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Proximal tibial osteosarcoma in young patients: early diagnosis, modular reconstruction

RĂZVAN ENE[1)], RUXANDRA DIANA SINESCU[2)], PATRICIA ENE[3)], DAN POPESCU[1)], MONICA MIHAELA CÎRSTOIU[4)], FLORIN CĂTĂLIN CÎRSTOIU[1)]

[1)]*Department of Orthopedics and Traumatology, Emergency University Hospital, Bucharest, Romania*
[2)]*Department of Plastic Surgery and Reconstructive Microsurgery, "Elias" Emergency University Hospital, Bucharest, Romania*
[3)]*Department of ENT, Emergency University Hospital, Bucharest, Romania*
[4)]*Department of Obstetrics and Gynecology, Emergency University Hospital, Bucharest, Romania*

Abstract

Osteosarcoma is the most common bone tumor that occurs in children and young adults with prevalence of teenage. There can be identified many subtypes of osteosarcoma by how they look on X-rays and under the microscope. Osteosarcoma can be classified as high-grade, intermediate grade, or low-grade. This has a significant prognostic value of tumor development suggesting the growth rate and the potential for expansion. Between 2009–2013, in the Department of Orthopedics and Traumatology, University Emergency Hospital of Bucharest, Romania, were treated seven cases of osteosarcoma of the proximal third of the tibia in young, early-diagnosed cases without metastasis. The treatment involved resection of tumor formation and reconstruction with a modular prosthesis. Postoperative patients were mobilized for a week without charging the operated limb under the protection of orthesis. During this period continued active and passive mobilization of the ankle and foot to prevent stiffness and to reduce postoperative swelling. From the second postoperative week, patients are mobilizing with progressive charging but not being allowed to do any flexion in order to protect de insertion of medial gastrocnemius muscle rotation flap used to cover the prosthesis and to protect the patellar tendon reinsertion. This extensive surgery does not improve survival rate of these patients compared to treatment by amputation of this pathology but greatly increases the comfort of life and in all cases ensure socio-professional reintegration of these patients. To ensure optimal postoperative results perform a complete diagnosis and preoperative oncological treatment before surgery, if applicable.

Keywords: osteosarcoma, modular prosthesis, functional recovery, oncological treatment.

Introduction

The osteosarcoma is so-called, because it is a cancerous tumor that is derived from a mesenchymal stem cell precursor that after becoming malignant produce immature woven bone, or osteoid, which is the reason for this tumor to be named osteosarcoma. This tumor may be starting from bone cells or can also rarely arise from soft tissues of the extremities [1, 2].

In addition to classification of osteosarcoma by aggressiveness and prognostic, there is another classification regarding the origin of the tumor: intramedullary (the most frequent), juxtacortical, intracortical. Of all types of osteosarcoma, the most commonly found in a proportion of 75% is the primary osteosarcoma with high grade of differentiation, intramedullary located [3].

This tumor has a high risk of metastasis, most often disseminating locally, in the same extremity or systemically, most commonly involving the lung, when worsens dramatically the prognosis and completely change the therapeutic attitude. Metastases that develop in the same extremity or exceed neighboring joints are called skip metastases. Eighty percent of the tumors at the time of diagnosis are metastases free [4].

Osteosarcoma develops radial, in an inside-outside manner penetrating the cortex and infiltrating the surrounding muscles, and creating a reactive tumoral area that during the operation should be removed between oncological limits.

Many decades ago, the only treatment for this disease was the amputation but, starting with the last years effective induction (neoadjuvant/preoperative) and adjuvant (postoperative) chemotherapy protocols have improved the ability to perform safe limb-sparing resections, and have also improved the survival rates [5, 6].

The purpose of this study is to determine the optimal attitude in front of a proximal tibial osteosarcoma case, knowing the high incidence of this type of tumor in young patients, requiring orthopedic surgeons to use limb rescue techniques avoiding amputation of the affected limb.

Patients and Methods

Between 2009–2013, in the Department of Orthopedics and Traumatology, University Emergency Hospital of Bucharest, Romania, were treated seven cases of osteosarcoma of the proximal third of the tibia in young patients. Mean age was 22 years, with a range between 17 and 29-year-old. Gender ratio: two males/five females. One of the patients was from rural areas and the other six were from urban areas. No patient had risk factors or family history.

Clinical symptoms of patients started with localized pain in the proximal third of the tibia for weeks or sometimes months, most often associated with a sports or domestic injury. Pain gradually become more severe and accompanied by swelling and limitation of motion.

In all cases, the pain was more pronounced at night awaking from sleep sometimes.

Clinical examination revealed tenderness, a certain degree of muscle atrophy, limitation of movement of adjacent joints and to palpation, swelling or deformity suggesting the presence of a mass. None of the patients had weight loss because there were no secondary determinations at the time of diagnosis. After clinical exam, standard X-ray (using a Swissray machine) examination was performed and in order to achieve better anatomical details, and the expansion of the tumor CT (Siemens single source CT scanner) and MRI was performed.

In order to exclude other secondary determinations, or associated pathology and the presence of metastases, chest, and abdomino-pelvic CT was taken in every case. For the biological activity of the tumor, and to evaluate secondary determinations, whole body bone scintigraphy was performed with Tc-99m, and SPECT was performed. Angiography was routinely performed in order to describe and to evaluate the blood supply of the tumor.

In order the exclude other malignant pathology or the presence of bone metastases the following tumor markers were examined: TNF-β, CA 125 and CA 19-9.

Diagnosis was made after imaging examinations, biological and histopathological examination of tumor tissue harvested performed by incisional biopsy and for tumor classification we used the Enneking system. After incisional biopsy the tissue samples was examined using standard paraffin slices, with Hematoxylin and Eosin (HE) staining, the following cellular aspects were highlighted: nuclear pleomorphism, number of atypical cell mitosis, hematic invasion of the tumor cells; due to the histological results, osteosarcomas were classified in low- and high-grade malignant osteosarcomas.

After the aforementioned examinations, the patients underwent to surgical removal of the tumor and to limb sparing surgery, with special modular prosthetic replacement of the affected joint and bone segment.

Results

The clinical appearance of osteosarcoma consists in palpable mass, with a fast growing aspect in last months. This aspect of the tumor often leads to skin lesions, night pain and in some cases diurnal pain (the pain occurred in the knee as well) and compressive vascular or nervous symptoms (Figure 1). These sarcomas were generated swelling in three cases, as they increased. One of the patients with advanced malignancy showed lameness at admission.

Routine laboratory examinations in tumoral pathology showed an increase of alkaline phosphatase (N: 40–136 U/L) and erythrocyte sedimentation rate – ESR (N: 5–10 mm/h). Other laboratory results and tumor markers like TNF-β, CA 125 and CA 19-9 were within normal ranges, excluding other malignant pathology or bone metastases.

For X-ray analysis, we used plain-film radiographs to cover the entire affected limb. Typical image of osteolysis was represented in some of the patients alternating with areas of osteosclerosis and in cases where the tumor was revealed as cortical exceeded there was revealed the formation of a soft tissue mass (Figure 2). In one case, a pathologic fracture was also identified.

MRI was useful to identify local extension of the tumor and the invasion in the surrounding soft parts. This way it was detected the relationship of the tumor to the neurovascular bundle, and resectability could be estimated. There was no neurovascular encasement. This investigation established accurately the limit of osteotomy 3 cm away from the tumor in order to have tumoral-free resection edges.

CT is complementary to MRI; it is useful in assessing extraosseous and intraosseous extension and in cases of necrosis and edema around the tumors, it was superior to MRI (Figures 3 and 4). It was also useful evaluating the response to preoperative chemotherapy and looking for pulmonary metastases.

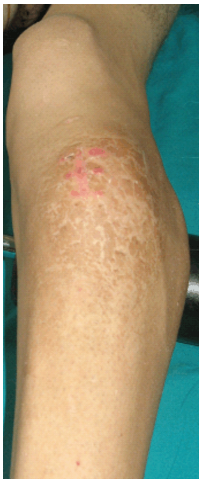

Figure 1 – ***Clinical deformity.***

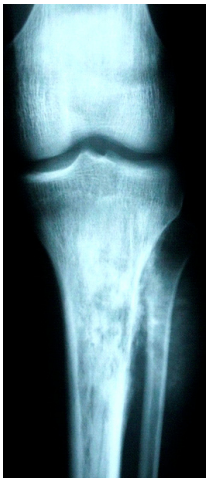

Figure 2 – ***Cortical exceed.***

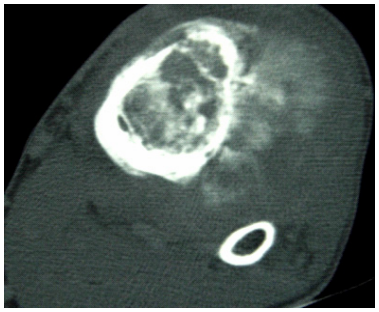

Figure 3 – ***Peri-tumoral edema.***

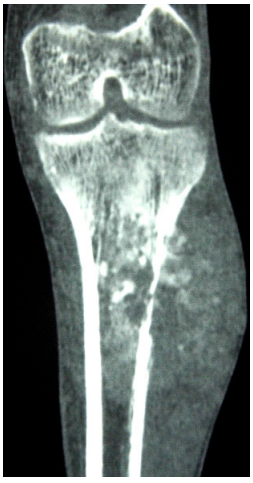

Figure 4 – ***Extraosseous extension.***

Whole body bone scintigraphy was performed in order to detect bone metastases and skip metastases. All of the affected regions have shown hypercaptation in metabolic phase, without secondary determinations of the tumor in other anatomical regions (Figure 5).

The angiographic exam showed an increase vascularization of the tumor tissue, in one case being necessary a preoperative embolization.

Regarding the Enneking system international classification, in five cases the tumor was stage IIA (high-grade,

intracompartmental, non-metastatic) and in two cases, it was stage IIB (high-grade, extra-compartmental, non-metastatic).

In all cases, incisional biopsy was the key step in the diagnosis, the collected tissue being sent for histopathological examination and immunohistochemistry (Figures 6–8).

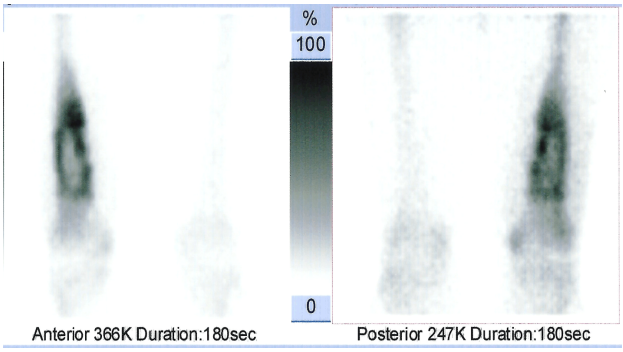

Figure 5 – ***Bone scintigraphy with Tc-99m showing hypercaptation in metabolic phase of the right distal femur.***

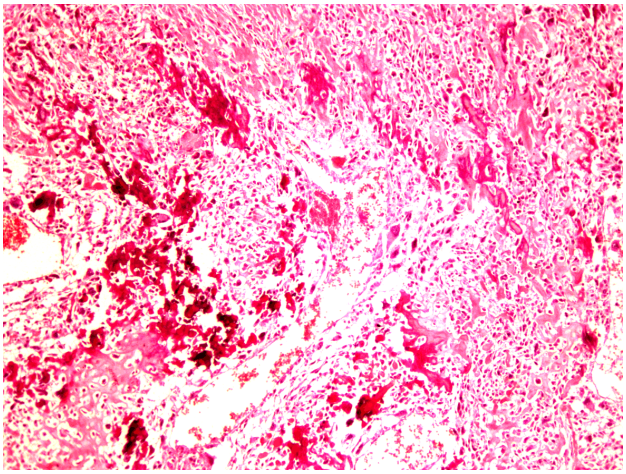

Figure 6 – ***Osteoid osteosarcoma, vascular gaps, pleomorphic atypical cells. HE staining, ×100.***

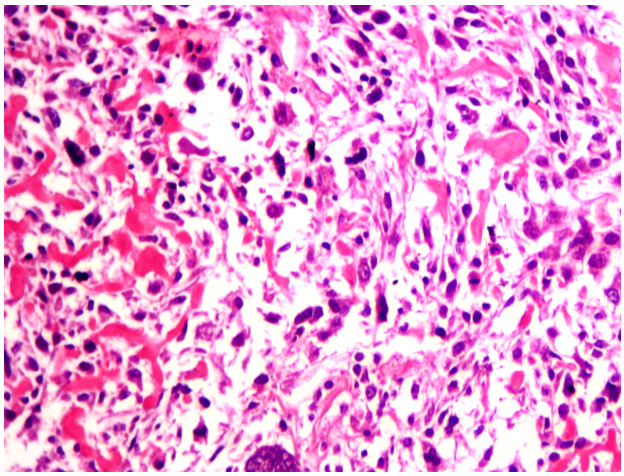

Figure 7 – ***Image detail of osteosarcoma, atypical mitosis, atypical cells. HE staining, ×400.***

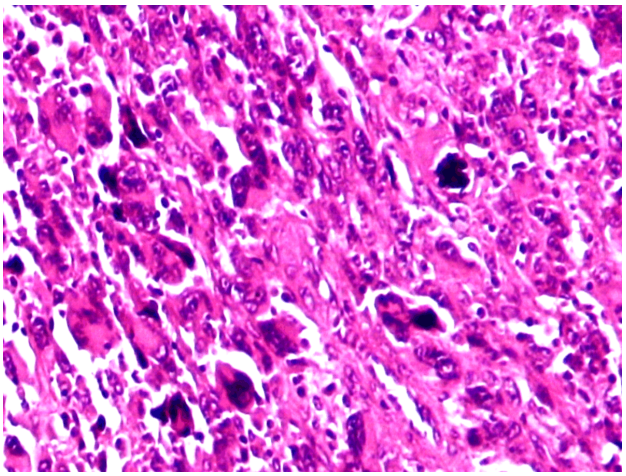

Figure 8 – ***High-grade malignant osteosarcoma, with atypical mitosis, atypical polymorphic hyperchrome cells. HE staining, ×400.***

Chemotherapy is very important in the treatment of osteosarcoma. It showed a substantial increase in survival after chemotherapy and also a decrease in the rate of relapse and the risk of metastasis.

In only half of the cases, we performed preoperative chemotherapy and in all of cases, postoperative chemotherapy. In patients in whom preoperative chemotherapy was performed, after the remove of the tumor, we worked the tumoral necrosis index, which had values between 70–90%, which means a very good response to chemotherapy. The percentage of tumor cell necrosis (cell death) seen in the tumor after surgery gave us an idea of the prognosis and also let the oncologist know if the chemotherapy regime should be altered after surgery.

All the patients were treated with limb sparing surgery and reconstruction of a viable, functional extremity. In the seven patients included in the study, we used two types of prostheses with different design but on the same principles (Figures 9–12). We performed a radical resection of proximal tibia with control, for margin clearance and reconstruction of the knee joint and upper tibia with modular titanium total knee hinge prostheses and also medial gastrocnemius muscle rotation flap to cover the prostheses and to protect the patellar tendon fixed to the tibial system.

After chemotherapy has been completed postoperatively, the orthopedic surgeon and oncologist followed the patients closely every three months for local and systemic recurrence.

Postoperative patients were mobilized for a week without charging the operated limb under the protection of orthosis. Two weeks after surgery, patients begin to walk with progressive loading on the operated limb without doing any flexion in order to protect the muscle flap that covers and protects the patellar tendon. Three weeks postoperatively the patients begin active and passive mobilization of the knee without registering any rupture or disinsertion of extensor apparatus in any patient. They had good joint stability, with good to excellent function in all cases (Figure 13, a and b). Tumoral endoprostheses were associated with only minimal early postoperative complications.

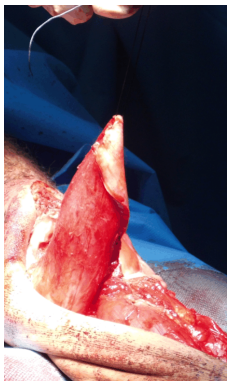

Figure 9 – ***Muscle flap preparation.***

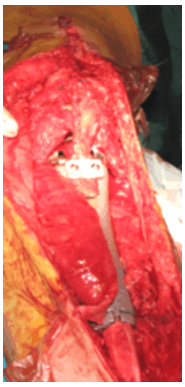

Figure 10 – ***Tendon attachment.***

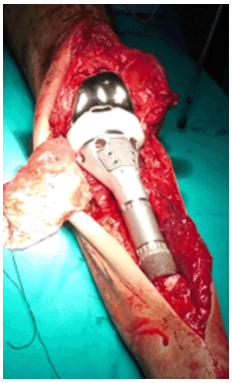

Figure 11 – ***Modular prosthesis.***

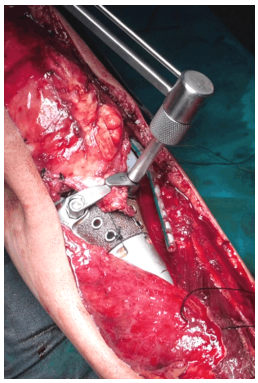

Figure 12 – ***Patellar tendon reattachment.***

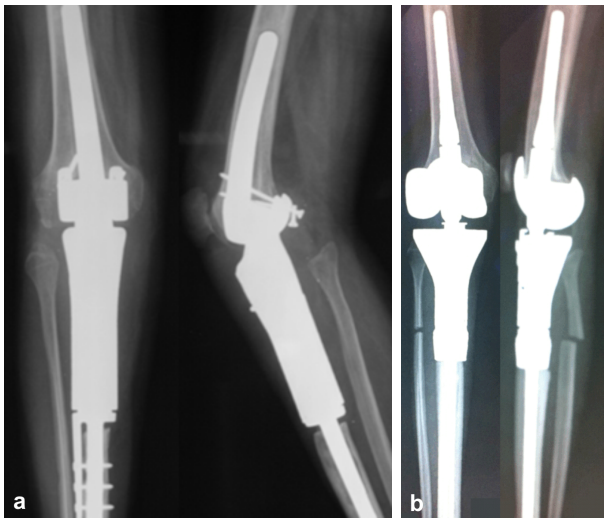

Figure 13 – ***(a and b) Post-operative X-ray aspects: two different types of prosthesis, antero-posterior and lateral incidence; knee prosthesis after limb-sparing surgery.***

So far, there are no signs of local recurrence. Three years after surgery one patient developed a septic complication of the prosthesis. After an attempt of rehabilitation trying to keep the prosthesis, we decided to remove the prosthesis and replace it with an acrylic cement spacer impregnated with antibiotics until getting local sanitation.

Patients showed a decrease in levels of physical activity without affecting postoperative limb function operated. Social and family reintegration was fast in all cases, two of the patients was planned to change their work with a physically less demanding one.

Discussion

The etiology of osteosarcoma is still unclear; several theories have been described, which may lead to malignant proliferation of bone cells. Fuchs and Pritchard underline the presence of chemical agents like beryllium, viruses, irradiation as potential factors in the etiology of osteosarcoma [6]. Recent studies show that hereditary diseases, like retinoblastoma, Rothmund–Thomson syndrome, Bloom syndrome, Li–Fraumeni syndrome increase the risk of developing osteosarcoma [7]. In our study, none of the aforementioned diseases were present. Viral infection may be an important etiological factor of osteosarcoma due to the intracellular growth, and DNA modification. The key investigation in our cases for the diagnosis is the histological examination; however, immunohistochemistry plays an important but limited role in primary bone tumors. Pringle, in a recent study, showed that immunohistochemistry may be more confusing than helpful; he also underlines the fact that the results should be carefully assessed taking into account the clinical and radiological features and the morphological aspects of HE sections [8].

The development of imagistic examination, like 3D CT, MRI, PET, whole body scintigraphy, and a good interdisciplinary cooperation between different specialties improved the prognostics of osteosarcoma. However, osteosarcoma is often diagnosed in late stages with metastases, which worsens the prognosis in which only palliative treatment can be applied [9–12]. Recent studies have proved that metastases can appear, with similar mechanism to prostatic cancer metastases, *via* Batson venous plexus. Hatori *et al.*, in a recent study, demonstrated lymphatic spread to the lungs as possible routes for metastases [13]. None of our cases had metastases in the time of investigations, and surgical treatment.

Thirty years ago, amputation was the sole treatment for a high-grade osteosarcoma, and more than half of patients died of metastatic disease, especially to the lungs [14]. Due to the current attitude, the use of chemotherapy as a (neoadjuvant/preoperative) and adjuvant (postoperative) protocol have improved the ability to perform safe limb-sparing resections seeing a significant increase in survival [15–18]. Today, over 90% of patients with osteosarcoma can be treated with limb-sparing surgery, and 70% of patients with localized disease are long-term survivors but this situation has accentuated the need for durable methods of reconstruction of large musculoskeletal defects [19].

Our study underlines the importance of early and correct diagnosis. Surgical treatment with modular prosthesis reconstruction of ostesarcoma, allows limb salvage and do not affect the quality of life. The surgical and chemotherapeutic combination in therapy has proven its efficacy [20, 21].

Conclusions

Due to the early diagnosis of osteosarcoma and the absence of metastases surgical removal and so-called limb-sparing treatment could be applied in every case

with modular prosthetic reconstruction. Surgical treatment and adjuvant chemotherapy makes this pathology to have a good prognostic index, without worsening the quality of life. We conclude that the function of the operated limb never achieves the same functional level as the opposite normal extremity, however the quality of life does not change significantly, allowing to the patient daily normal activities. It must be emphasized that the main goal of generally treatment of osteosarcoma is to provide a longer relapse-free survival and only the second goal is to preserve the limb function.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Beaty JH. Malignant tumors of bone. In: Canale ST, Beaty JH. Campbell's operative orthopaedics. 11th edition, Mosby, 2007, 901–907.

[2] Huth JF, Eilber FR. Patterns of recurrence after resection of osteosarcoma of the extremity. Strategies for treatment of metastases. Arch Surg, 1989, 124(1):122–126.

[3] Meyers PA, Heller G, Healey JH, Huvos A, Applewhite A, Sun M, LaQuaglia M. Osteogenic sarcoma with clinically detectable metastasis at initial presentation. J Clin Oncol, 1993, 11(3):449–453.

[4] Bacci G, Picci P, Ferrari S, Ruggieri P, Casadei R, Tienghi A, Brach del Prever A, Gherlinzoni F, Mercuri M, Monti C. Primary chemotherapy and delayed surgery for nonmetastatic osteosarcoma of the extremities. Results in 164 patients preoperatively treated with high doses of methotrexate followed by cisplatin and doxorubicin. Cancer, 1993, 72(11):3227–3238.

[5] Bacci G, Ferrari S, Mercuri M, Longhi A, Capanna R, Tienghi A, Brach del Prever A, Comandone A, Cesari M, Bernini G, Picci P. Neoadjuvant chemotherapy for extremity osteosarcoma – preliminary results of the Rizzoli's 4th study. Acta Oncol, 1998, 37(1):41–48.

[6] Fuchs B, Pritchard DJ. Etiology of osteosarcoma. Clin Orthop Relat Res, 2002, 397:40–52.

[7] Ottaviani G, Jaffe N. The etiology of osteosarcoma. Cancer Treat Res, 2009, 152:15–32.

[8] Pringle J. The value of immunohistochemistry in the diagnosis of primary bone tumors. Symposium 15: Progress in Bone Pathology, Rev Esp Patol, 1999, 32(3):362–366.

[9] van der Bijl AE, Taminiau AH, Hermans J, Beerman H, Hogendoorn PC. Accuracy of the Jamshidi trocar biopsy in the diagnosis of bone tumors. Clin Orthop Relat Res, 1997, 334:233–243.

[10] Bickels J, Jelinek JS, Shmookler BM, Neff RS, Malawer MM. Biopsy of musculoskeletal tumors. Current concepts. Clin Orthop Relat Res, 1999, 368:212–219.

[11] Mankin HJ, Mankin CJ, Simon MA. The hazards of the biopsy, revisited. Members of the Musculoskeletal Tumor Society. J Bone Joint Surg Am, 1996, 78(5):656–663.

[12] Aisen AM, Martel W, Braunstein EM, McMillin KI, Phillips WA, Kling TF. MRI and CT evaluation of primary bone and soft-tissue tumors. AJR Am J Roentgenol, 1986, 146(4):749–756.

[13] Hatori M, Ohtani H, Yamada N, Uzuki M, Kokubun S. Synchronous multifocal osteosarcoma with lymphatic spread in the lung: an autopsy case report. Jpn J Clin Oncol, 2001, 31(11):562–566.

[14] Marcove RC, Miké V, Hajek JV, Levin AG, Hutter RV. Osteogenic sarcoma under the age of twenty-one. A review of one hundred and forty-five operative cases. J Bone Joint Surg Am, 1970, 52(3):411–423.

[15] Link MP, Goorin AM, Miser AW, Green AA, Pratt CB, Belasco JB, Pritchard J, Malpas JS, Baker AR, Kirkpatrick JA, Ayala AG, Shuster JJ, Abelson HT, Simone JV, Vietti TJ. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med, 1986, 314(25):1600–1606.

[16] Eckardt JJ, Eilber FR, Dorey FJ, Mirra JM. The UCLA experience in limb salvage surgery for malignant tumors. Orthopedics, 1985, 8(5):612–621.

[17] Eilber F, Giuliano A, Eckhardt J, Patterson K, Moseley S, Goodnight J. Adjuvant chemotherapy for osteosarcoma: a randomized prospective trial. J Clin Oncol, 1987, 5(1):21–26.

[18] Meyers PA, Heller G, Healy J, Huvos A, Lane J, Marcove R, Applewhite A, Vlamis V, Rosen G. Chemotherapy for non-metastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. J Clin Oncol, 1992, 10(1):5–15.

[19] Henshaw RM, Bickels J, Malawer MM. Modular endoprosthetic reconstruction for lower extremity skeletal defects: oncologic and reconstructive indications. Semin Arthroplasty, 1999, 10(3):180–187.

[20] Thompson RC Jr, Cheng EY, Clohisy DR, Perentesis J, Manivel C, Le CT. Results of treatment for metastatic osteosarcoma with neoadjuvant chemotherapy and surgery. Clin Orthop Relat Res, 2002, 397:240–247.

[21] Harris MB, Gieser P, Goorin AM, Ayala A, Shochat SJ, Ferguson WS, Holbrook T, Link MP. Treatment of metastatic osteosarcoma at diagnosis: a Pediatric Oncology Group Study. J Clin Oncol, 1998, 16(11):3641–3648.

Corresponding author

Răzvan Ene, MD, PhD, Department of Orthopedics and Traumatology, Emergency University Hospital, 169 Independenţei Avenue, 050098 Bucharest, Romania; Phone +40740–082 338, e-mail: razvan77ene@yahoo.com

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