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FUNCTION AND COMPLICATIONS AFTER ENDOPROSTHETIC REPLACEMENT OF KNEE BONE-FORMING TUMORS EXPOSED TO RADIOTHERAPY AND MULTIAGENT CHEMOTHERAPY

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ABSTRACT — We discuss analysis of function outcome and complications in 65 patients undergoing endoprosthetic knee replacement for osteosarcoma after radiotherapy and multiagent chemotherapy. Specifically, we found that multiagent chemotherapy caused a periprosthetic infection in 7.7% of cases. Major complications of radiotherapy included periprosthetic infection (27.3%), bone fracture at the site of endoprosthesis stem implantation (27.3%), aseptic loosening of stem (18.2%) and in 9.1% of patients a post-radiation skin ulcer was observed. Strategies for eliminating complications of periprosthetic infection included: removal of the endoprosthesis, installation of a metal-cement spacer followed by repeated joint endoprosthesis replacement. Then metal osteosynthesis was performed with cover plates and cable grip in case of bone fractures at the site of endoprosthesis stem implantation. A revision knee replacement surgery was performed in case of aseptic loosening of stem; removal of ulcer, removal of necrotic tissue, wound revision, and wound closure by means of muscle reposition with the subsequent free skin grafting was carried out during removal of postradiation ulcer. Hip amputation or disarticulation of the thigh was carried out in case of recurrence; multiagent chemotherapy with metastasioctomy was performed in case of metastases in lung.

KEYWORDS — knee joint, endoprosthetic replacement, chemotherapy, radiotherapy, complications, methods of eliminating complications.

INTRODUCTION

The review of literature confirms that a combined treatment is used in cases of osteosarcoma of high grade. It includes neoadjuvant chemotherapy (CT) cycle, definitive surgery, adjuvant CT cycle. It is also recommended to use modular endoprosthesis replacement systems, which considered most relevant and advanced. Furthermore, they meet the basic requirements for reconstruction of bone defects in cases of bone sarcomas [1, 2, 4]. A surgical treatment alone for osteogenic sarcoma is impractical, as within 1.5 years after surgery 80–90% of patients are diagnosed with metastases in lungs and local recurrences. CT as part of multimodal treatment significantly improves the 5-year survival in patients with osteogenic sarcoma with a localized process (20% to 60%). The advantages of preoperative CT include the ability to assess the in vivo activity of chemotherapeutic preparations and to facilitate the surgery conducting [5]. Usually 3–4 cycles of preoperative CT are followed by the endoprosthetic knee replacement. After tumor removal, the degree of tumor necrosis after preoperative CT is determined, which is a reliable independent prognostic factor. With a positive response of the tumor to the treatment (tumor necrosis of 90% or more) there is a high probability of recurrence-free and overall survival of patients [1]. Regarding patients with failure response after preoperative CT, as a rule, postoperative CT does not lead to improved survival [2, 4]. Radiotherapy (RT) has been used successfully in the treatment of malignancies of various localizations. The majority of patients with bony spread suffer from pain syndrome and in whom RT reduces or completely cures pain [12]. According to the literature, due to radiation, a partial effect can be achieved in 60–80% of cases, and Total Pain Relief can be achieved in 15–40% of patients [6]. One of the possible ways to increase the effectiveness of therapy for patients with metastatic lesions of skeletal system may be an external-beam RT in combination with the injection of bisphosphonates. During radiotherapy conducting, in most cases, soft tissues, bone tissue and visceral organs located in the immediate vicinity of the tumor fall into the radiation area, which leads to their destruction [8]. Late radioreactions develop in several years after treatment and consist of dysfunction of osteoblasts, osteotabes and replacement of bone marrow by connective tissue, pathological bone fragility, trophism disorders, development of osteonecrosis and osteomyelitis [3, 11]. The above complications are characterized by the term "radiation osteitis". Factors contributing to the development of post-radiation pathological fractures include

a large dose of radiation, high beam energy and the presence of a history of osteoporosis [11]. When using RT in the combined therapy of malignant neoplasms, the typical complications include radiation damage to the integumentary tissues (fibrosis, ulcer in the area of radiation fields, radiation plexopathy, secondary lymphostasis of the upper and lower extremities, radionecrosis (osteoporosis, radiation osteomyelitis) of bones, intrapelvic radiation fibrosis, radiation damage to the intestines, urinary bladder, esophagus, heart, etc. [3, 11] It should be noted that increasing effectiveness of combined treatment of malignant neoplasms, including radiation therapy extends life expectancy of the patients, and therefore detection of radiation damage to bones has become more common, although its development requires a long period of time [9]. In most cases, correction of this pathology requires a surgical treatment due to ineffectiveness of conservative measures. In cases where the diagnosis of radiation damage to the bone is confirmed, it is necessary to partially or completely remove the affected fragment. In addition, radiation osteoradionecrosis and osteomyelitis are usually accompanied by damage to the surrounding soft tissues with the development of radiation ulcers and fistulas. This requires the use of certain types of corrective skin surgery [10]. This paper expands the understanding of the causes of complications after the use of radiotherapy and multiagent chemotherapy during endoprosthetic knee replacement in case of bone tumors, and provides methods for their elimination.

PURPOSE

The purpose of our research was to analyze the complications occurring after the use of radiotherapy and multiagent chemotherapy during knee endoprosthesis replacement for bone tumors.

MATERIALS AND METHODS

During the period from 2009 to 2020, endoprosthetic knee replacement was performed in 65 patients with knee bone-forming tumors. Among the treated patients there were 29 women (44.6%), and 36 men (55.4%). The mean age of patients amounted to 27.6 ± 1.4 years. Patients underwent knee joint endoprosthesis replacement using individual modular oncological endoprostheses produced by Stryker and W.Link companies and individual oncological endoprostheses produced by Inmed and Beznoska companies. The use of a modular system simplifies the performance of both the endoprosthesis replacement itself and subsequent revision surgery, increasing the biological reserve of bones. The possibility of manufacturing individual components of the endoprosthesis for revision surgery, with the development of instability allows, without removing the entire endoprosthesis, to replace a part of it. Table 1 presents the histological forms of the tumor and the number of patients who underwent chemoradiation treatment before knee joint endoprosthesis replacement.

In case of osteogenic sarcoma (giant-cell sarcoma of bone, fibrosarcoma of bone, malignant fibro histiocytoma of the bone, Ewing sarcoma, metastatic tumor), depending on the size of the primary site and degree of tumor extension it was decided by a team of surgeon-oncologist-orthopedist-chemotherapist on the feasibility of chemotherapeutical treatment. Chemotherapy in some cases can reduce primary tumor size and metastases, promote its delimitation by a pseudocapsule that allows to transfer a tumor to a resectable condition. 39 patients underwent courses of neoadjuvant and adjuvant multiagent chemotherapy according to treatment protocols of these nosological entities, of which 26 patients had osteogenic sarcoma, 5 of them had giant cell sarcoma of bone, 4 of them had fibrosarcoma of bone, 1 of them had malignant fibro histiocytoma of bone, and 1 of them had metastatic tumor (metastasis of kidney cancer). In case of osteogenic sarcoma (giant cell sarcoma of bone, fibrosarcoma of bone, malignant fibro histiocytoma of bone), we introduced the following regimens of chemotherapy: AP regimen: doxorubicin: 90 mg/m^2 intravenous, 96-hour infusion; cisplatin 120 mg/m^2 intravenous infusion on the 1st day every 4 weeks of the 4th cycle, regimen I (used at low efficiency after 2 cycles of AR): ifosfamide (with uremitexan) 2000 mg/m^2 intravenous on the 1st–7th day of the 2nd cycle. During postoperative period we used the following regimens: if the tumor necrosis was more than 90%: doxorubicin: 25 mg/m^2 on the 1st–3rd day intravenous as a 72-hour continuous infusion; ifosfamide: 2500 mg/m^2 on the 1st–4th day intravenous with uremitexan, if the tumor necrosis amounted from 50 to 90% then regimen I was used: ifosfamide: 2 g/m^2 (with uremitexan) intravenous infusion on the 1st–7th day, of the 2nd cycle with an interval of 3 weeks, in 3 weeks — MTX: methotrexate: 12 g/m^2 intravenous infusion with leucovorin, 4 injections with an interval of 14 days for young patients, after 3 weeks AI regimen was introduced: doxorubicin: 25 mg/m^2 on the 1st–3rd day intravenous as a 72-hour continuous infusion, ifosfamide: 2500 mg/m^2 on the 1st–4th day intravenous with uremitexane. All three regimens were repeated 3 times. If the tumor necrosis was less than 50%, the same regimens were used three times, but with the replacement of the AI regimen with the GemTax regimen: gemcitabine 900 mg/m^2 on the 1st, 8th day as a 90-minute infusion, docetaxel: 100 mg/m^2 on the 8th day. The

Table 1. *Histological Forms of the Tumor and the Number of Patients Who Underwent Chemoradiation Treatment before Endoprothetic Knee Replacement*

Nosological entity of the tumor	Number of cases, %	Chemoradiation, number of cases, %
Giant cell tumor of bone	26 (40%)	7 (26,9%) patients underwent radiotherapy
Osteogenic sarcoma	26 (40%)	26 (100%) patients underwent multiagent chemotherapy
Giant-cell sarcoma of bone	5 (7.7%)	5 (100%) patients underwent multiagent chemotherapy, of them 3 (60%) patients additionally underwent radiotherapy
Fibrosarcoma of bone	4 (6.2%)	4 (100%) patients underwent multiagent chemotherapy
Malignant fibro histiocytoma of bone	2 (3.1%)	2 (100%) patients underwent multiagent chemotherapy
Ewing sarcoma	1 (1.5%)	1 (100%) patient underwent multiagent chemotherapy and radiotherapy
Metastatic tumor	1 (1.5%)	1 (100%) patient underwent multiagent chemotherapy and radiotherapy
Total amount	65 (100%)	39 (60%) patients underwent multiagent chemotherapy, 12 (18,4%) patients underwent radiotherapy, a total number of 51 (78.5%) patients were treated

duration of treatment amounted to about 12 months. In case of Ewing sarcoma without metastases, we carried out chemotherapy according to the Scandinavian protocol. The treatment regimen included the following cytostatics: doxorubicin, ifosfamide, vincristine, dactinomycin. In the case of metastatic kidney tumor, targeted therapy was performed, which consisted of taking nexavar orally at a dose of 400 mg per day for a long time. In cases of giant cell tumor of bone, we used regimens, which included denosumab (prolia) 60 mg on the 1st, 8th, and 15th day, followed by organ-sparing surgery in the form of resection of bone with the tumor and knee joint endoprosthesis replacement. Twelve patients in the preoperative stage underwent a course of external-beam radiotherapy to a total radiation dose of 40 Gy, at a single tumour dose (amounts to 2–2.5 Gy), among which there were 7 patients with giant cell tumor of bone, 3 patients were with malignant giant cell tumor of bone, 1 patient with Ewing sarcoma, and 1 patient with metastatic tumor. Radiotherapy was indicated for treatment in case of these nosological entities due to the fact that these tumors according to experimental-clinical studies are sensitive to radiotherapy. The scope of surgical interference consisted of resection of the articular segment of the bone with an *en block* tumor and replacement of the bone defect with an individual oncological or individual modular oncological endoprosthesis. The functional result of the operated limb was calculated according to the MSTS scale (Musculo-Sceletal Tumor Staging/System/). Quality of life was determined as per EORTIC-QLQ-C30 questionnaire. Patient survival was assessed using the Kaplan-Meier method.

RESULTS AND DISCUSSION

As a result of knee endoprosthesis replacement conducted for the group (n = 39) of patients, who underwent courses of neoadjuvant and adjuvant multiagent chemotherapy, 16 (41%) patients presented with complications after endoprosthesis replacement: 3 (7.7%) patients presented with periprosthetic infection, 3 (7.7%) patients presented with tumor recurrence, 10 (25.6%) patients presented with metastases in lungs. After multiagent chemotherapy, almost all patients had leukopenia, anemia, thrombocytopenia, which was corrected by replacement therapy (administration of the Zarsio or Filstim drug, transfusion of one-group blood, platelet concentrate or thrombo-concentrate). 8 (20.5%) patients died during treatment due to metastases in lungs. In the group (n = 12) of patients who underwent a course of radiotherapy up to total radiation dose of 40 Gy in the preoperative period, 9 (75%) patients presented with complications after endoprosthesis replacement: 3 (27.3%) patients presented with periprosthetic infection, 3 (27.3%) patients presented with bone fracture at the site of endoprosthesis stem implantation, 2 (18.2%) patients presented with aseptic loosening of stem, 1 (9.1%) patient, having metastatic tumor (metastases of kidney cancer), presented with a post-radiation skin ulcer in the proximal crural region, suture line disruption, fistula, although inoculation from fistula to the microflora was negative. Data on complications patients presented with after chemoradiation during knee joint endoprosthesis replacement in terms of each nosological entity of the tumor are shown in Table 2.

3 patients having giant cell tumor of bone with periprosthetic infection underwent the following: in 2 cases revision of postoperative wound has been conducted, dialysis and a powerful course of antibiotic therapy has been produced, in the 1st case it was a removal of the endoprosthesis, an installation of a metal-cement spacer device followed by repeated joint endoprosthesis replacement. In cases of bone fracture at the site of endoprosthesis stem implantation in 2 cases metallic osteosynthesis was performed with cover

Table 2. *Complications caused by chemoradiation during knee replacement*

Nosological entity and number of patients	Provided treatment	Complications after treatment (including endoprosthesis replacement)
Giant cell tumor of bone – 26 patients	7 patients had radiotherapy	periprosthetic infection – 3 (42,8%), bone fracture at the site of endoprosthesis stem implantation – 2 (28,6%), aseptic loosening of stem – 2 (28,6%)
Osteogenic sarcoma – 26 patients	26 patients had multiagent chemotherapy	Periprosthetic infection – 2 (7,6%), tumor recurrence – 2 (7,6%); metastases – 9 (34,6%)
Giant-cell sarcoma of bone – 5 patients	5 patients had multiagent chemotherapy, 3 of them – radiotherapy	Bone fracture at the site of endoprosthesis stem implantation – 1 (33,3%)
Fibrosarcoma of bone – 4 patients	4 patients had multiagent chemotherapy	Periprosthetic infection – 1 (25%)
Malignant fibro histiocytoma of bone – 2 patients	2 patients underwent multiagent chemotherapy	Metastases – 1 (50%)
Ewing sarcoma – 1 patient	This patient underwent multiagent chemotherapy and radiotherapy	Tumor recurrence – 1 (100%)
Metastatic tumor (metastases of kidney cancer) – 1 patient	This patient underwent multiagent chemotherapy and radiotherapy	Post-radiation ulcer – 1 (100%)
Totally 65 patients	39 patients underwent multiagent chemotherapy, 12 patients underwent radiotherapy, totally 51 patient underwent treatment	Periprosthetic infection – 6 (11,8%), bone fracture at the site of endoprosthesis stem implantation – 3 (5,9%), aseptic loosening of stem – 2 (3,9%), post-radiation ulcer – 1 (2,0%), tumor recurrence – 3 (5,9%), metastases – 10 (19,6%)

plates and cable grip. In case of aseptic loosening of stem in 2 cases repeated joint endoprosthesis replacement was performed, in one case replacement was performed of complete endoprosthesis; in the other case only one femoral stem of endoprosthesis was replaced with the longer one. In respect of 2 patients with osteogenic sarcoma of bone with periprosthetic infection, removal of the endoprosthesis, and installation of a metal-cement spacer followed by repeated joint endoprosthetic replacement was performed, in respect of 2 patients with tumor recurrence in the 1st case hip amputation was performed, in the 2nd case hip disarticulation of hip joint was performed. In case of metastases in lungs, cycles of multiagent chemotherapy with metastasectomy were performed. Regarding the patient with a giant cell sarcoma of bone with a bone fracture at the site of endoprosthesis stem implantation, metallic osteosynthesis with periosteal plate and cable grip was performed. Regarding the patient with fibrosarcoma of bone with periprosthetic infection, the endoprosthesis was removed and a metal-cement spacer was installed, followed by repeated joint endoprosthetic replacement. The patient with a malignant fibrous histiocytoma of bone with multiple metastases in lungs received cycles of multiagent chemotherapy. The patient with Ewing sarcoma underwent hip amputation and courses of multiagent chemotherapy due to tumor recurrence. The patient with a metastatic tumor, where post-radiation ulcer complications were observed, underwent removal of the ulcer, removal of necrotic tissue, revision of the knee joint, and closure of the soft tissue defect and skin defect by shifting the medial gastrocnemius followed by free skin grafting. Stages of surgical interference are shown at Fig. 5–7.

The functional result (MSTS scale) of the lower extremity amounted to 88.2% after resection of the distal femur and knee joint endoprosthetic replacement, and functional result (MSTS scale) of the lower extremity amounted to 82.4% after resection of the proximal tibia and knee endoprosthetic replacement. Quality of life after knee joint endoprosthesis replacement (EORTIC-QLQ-C30 questionnaire) increased from 40 points before endoprosthesis replacement, to 80 points after endoprosthetic replacement. The overall three-year survival of patients was 68.2 ± 2.4%, the five-year survival of patients was 51.8 ± 3.2%.

An case study from our practice: Patient G., 62 years-old was admitted to the Institute of Traumatology and Orthopedics (Kyiv, Ukraine), with the following diagnosis: metastasis of kidney cancer to the distal segment of femoral bone, clinical group II. According to her medical case history she underwent nephrectomy in 2018. In 2019 the patient felt pain in her left thigh. The destruction in the distal femur of her thigh was detected at an additional x-ray examination (Fig. 1). Core needle biopsy of a neoplasm of the femoral bone was performed. Pathohistological findings: metastasis of clear cell renal cell cancer. After that the patient received a cycle of radiotherapy for femoral metastasis in the total radiation dose of

40 Gy. Two weeks after radiotherapy a pathological fracture of the femoral bone was observed on the radiograph (Fig. 2). Six weeks later, on August 5, 2020, the patient was operated on: resection of the tumor in distal segment of the left femoral bone followed with knee endoprosthetic replacement using an individual Beznoska endoprosthesis (Fig. 3). In the post-surgery period, a post-radiation skin ulcer in the lower third of the thigh and disruption of the suture line of the postoperative wound were observed (Fig. 4). Inoculation of the postradiation ulcer of the knee joint was carried out, conclusion: no microorganisms were detected. On October 8, 2020, the Patient underwent surgical interference — removal of post-radiation ulcer and necrotic tissue, revision of the knee joint, sanation and transposition of Gastrocnemius medial head to the anterior surface of the knee joint to cover the soft tissue defect (Fig. 5–6). On October 15, 2020, the Patient underwent another surgical interference — free skin grafting of the skin defect of the anterior surface of the left lower leg with an autodermal graft, which was taken from the lateral surface of the left thigh (Fig. 7). In the post-surgery period, complications connected with skin and postoperative wound were not observed, the stitches were removed. The patient was discharged under the supervision of an oncologist.

Fig. 1. *Patient G., metastatic lesion of the femoral bone*

Fig. 2. *Patient G., pathological femur fracture on the background of metastatic lesions after radiotherapy*

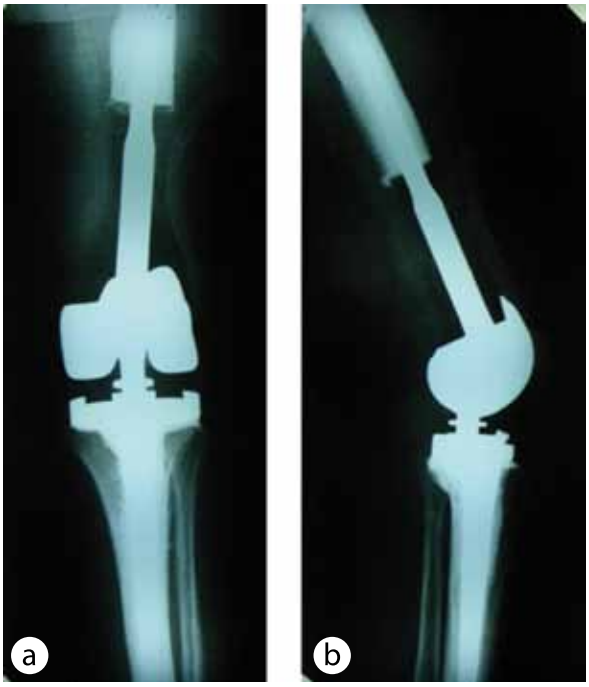

Fig. 3. *Patient G, a — frontal view, b — lateral view — after resection of the distal segment of the femur with a tumor and endoprosthetic replacement using Beznoska endoprosthesis*

RESULTS AND DISCUSSION

Our outcomes have shown the complications from exposure to multiagent chemotherapy on knee reconstruction. A periprosthetic infection was found in 7.7% of cases. We believe that this complication is related to a decrease in the patient's phylactic power. When using radiotherapy in the preoperative stage, the patients presented with the following complications after endoprosthesis replacement: periprosthetic infection in 27.3% of cases, bone fracture at the site of endoprosthesis stem implantation in 27.3% of cases, aseptic loosening of stem in 18.2% of cases, and post-radiation ulcer in 9.1% of cases. We believe that bone fracture at the site of endoprosthesis stem implantation and aseptic loosening of stem takes place due to the effect of radiotherapy on sound bone, which is located in close proximity to the tumor. We evaluate the post-radiation ulcer of the skin in Patient G, as the effect of inadequate dose of radiotherapy on the skin. Several methods of eliminating complications of periprosthetic infection were as follows: removal of the endoprosthesis, installation of a metal-cement spacer followed by repeated joint endoprosthesis replacement; in cases of bone fractures at the site of endoprosthesis stem implantation it included metallic osteosynthesis with periosteal plates and cable grip; repeated joint endoprosthesis replacement was performed in cases of aseptic loosening of stem; revision of the wound, removal of necrotic tissue and closure of the wound by moving the Gastrocnemius medial head with subsequent free skin grafting was carried out in case of postradiation ulcer, hip amputation or disarticulation was carried out in case of recurrence;

Fig. 4. Patient G. Area of the knee joint with post-radiation ulcer

Fig. 7. Patient G., Free skin grafting of the skin defect on the anterior surface of the lower leg with autodermal graft

Fig. 5. Patient G., revision of the knee, removal of necrotic tissue.

Fig. 6. Patient G., transposition of the medial gastrocnemius to the anterior surface of the lower leg to cover the soft tissue defect

multiagent chemotherapy with metastasectomy was performed in case of metastases in lung. According to the literature, post-radiation damage to bones is usually accompanied by postradiation changes in skin and subcutaneous tissue [3, 11]. The main task of surgical repair regarding patients with local post-radiation lesions includes a radical excision of the diseased tissues and adequate replacement of the defect. In such cases, it is advisable to use myocutaneous flaps and muscle flaps [10]. Patients having malignant tumor of bone, who underwent the complete multimodal treatment phase, were recommended to undergo case follow-up every 3 months for the first 2 years, then every 6 months for the next 3 years. According to some researchers, mandatory examinations shall include computed tomography of thoracic cavity, x-ray examination of the implant intallation area, and ultrasonic investigation of the postoperative cicatrix [7]. Case follow-up is done to detect early orthopedic complications, instability of endoprosthesis stem, recurrence and metastases of the tumor and to address the further treatment strategy: to conduct chemoradiation or surgical treatment of recurrent tumors and resectable metastatic sites.

CONCLUSION

1. The use of multiagent chemotherapy arises complications during knee replacement, such as periprosthetic infection in 7.7% of cases due to a decrease in the patient`s phylactic power. The main strategy for eliminating complications of periprosthetic infection included removal of the endoprosthesis, installation of a metal-cement spacer, followed by repeated joint endoprosthesis replacement.

2. The use of radiotherapy also arises complications, such as periprosthetic infection, bone fracture

at the site of endoprosthesis stem, aseptic loosening of stem and post-radiation ulcer due to the impact of radiotherapy on the skin and sound bone in the immediate vicinity of the tumor.

3. Surgical treatment of postradiation osteomyelitis, fibrosis and ulcers involves extensive excision of all affected tissues in a single block, and replacement of soft tissue defects with myocutaneous flaps and muscle flaps.

Conflict of interest

This paper does not cause any conflict between the authors, has not been and will not be the subject of commercial interest or reward in any form.

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