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Current Therapeutic Approaches for Osteosarcoma

Recep Öztürk

Abstract

Osteosarcoma is classically defined as a high-grade spindle-shaped neoplasm with malignant cells that produce osteoid. It is the most common primary malignant bone tumor in children and young adults. It is <1% of all cancers diagnosed, approximately 3.4% of all childhood cancers. The age-adjusted incidence of osteosarcoma is bimodal, with an initial peak in adolescence and then a second peak in patients over 60 years of age. Osteosarcoma is divided into two main groups. In most of the osteosarcomas, the etiological agent cannot be determined and it is called primary osteosarcoma. Osteosarcoma, which develops due to etiologies such as Paget's disease, radiotherapy or osteonecrosis, is called seconder osteosarcoma. Osteosarcomas are most commonly located in the appendicular skeleton. The most common settlement here is the knee circumference. The distal femur and proximal tibia are the most common locations in the knee. A multidisciplinary approach is indicated in the management of osteosarcoma. The treatment is multimodal, including systemic chemotherapy and local therapy. In this section, we will outline the current standard of care for the systemic and surgical approach to osteosarcoma treatment, as well as an overview of current studies.

Keywords: osteosarcoma, recent advances, management, current approach, treatment

1. Introduction

Osteosarcoma is the most common primary malignant bone tumor. It consists of malignant mesenchymal cells that tend to form osteoid matter. It is defined as the most common bone malignant tumor after multiple myeloma and metastases [1, 2].

Three-quarters of all cases are between the ages of 10–25. The age-adjusted incidence of osteosarcoma is bimodal, with an initial peak in adolescence and then a second peak in patients over 60 years of age [3].

Osteosarcoma is most often located around the knee. Distal femur and proximal tibia are the most common knee localizations. The most common location after knee circumference is the proximal humerus. The most common location of the tumor in the bone is the metaphysis like many other tumors. It can rarely settle in the diaphysis [4].

2. Etiology and risk factors

In osteosarcoma cases in pediatric patients, almost all cases do not have any identifiable associated risk factors.

It has been determined that in almost half of the osteosarcoma cases seen in adult patients, various risk factors such as Paget's disease and radiation are involved in the etiology. In addition, some syndromes such as Li Fraumeni Syndrome, hereditary retinoblastoma syndrome, have been reported as risk factors for osteosarcoma [5].

Studies have been conducted on the genetic profile of osteosarcoma in recent years. Studies have reported that Germline TP53 mutations may be high in osteosarcomas, especially at younger ages. In osteosarcomas seen at a young age, if the location of the tumor is unusual, further examination is recommended in terms of Li-Fraumeni syndrome [6].

3. Classification

Osteosarcoma is divided into two main groups as primary and secondary osteosarcoma. Primary osteosarcoma is divided into subtypes such as classical osteosarcoma, telangiectatic osteosarcoma, small cell osteosarcoma, multicentric osteosarcoma, high grade central osteosarcoma, low grade surface osteosarcoma, and superficial (parosteal-periosteal) osteosarcoma [7].

Various etiological factors play a role in secondary osteosarcoma. Osteosarcoma secondary to Paget's disease, osteosarcoma secondary to radiotherapy, osteosarcoma secondary to osteonecrosis, osteosarcoma secondary to fibrous dysplasia are some of the secondary osteosarcoma types [5].

4. Clinical findings and diagnosis

The most common clinical finding is pain and is seen in approximately 90% of patients. The second most common finding is swelling in the bone localization and is detected in approximately 50% of cases. Generally, patients present with complaints of pain and swelling in that area for weeks-months. Another finding is limitation of movement and is seen in approximately 45% of cases. In addition, patients rarely present with pathological fractures (about 8%) [8].

Alkaline phosphatase was found to be high in about half of osteosarcoma patients. High levels of lactate dehydrogenase at the time of diagnosis were found to be associated with relapse. In addition, Lactate dehydrogenase levels are also high in metastatic patients [8, 9].

In radiological evaluation, firstly, anteroposterior and lateral radiographs of the relevant region should be taken (**Figure 1**). When direct X-ray findings, bone involving the lesion, location of the tumor in the bone, age and gender of the patient are evaluated together, a correct diagnosis can be made in most of the cases (more than three quarters of the cases) [10].

Cortex destruction, geographic or moth-eaten-like medullary lesion, sunlight-like periosteal reaction, Codman triangle, and soft tissue shadow in the bone neighborhood can be seen on plain X-ray [11].

Whenever there is any doubt about the nature of a bone lesion in a young patient, CT and/or MRI should be performed. Thus, new bone formation, cortical destruction, or soft tissue component that may indicate malignancy can be detected (**Figure 2**). In addition to imaging the primary tumor, MRI should be taken to view the entire bone to detect possible skip metastases [12].

Performing the MRI test before any biopsy attempt is vital, as reactive changes due to biopsy reduce staging accuracy [13].

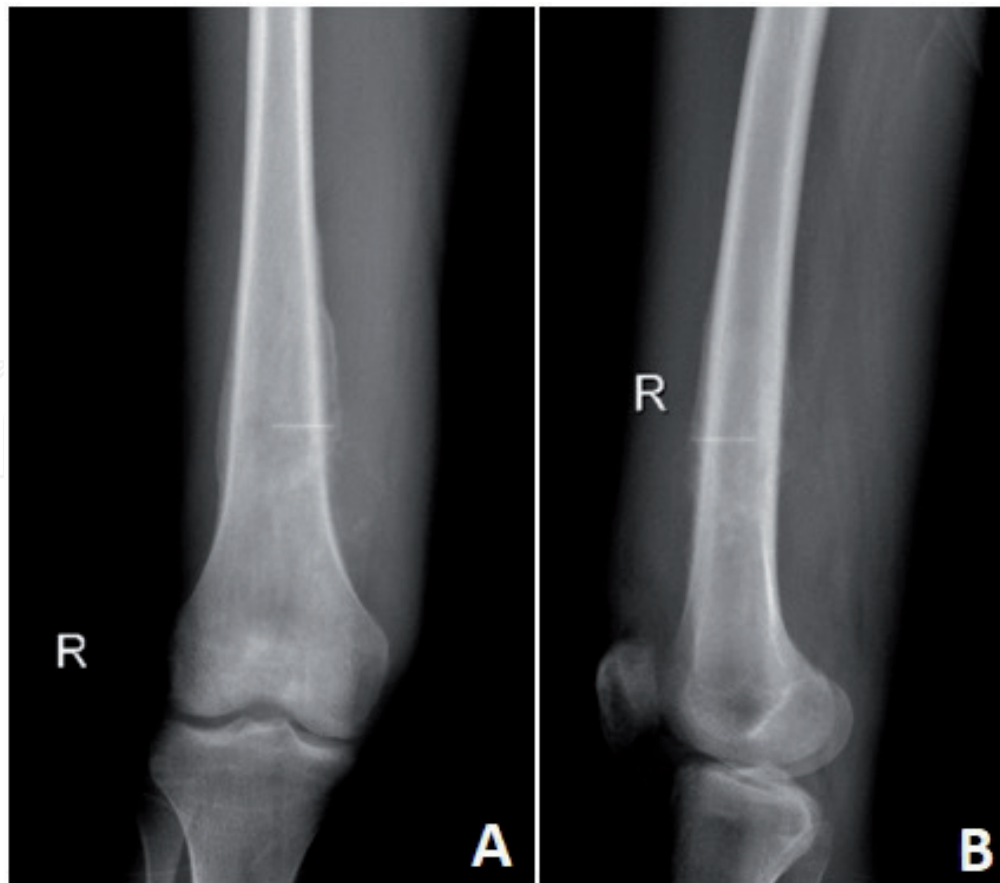


Figure 1.
Right femur distal located osteosarcoma, a) anteroposterior and b) lateral radiography.

Radiological examinations are examined for the presence of findings specific to malignant bone tumors. These findings are sclerotic lesions that are located mostly in the metaphysis, progressing towards the epiphysis or diaphysis or laterally, radial calcified areas, disruption of the cortex integrity, fragmentation or elevation of the periosteum, Codman triangle and extension of the lesion to the soft tissue [11, 14].

The definitive diagnosis is made after the histopathological examination of the biopsy specimen. Biopsy should be done by the team that will make the definitive treatment of the patient. The formation of osteoid material and the presence of atypical osteoblasts are diagnostic. CT-assisted needle biopsies and, if necessary, incisional biopsy should be performed in the trace of the original surgical incision [2].

5. Staging

Osteosarcoma is considered a systemic disease. Tumor cells are present in the circulating blood and tumor micro-metastases are possible in the lungs. Approximately 10–20% of osteosarcoma patients are metastatic at the time of diagnosis [15].

It is a three-grade system generally used in determining tumor grade. Grade 1 represents low grade. There is a well-differentiated tumor. Grade 2 represents middle grade, there is a moderately differentiated tumor. Grade 3 represents high grade, there is an undifferentiated tumor. If the tumor grade is low, the tumor is resistant to chemotherapy and radiotherapy [2, 7].

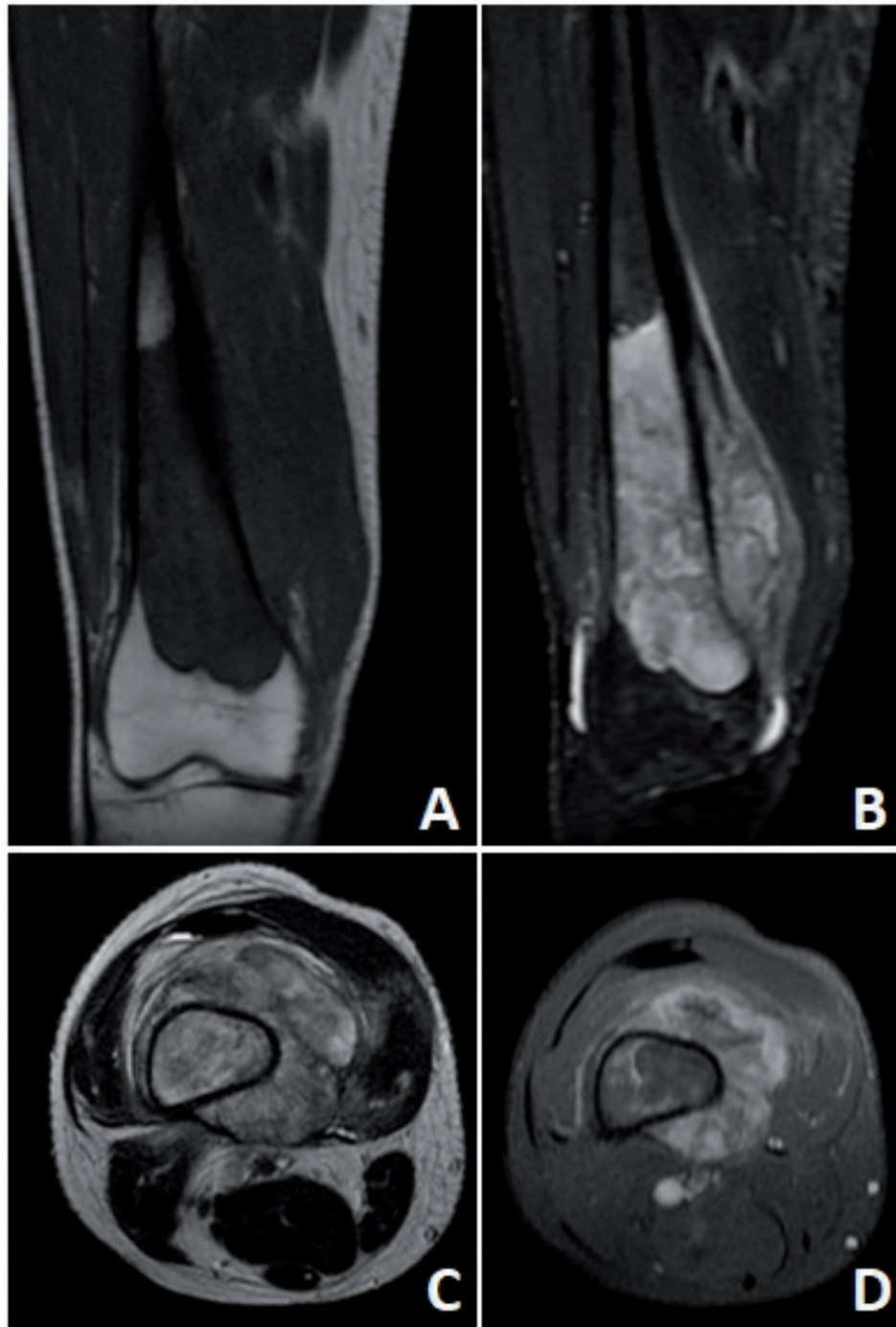


Figure 2. MRI images involving the right femur distal and joint; a) coronal T1 sequence, b) coronal T2 - STIR image, c) axial T2 sequence and d) T1 + contrast image. In the images, the distal third of the right femur has an extension to the superior part of the inner femoral condyle and the midline distal of the femur, and has a satellite nodular structure of approximately 5.5 mm in the epiphyseal line, especially in the T1A series, the heterogeneous hyperintense signal in the T2A series, infiltrating bone marrow fat 12.5 there is a mass lesion of x4cm. Especially when T2 sequence was examined, it was determined that the mass showed extra cortical and extra osseous spread in the inner part, periosteal reaction and accompanying a soft tissue mass in the intramuscular localization with an intramuscular localization of approximately 84x48mm with a heterogeneous necrotic contrast in the soft tissue. Low-intensity, especially peripherally wavy rim-style contrast enhancement was noted in post-contrast series.

Osteosarcoma most often metastasizes to the lungs. This is followed by bone metastases. Contrast-enhanced thin-section CT of the lung is the gold standard in detecting the presence of metastasis in the lung. Skip metastases in the same bone and distant bone metastases can be detected by Whole-Body Bone Scintigraphy. PET-CT is valuable in showing all body metastases and evaluating the chemotherapy response after treatment. Also useful for detecting nucleus [7, 8, 11].

6. Treatment management

In the past, patients with osteosarcoma were tried to be treated with amputation, but patients were lost due to micro-metastatic disease and lung metastases. With the discovery that chemotherapy can eliminate micro-metastases (1970's), limb-sparing surgeries came to the fore [16]. The application of neoadjuvant chemotherapy and limb-sparing surgeries became standard in the 1980s. This paved the way for the development of limb salvage procedures that can achieve limb with better functional and cosmetic results. With the advances in treatment, studies on long-term functional and cosmetic extremity acquisition methods have increased.

With the development of induction and adjuvant chemotherapy protocols and advances in surgical techniques and radiological staging studies, approximately 90–95% of patients are now treated with limb-sparing methods instead of amputation. In limb-sparing surgery, reconstruction is applied in necessary patients in addition to tumor resection. And after all these advances, the chance of long-term survival and cure rate of these patients increased to 60–80% in localized (non-metastatic) diseases [17].

In classical osteosarcoma, the general treatment plan is preoperative (neoadjuvant) chemotherapy, extremity conserving surgery if possible, and postoperative chemotherapy regimen based on the extent of tumor necrosis. In surgical treatment, the tumor is resected with wide margins. Amputation is performed for patients who cannot undergo limb-sparing surgery [18]. Osteosarcoma is a radioresistant tumor and radiotherapy does not have therapeutic properties.

The high-dose methotrexate with leucovorin rescue (HDMTX), doxorubicin and cisplatin (MAP) trio is the basis of standard systemic chemotherapy and is administered for approximately 30 weeks [16]. In a newly diagnosed osteosarcoma patient, 2 cycles of neoadjuvant chemotherapy (2 MAP cycles for approximately 10 weeks) are applied first.

After the HDMTX infusion administered for 2 weeks, a 1-week break is taken, then doxorubicin and cisplatin are administered for 2 days. And a 2-week break is given for bone marrow recovery. And the cycle repeats. Then, surgical treatment is applied [19].

Histological response value evaluated during surgical treatment is a strong prognostic factor. High tumor necrosis rate has better clinical outcomes after neoadjuvant chemotherapy [20].

The results of surgery alone are very poor in osteosarcoma treatment. And with chemotherapy alone, only about 10% of the patients responded [21].

Local control can be achieved through limb salvage surgery or ablative surgery (**Figure 3**). There is no significant difference between amputation and wide resection in local surgery in terms of recurrence and survival rates. Metastasectomy should be considered in lung metastases [14].

In recent years, many studies have been conducted on reconstruction after tumor resection with wide margins in local treatment and reconstruction options have been diversified. Custom-made or modular tumor resection prostheses are one of them. In addition, osteoarticular allografts and composite allografts are other options. With the advances in microsurgery, vascular fibula and myo-cutaneous flaps have also become an alternative for reconstruction. Another option is the method of recovered bone (reconstruction of the bone with the tumor tissue covered by removing the tumor, autoclaving or irradiating it or treating the bone with liquid nitrogen) [11, 22].

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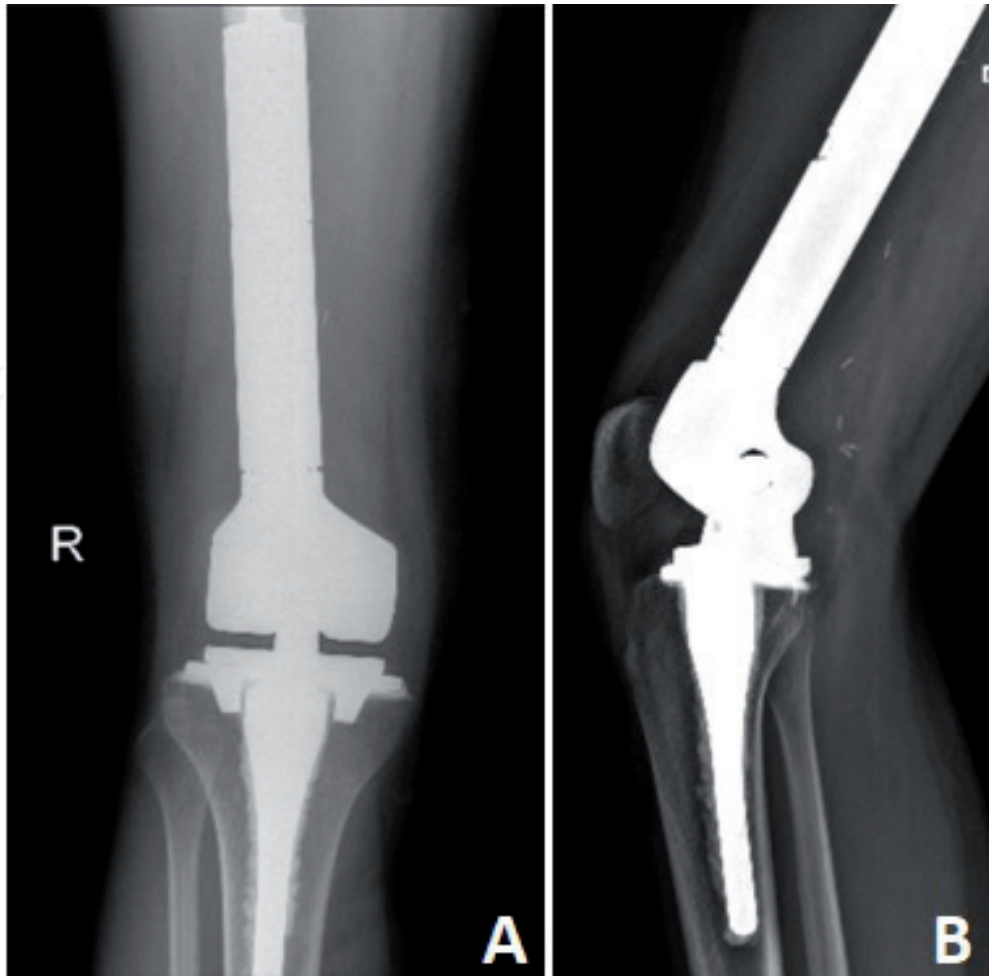


Figure 3.

Right femur distal located osteosarcoma, post-operatively a) anteroposterior and b) lateral radiography. There was skip metastasis in the epiphysis localization of the distal femur. Tumor resection with white margins and reconstruction operation with distal femur tumor resection prosthesis were performed as local treatment.

given for bone marrow recovery. And the cycle repeats. Then, surgical treatment is applied [16].

Overall survival for lower limb reconstructions ranges from about 70–85% at 5 years [23].

Adjuvant MAP therapy should be initiated within 3 weeks after surgical treatment. Because especially in patients with low tumor necrosis rate, a delay of more than 3 weeks is associated with high recurrence rates. Current standard adjuvant chemotherapy includes a total of 29 weeks of MAP cycles.

7. Prognosis

Several prognostic factors have been identified in the management and follow-up of osteosarcoma. Stage (local-systemic spread) is a poor prognostic factor. As the tumor stage increases, the prognosis worsens. Another prognostic factor is tumor grade. Low grade types are parosteal osteosarcoma, periosteal osteosarcoma and low-grade intramedullary osteosarcoma. Tumor size is poor prognostic. As the tumor size increases, the prognosis worsens. Tumor localization affects the prognosis. Tumors located distal to the elbow in the upper extremity and tumors located distal to the knee in the lower extremity have a relatively better prognosis. It has been reported that the presence of pathological fractures does not affect the prognosis. Gender has also been reported as a prognostic factor. The prognosis is

relatively better in female patients. Prognosis is worse in secondary osteosarcoma. Five-year survival is less than 10% in osteosarcoma patients developing on the basis of Paget's disease, and 5-year survival is less than 20% in patients with osteosarcoma developing on a radiation background [11, 14, 24]. The presence of metastatic disease is another poor prognostic factor.

Patients should be followed for at least five years in terms of systemic metastases postoperatively.

In patients with macro-metastasis at the time of diagnosis, despite systemic chemotherapy and surgery, 5-year disease-free survival is approximately 20% [25]. In addition, 10-year survival is less than 20% in relapse cases [26].

8. Recent advances

Studies on intensified chemotherapy are continuing in patients who underwent surgery after neoadjuvant chemotherapy and in patients with poor histological response detected during surgery. Poor histological responders are defined as patients who maintain more than 10% viable tumors following surgery. Current studies report that chemotherapy intensification has less successful results than thought [20, 27].

Several clinical studies have been investigating the intensification of adjuvant chemotherapy by adding high-dose ifosfamide with or without etoposide to MAP for poor histological responders following definitive surgery. However, it has not been shown to be superior to standard chemotherapy. In addition, studies with cytokine interferon alfa-2b showed that this agent did not provide superiority to standard therapy [20, 27].

Studies with high-dose ifosfamide to avoid the long-term nephrotoxic effects of methotrexate have shown equivalent effect rates [28]. Similarly, studies have been conducted with dexrazoxane to avoid long-term nephrotoxic effects of doxorubicin. [29].

9. Conclusions

The current standard of care for a patient with newly diagnosed osteosarcoma includes 2 cycles of MAP neoadjuvant chemotherapy followed by local tumor surgery and 29 weeks of adjuvant MAP chemotherapy. With this standard approach, disease-free survival is approximately 70% in patients with localized disease at the time of diagnosis.

Treatment outcomes for patients with osteosarcoma, for localized, metastatic, or relapse patients, have not improved significantly and have not gotten better in the last 10 years, despite many improvements and extensive studies.

The poor results of patients with low necrosis during surgery after neoadjuvant chemotherapy still appear as a treatment challenge. It has been shown that intensified chemotherapy methods, which have been emphasized in recent years, are not superior to conventional treatment. It is clear that more work is needed.

Conflict of interest

The authors declare no conflict of interest.

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