ORIGINAL PAPERS

Osteosarcoma in Children and Adolescents – a Single Center Review of Presentation, Therapy and Outcome

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Abstract

Purpose: High-grade osteosarcoma is the most common bone malignancy in children. This paper reports clinical and therapeutical aspects of all patients with osteosarcoma, surgically treated at a single institution, over an 8-year period, including all histopathological varieties, sites of disease, stage, age and treatment. **Material and methods:** Patients diagnosed with osteosarcoma and treated surgically in a single center – the Department of Pediatric and Orthopedic Surgery – Maria Sklodowska Curie Emergency Hospital for Children, from 2005 to 2012, were reviewed. Osteosarcoma was diagnosed on the basis of tumor biopsy reports. **Results:** A total of 43 patients, with age range of 6 – 19 years, was found. The osteoblastic type was the most common histologic type (29/43 patients – 67.44%), and the femur was the most common primary tumor location (15/43 patients – 34.88%). The mean tumor volume was 363.65 cm^3 (range 6 – 2400 cm^3). Chemotherapy treatment was accomplished in 90.69% of cases and local therapy consisted of surgery in all patients. After a median follow-up of 41.7 months – 19 patients have died, 22 (51.16%) patients are alive and free of disease and 2 patients are alive with disease. **Conclusion:** Even though our series contained a small number of patients, our results suggest that Romanian young patients with osteosarcoma appear to have a prognosis quite comparable to that of Western countries, if they receive contemporary and multidisciplinary treatment in a specialized pediatric oncology center.

Keywords: osteosarcoma, malignant bone tumors, children and adolescents

Rezumat

Osteosarcomul de grad înalt este cea mai frecventă tumoră malignă osoasă la copii. Această lucrare prezintă aspectele clinice și terapeutice ale tuturor pacienților cu osteosarcom, tratați chirurgical într-o singură instituție, pe o perioadă de 8 ani, incluzând toate tipurile histopatologice, localizările bolii, stadiile, vârsta și tratamentul. **Material și metodă:** Au fost incluși pacienții diagnosticați cu osteosarcom și tratați chirurgical într-un singur centru – Clinica de Ortopedie Pediatrică – Spitalul de Urgență pentru Copii Maria Sklodowska Curie, din 2005 până în 2012. Osteosarcomul a fost diagnosticat pe baza rapoartelor de biopsie tumorală. **Rezultate:** Au fost găsiți 43 de pacienți, cu vârste cuprinse între 6-19 ani. Tipul histologic cel mai frecvent a fost cel osteoblastic (29/43 pacienți – 67,44%) și femurul a fost cea mai frecventă localizare a tumorii primare (15/43 pacienți – 34,88%). Volumul mediu tumoral a fost de 363.65 cm^3 (între 6-2400 cm^3). Chimioterapia a fost administrată la 90,69% dintre cazuri și terapia locală a constat din intervenții chirurgicale la toți pacienții. După o perioadă medie de urmărire de 41.7 luni – 19 pacienți au decedat, 22 (51,16%) pacienți sunt în viață și fără boală și 2 pacienți trăiesc cu boala. **Concluzii:** Deși numărul de pacienți este mic, rezultatele noastre sugerează că pacienții tineri români cu osteosarcom par să aibă un prognostic comparabil cu cei din țările occidentale, în cazul în care primesc un tratament multidisciplinar contemporan într-un centru specializat de oncologie pediatrică.

Cuvinte cheie: osteosarcom, tumori maligne osoase, copii și adolescenți

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INTRODUCTION

Worldwide, cancer is the second leading cause of death, following heart disease, accounting for 23% of all deaths. Although most cancers causing death are carcinomas of lung, prostate and breast, primary malignancy of the bone is ranked as the third leading cause of death in patients with cancer who are younger than 20 years[1]. While malignant bone tumours comprise more than 20 different sub-types, the majority diagnosed in children and young adults are osteosarcoma (52%) and Ewing sarcoma (34%)[2]. Osteosarcoma (OS) incidence in this population varies significantly with age, with peak incidence occurring in the second decade of life during the adolescent growth spurt, a feature that suggests a relationship between rapid bone growth and the development of malignancy typically in metaphyseal location[3].

Osteosarcoma (OS) is an ancient disease that is still incompletely understood. The term sarcoma was introduced by the English surgeon John Abernathy in 1804 and was derived from Greek roots meaning "fleshly excrescence". In 1805, the French surgeon Alexis Boyer, personal surgeon to Napoleon, first used the term osteosarcoma. Boyer realized that osteosarcoma is a distinct entity from other bone lesions, such as osteochondromas – exostoses.

OS is classified as an orphan disease with an overall incidence of 0.2-3/100000 per year (0.8-11/100000 per year in the age group 15-19 years) in the European Union[4]. Despite its rarity, it has been reported to be the third most common cancer in adolescence, occurring less frequently than only lymphomas and brain tumors in this age group[5]. OS is extremely rare in children before the age of 5 years and the incidence declines rapidly after the age of 206. In Romania, there are about 37 children and adolescents diagnosed with malignant bone tumors, annually; 60% are osteosarcomas, 24% Ewing sarcomas and 16% other types of rare sarcomas[7]. There is limited information regarding the clinical and therapeutical aspects of osteosarcomas in Romania. We present here our single-center experience of children and adolescents with OS.

Arising from primitive bone-forming mesenchymal cells, the vast majority of OS involve the long bones of the extremity, especially distal femur, proximal tibia and proximal humerus[8]. These tumors can also occur in other bones of the skeleton and in extra-skeletal sites. OS are generally locally aggressive and tend to produce early systemic metastases.

Today, there are three major therapeutic options for patients suffering from osteosarcoma: surgery, chemotherapy and palliative radiotherapy. Intensive, multiagent chemotherapy maximizes outcome in OS patients. The current treatment is neoadjuvant chemotherapy, followed by wide excision surgery and then adjuvant chemotherapy. Radiotherapy is administered with a surgical resection in some cases. Currently, surgery remains an indispensable part of osteosarcoma treatment together with chemotherapy[9].

MATERIALS AND METHODS

A retro- and prospective review was conducted at Department of Pediatric and Orthopedic Surgery, from Maria Sklodowska Curie Emergency Hospital for Children, Bucharest, Romania. Patients with osteosarcoma newly diagnosed were included in the study, during a period of 8 year (2005 – 2012). The patients with incomplete medical records or lost from evidence after biopsy or resection were excluded. Data collected included age at diagnosis, gender, symptoms, duration of symptoms, location of primary disease, tumor size, type of biopsy, histological subtype, stage, treatment, timing and location of recurrence and outcome. In addition, treatment modalities (cytotoxic agents, number of cycles of chemotherapy, surgery), treatment outcome (response, progression, pathological response), time to progression, time to death or end of follow-up were recorded. This analysis used data obtained until January 2015.

We analyzed the group based on clinical records and laboratory data. The physical examination of all patients included evaluation of the patient's general health, as well as a carefull examination of the lesion - the mass was measured, and its location, consistency, shape, sensitivity, mobility, tenderness, local temperature, change with position, as well as joint contractures and skin condition were noted.

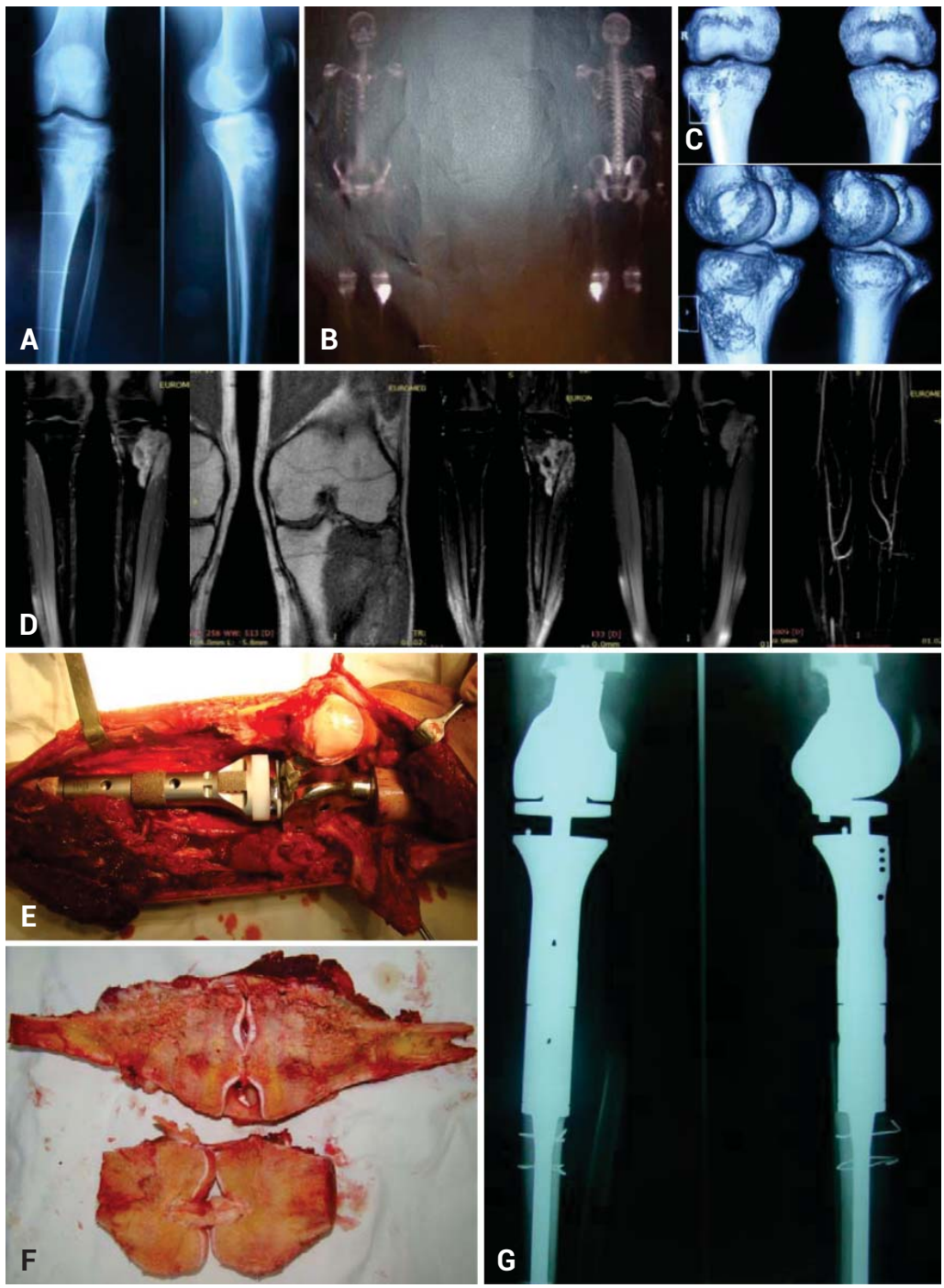
The pathologic diagnosis was confirmed on the basis of routine histopathological and immunohistochemical examinations of biopsy specimens before starting the treatment. Open biopsies were performed in 41/43 patients – 95.34%. We performed only 2 excision biopsies, when tumors were located at fingers. No major complications were noted after biopsy. Molecular genetic studies were not carried out routinely.

A total of 43 patients, from all over the country, were identified, 29 boys and 14 girls, with a male: female ratio of 2.07:1. The patients ranged in age from 6 to 19 years (median – 12.96 years) at initial presentation. The majority of patients were from rural environment – 28/43 (65.11%).

The latest AJCC classification of bone sarcomas (Tumor-Node-Metastasis [TNM] system) is based on

tumor grade and size and the presence and location of metastases. Stage I tumors are low grade. Stage II tumors are high grade. Stages I and II are subdivided based on size of lesion. Stages I-A and II-A are less than or equal to 8 cm in their greatest linear measurement. Stages I-B and II-B are greater than 8 cm in size. Stage III tumors are those that have "skip" metastases, which are defined as discontinuous lesions within the same bone. Stage IV-A includes patients with pulmonary metastases only, whereas Stage IV-B includes patients with non-pulmonary metastases (eg, bone, liver, lymph node)[10].

The primary tumors were staged using plain radiography, technetium-99 bone scans, computed tomography (CT) and magnetic resonance imaging (MRI) – Figure 1. Bone scintigraphy and CT scans of the



lungs were used to investigate the presence of metastases. All the examinations were repeated before definitive surgery. After surgery, chest and primary lesion X-rays, chest CT, and whole-body bone scanning were performed every 3 months throughout the period of adjuvant chemotherapy. After completion of the entire treatment course, all patients were followed every 3 months during the first 2 years, every 6 months for the following 3 years and yearly thereafter. The follow-up evaluations consisted of a history and physical examination. CT scans were obtained at intervals of 3–6 months or more frequently if clinically indicated.

RESULTS

Duration of symptoms before presentation ranged from 0.5 to 15 months. The time until diagnosis was long, in 18.6% (8/43) it was less than 3 months, in 41.86% (18/43) it was between 3-6 months and in 39.53% (17/43) was more than 6 months. The long period of time between the first symptoms and the moment of diagnosis was found to be a poor prognosis. The most common presenting symptoms were local pain and functional disability and in 6 cases we have pathologic fracture.

The characteristics of the 43 patients diagnosed with OS are presented in Table 1. The localization of the malignant bone tumors was found to be mainly at the limbs. Lower limbs were the most frequent site of the lesions: femur – 15, tibia – 11, fibula – 4 and calcaneus – 1. In the upper limb, the humerus was most common affected – 5 cases, followed by hand – 3 cases and radius – 2 cases. We noted the predilection for the distal femur and proximal tibia or fibula for more than half of the patients – 24/43, corresponding to the most active growth plates during the childhood and adolescent growth spurt.

The mean tumor volume was 363.65 cm^3 (range 6 – 2400 cm^3). Tumor volume was found to be a poor prognosis factor, the survival rate of the patients with high tumor volume was lower than in those with small tumor volume. Regarding the histologic subtype, the osteoblastic was the most common – 29 patients (Table 2). We have not noticed any significant correlation between histological subtype and tumor stage at diagnosis. The majority of patients (30/43 – 69.76%) had localized disease at the time of diagnosis, which includes stages IIA, IIB and III. All patients with extensive disease (13/43 – 30.23%) had only lung metastases.

Therapeutic approaches are generally based on various factors: tumor entity, tumor stage, age, gender, general condition, quality of life and life expectancy. In terms of therapies received, all the patients included in the study underwent surgery. Four patients refused administration of neo- or adjuvant chemotherapy. Chemotherapy treatment was accomplished according to COSS 96 (*Cooperative Osteosarcoma Study Group*) regimen in 27 patients – 62.79% and EURAMOS (*European and American Osteosarcoma Studies*) regimen in 12 patients – 27.9%. Neoadjuvant chemotherapy corresponded to COSS 96 regimen included administration of doxorubicin, methotrexate, ifosfamide and cisplatin; EURAMOS comprised MAP regimen, comprising pre-operatively of two 5-week cycles of cisplatin 120 mg/m^2, doxorubicin 75 mg/m^2 and methotrexate 12 g/m^2 (MAP) The purpose of preoperative chemotherapy was to eradicate any micro metastases that exist at the time of diagnosis and to reduce the volume of the tumor in order to facilitate its excision. Chemotherapy related complications probably darkened the prognosis. The most frequent complications were bone marrow aplasia – 84.61%, infections (pharyngo-tonsilitis, urinary tract infections, pneumonia, sepsis) – 71.79%, mucositis – 61.53%, post-therapeutical toxicity (hepatitis, pancreatitis, dermatitis) – 56.41% and bleeding – 15.38%; which lead to delays in treatment.

For local control, all the patients diagnosed with OS underwent surgery with curative intent. Local therapy was individually planned for each patient after discussions between the surgeon and pediatric oncologist. We follow the principles of oncologic surgery when perform a tumor resection – the tumor must be removed with wide or radical, non-contaminated surgical margins. The surgical margins were large in 27 patients – 62.79% and radical in 16 patients – 37.2%. The type of surgery procedure depended on the location and extension of the tumor – tumor stage, response to

Table 1. Patients characteristics

Variable	No. of patients (n=43)
Gender	
Female	14
Male	29
Age	
<10	7
10-14	20
15-19	16
Site of primary tumor	
Lower limb	31
Upper limb	10
Clavicula	1
Pelvic ring	1
Volume of primary tumor	
<100	8
100-200	16
>200	19

neoadjuvant chemotherapy, neurovascular involvement and the presence of complications such as pathologic fractures. The reconstruction procedures after tumor resection included the use of prosthesis, autograft or allograft. In 22 patients (51.16%) we performed amputation and in 21 patients (48.83%) resection with endoprosthesis (15 cases) or reconstruction with autograft / allograft (6 cases).

The adjuvant chemotherapy consisted of MAP regimen (cisplatin + doxorubicin + methotrexate) for 17 patients, MAPI regimen (MAP + ifosfamide) for 17 patients, MAPIE regimen (MAP + ifosfamide + etoposide) for 4 patients and in one case MAPIfn regimen (MAP + Interferon).

With a median follow-up of 41.74 months (range 8–118 months) for the patients overall and 58.4 months (range 24–118 months) for the survivors, the final status of the study subjects was 19 dead of disease, 22 (51.16%) continuously disease-free and 2 patients alive with disease.

DISCUSSION

Osteosarcomas are uncommon tumors and majority in children are sporadic, while inherited predisposition accounts for a minority of cases. Genetic predisposition plays a role. Bone dysplasias, including Paget disease, fibrous dysplasia, enchondromatosis, and hereditary multiple exostoses and retinoblastoma (germline form) are risk factors. The combination of constitutional mutation of the RB gene (germline retinoblastoma) and radiation therapy is linked with a particularly high risk of developing osteosarcoma, Li-Fraumeni syndrome (germline p53 mutation) and Rothmund-Thomson syndrome (autosomal recessive association of congenital bone defects, hair and skin dysplasias, hypogonadism, and cataracts).

It is well known that OS tumor cells exhibit karyotypes with a high degree of complexity and are characterized by a high level of genomic instability, in particular one subcategory of instability known as chromosomal instability. Chromosomal instability is the elevated rate of gain or loss of entire chromosomes or sections of chromosomes, and it appears to be significant in the pathogenesis of osteosarcoma tumours, resulting in complicated structural and numerical aberrations and wide variability between cells[11]. Clinical features of OS are remarkably homogeneous, in terms of their aggressive phenotype and response to chemotherapy, suggesting the common molecular pathway for the development of this type of tumors[12]. Unfortunately, even though several alterations are relatively consistent across cohorts of tumors, the accumulated knowledge of genetic changes in osteosarcoma has yet poor impact on survival rates. Clinical markers continue to be the most reliable indicators for prognostication[13].

There are few Romanian studies that have investigated the results of treatment for OS in children and adolescents because of the relative rarity of the disease and the lack of well-organized study groups, so we do not know if there is an increase in incidence over the last period. In this study, we present the outcomes of OS in children and adolescents, who underwent surgery at Maria Sklodowska Curie Emergency Hospital for Children, in addition to intensive multidrug chemotherapy. To the best of our knowledge, this is the largest series of Romanian pediatric population with osteosarcoma. We believe that the present results closely reflect the actual prognosis of Romanian OS patients treated with contemporary methods, although the number of patients was small.

There was a long period of time before establishing the diagnosis (81.39% of patients with duration of symptoms longer than 3 month) which, additionally, to high volume tumor (81.39% of patients with volume greater than 100 cm^3) and 30.23% of patients with advanced disease, lead to unfavorable prognosis. We have to minimize the time interval between appearance of symptoms and start of treatment. The use of screening protocols in oncological centers is mandatory. In addition, we suggest implementation of educational measures so that general physicians and general orthopedic surgeons become sufficiently aware of this

Table 2. Staging of tumors at the moment of diagnosis – according to AJCC system for bone sarcomas

Histologic subtype of OS	Stage				
	II A	II B	III	IV A	Total
Osteoblastic	14	4	3	8	29
Chondroblastic	1			2	3
Fibroblastic		1	1	1	3
Teleangiectatic	2		1	1	5
Periosteal	2		1		3
Total	19	5	6	13	

pathology to send possible patients immediately to reference centers.

In our study, the localization of the OS was found to be mainly at the limbs, with a predilection for the inferior limbs, similar to other studies from European countries. They occur primarily in the metaphyseal region and tend to invade the epiphysis, even in the presence of a growth plate[14]. Sixty percent of cases arise around the knee (40% in the distal femur and 20% in the proximal tibia) and 10% occur in the proximal humerus. Axial tumours comprise a further 10%; 7-9% in the pelvis and 1-3% in the spine[8,14].

Well-known poor prognostic factors for osteosarcoma include tumors arising in the axial skeleton, large tumor volume (size >10 cm), metastases at the time of presentation, increased alkaline phosphatase or lactate dehydrogenase levels, poor response to preoperative chemotherapy, skip metastases or discontinuous tumor in bone and lymph node involvement[15,16]. The biological complexity of this tumor is evidenced by a relapse rate in 30%-40% of patients within 3 years, despite current surgical and chemotherapeutic treatment regimens[9].

The survival of patients with malignant bone sarcomas has improved dramatically over the past 30 years, largely as a result of the use of effective chemotherapy. Previously 80 to 90 percent of patients with bone sarcomas developed metastases, despite achieving local tumor control, and died of their disease. Currently, the long-term survival rates are 60%-78% for patients with localized OS. This improvement is largely attributed to adjuvant and neoadjuvant chemotherapy[15,17]. Even in patients with poor prognosis, such as those with metastases at diagnosis, the 5-year survival rate has reached 20–30% due to chemotherapy and the surgical removal of metastases and primary tumor[4]. In our series, the survival rate are lower, but can be explain by large tumors volume and almost a third of patients with metastases at presentation. Also, these factors explain the high number of amputations in our patients.

It is clear that for optimal efficacy of combined modality therapy with a curative intention, a multidisciplinary approach by experienced medical oncologists, radiologists, pathologist and pediatric orthopedic surgeons is essential. There are improved results due to chemotherapy, which ensures a better overall control and, often, the local disease has allowed surgeons to develop a generally conservative surgery[18].

CONCLUSION

We think that the best approach to osteosarcoma can be obtained in specialized centers with a very skilled multidisciplinary team and the possibility to evaluate statistically the data from large series of patients and cumulate the experience to properly individualize the principles of multidisciplinary treatment. Although we were unable to draw any definite conclusions, as to whether the treatment strategy we employed was responsible for the results we obtained, we were at least able to demonstrate that Romanian children and adolescents with OS could achieve treatment outcomes comparable to those from other countries from Europe.

We suggest implementation of educational measures so that general physicians and pediatric orthopedic surgeons become sufficiently aware of this pathology to send possible patients immediately to reference centers, in order to improve outcome.

Acknowledgements: none declared.

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