unipolar (anatomical) endoprosthesis replacement was performed in one patient, and reverse arthroplasty was performed in the other patient. In two more patients, dislocation occurred after hip arthroplasty on the days 3 and 35 after surgery. All patients underwent surgical intervention in the scope of the revision with reduction of the dislocation. Various types of reconstruction and grafting were used to prevent repeated dislocations.

As a rule, dislocation after oncological arthroplasty is associated with massive removal of the soft tissues surrounding the tumor and the entire ligamentous apparatus. Surgical prevention of dislocations includes the restoration of tendon fixation points and the use of various types of plasty by biosynthetic materials.

## 4. Other factors

One patient underwent joint replacement for breast cancer with metastases to the femur in combination with pathological fractures; 19 months after the surgery, she was hospitalized again with a fracture due to an accidental fall, while the X-ray showed implants failure. This patient underwent revision joint replacement.

## Study limitations

This study was a single-center, represented a retrospective analysis, and had a limited data sample size. Multicenter prospective studies are required to clarify the factors leading to revision surgery in long bone metastases.

## CONCLUSION

The study showed that the main causes of revision surgery in patients with bone metastases were insufficiently accurate preoperative diagnostics, associated errors in the choice of surgical intervention options, as well as postoperative complications.

In our opinion, for the effective treatment of patients with metastases in long bones, a multidisciplinary approach is required with the development of treatment approach at a case conference with the participation of chemotherapists, radiologists, and orthopedic oncologists, as well as using specialized scales of oncological prognosis. The surgical team should have experience in working with cancer patients. This will increase the probability of success of the surgery, restore the function of the affected limb, improve the quality of life of patients, and reduce the risk of revision surgery.

## DISCLAIMERS

### *Author contribution*

*Wang J.* — concept and research design, collection and statistical processing of data, writing text.

*Kharchenko N.V.* — research concept and design.

*Zapirov G.M.* — collection and analysis of materials, editing text.

*Kaprin A.D.* — research concept and design.

*Bucharov A.V.* — concept and research design, writing text, text editing.

*Derzhavin V.A.* — collection and analysis of materials, text preparation and editing.

*Yadrina A.V* — collection and analysis of materials, text preparation and editing.

All authors read and approved the final version of the manuscript in the article. All authors agree to be responsible for all aspects of the work to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

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