

CLINICAL AND THERAPEUTICAL ASPECTS OF EWING SARCOMA IN CHILDREN AND ADOLESCENTS – A SINGLE CENTER EXPERIENCE

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ABSTRACT

Ewing sarcoma, a rare malignancy of childhood and adolescence, has become a model of progress in diagnosis and treatment through long-standing research efforts in multinational clinical trials. The aim of this study is to present the specific diagnostic and therapeutic approach of Ewing sarcoma in children and adolescents.

Materials and method. A retrospective and prospective analysis of all Ewing sarcoma treated in a large referral center – the Department of Pediatric and Orthopedic Surgery, Maria Sklodowska Curie Emergency Hospital for Children, between 2005 and 2012 is presented. A total of 28 patients were identified, 19 boys and 9 girls, with a male to female ratio of 2.11:1. Diagnosis was based on the result of the histopathological examination of tumor biopsy.

Results. The mean age of the patients was 12.3 years (range 3-19 years) and the mean tumor volume was 197.96 cm³ (range 8-1,200 cm³). 8/28 patients (28.57%) had metastatic disease at diagnosis, mainly in the lungs (7 cases). Chemotherapy was administered to 26 patients (92.85%). Local therapy consisted of surgery in all patients and of surgery combined with radiation, in 5 patients. After a mean follow-up of 51.5 months, 9 patients have died, 17 (60.71%) patients are alive and free of disease and 2 patients are alive with disease.

Conclusions. The management of a child or adolescent with Ewing sarcoma is best carried out in a specialized center under the care of a multidisciplinary team, in order to obtain the best outcome for the patient. Ewing sarcoma has a high mortality rate in Romania, especially because of late diagnosis.

Keywords: Ewing sarcoma, malignant bone tumors, children and adolescents

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INTRODUCTION

Ewing sarcoma (ES), a rare malignancy of childhood and adolescence, has become a model of advances in diagnosis and treatment through long-standing research efforts in multinational clinical trials. It is a primitive malignant bone tumor, first reported by James Ewing in 1921 as a diffuse endo-

thelium or endothelial myeloma of bone. Osseous Ewing sarcoma is the most common of the Ewing family of tumors, which also includes extraskeletal Ewing sarcoma, primitive neuroectodermal tumor and Askin tumor – when in the chest wall. (1) They are tumours of young people, 80% of them occurring in patients under 20 years. In the early 1980s, these tumors were found to share a karyotype abnor-

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mality, namely a translocation involving chromosomes 11 and 22 [t(11;22)(q24;12)]. Histologically they demonstrate crowded sheets of small round blue cells divided by a small amount of fibrous stroma. (1,2)

Ewing sarcoma (ES) is the second most common primary bone tumor in children and adolescents, only exceeded in prevalence by osteosarcoma; the overall annual incidence is 2.93 cases per 1,000,000 people (3). It is rare in patients younger than 5 or older than 30, with 95% of cases reported between the ages of 4 and 25 years and has a slight male predilection (M:F 1.5:1) (1,4). The most common locations include the metaphyses of long bones (often with extension into the diaphysis) and the flat bones of the shoulder and pelvic girdles. Rarely, it occurs in the spine or in the small bones of the feet or hands. (3)

In Romania, there are about 37 children and adolescents diagnosed with malignant bone tumors, annually; 60% of these tumors are osteosarcomas, 24% Ewing sarcomas and 16% other types of rare sarcomas. (5) There is limited information regarding the clinical presentation, diagnosis and treatment of malignant bone tumors in Romania.

The treatment of Ewing's sarcoma of the bone is currently based on combined therapy: neoadjuvant chemotherapy, radiation therapy and surgical resection of the primary tumor. (6) Modern combined therapies with multiactive chemotherapy have caused a significant improvement in the prognosis of Ewing's sarcoma of bone. Due to the complexity of the treatment, it is mandatory for the members of the multidisciplinary team (oncologists, orthopedic pediatric surgeons, as well as pathologists and radiologists) to work together closely, to customize treatments to the histologic response and to the tumor volume and site, in order to offer the best treatment to each patient.

Dramatic improvements in survival have been achieved for children and adolescents with cancer. Prior to the era of chemotherapy, survival in ES was less than 10%, although the radiosensitivity of this tumor was well known. With the modern multimodal therapeutic regimens including induction chemotherapy and local control with surgery, radiotherapy or a combination of both modalities, cure rates of approximately 70% can be achieved in patients with localized disease. (7) The prognosis of patients with metastasis at diagnosis, however, has remained not good, indicating the limitations of current treatment strategies. While significant progress has been made in the diagnosis and treatment of localized disease over the past 30 years, there still is much room for improvement.

MATERIALS AND METHODS

A combined retrospective and prospective review was conducted at a large referral center – the Department of Pediatric and Orthopedic Surgery, from Maria Sklodowska Curie Emergency Hospital for Children, Bucharest, Romania. Newly diagnosed patients with Ewing sarcoma were included in the study, during a period of 8 years (2005-2012). Records were analyzed for patient demographics, age, sex, symptoms, duration of symptoms, site of lesion, dimensions of the tumors, type of biopsy, stage, treatment and results. In addition, treatment modalities (cytotoxic agents, number of cycles of chemotherapy, surgery, radiotherapy), treatment outcome (response, progression, pathological response), time to progression, time to death or end of follow-up were recorded. The analysis used data obtained until January 2015.

We analyzed the clinical records and the laboratory data. 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 all cases, in order to avoid sampling error and to provide adequate tissue for biologic studies. Molecular genetic studies to investigate specific chromosomal translocations were not carried out routinely.

A total of 28 patients, from all over the country, were identified, 19 boys and 9 girls, with a male to female ratio of 2.11:1. The patients ranged in age from 3 to 19 years (mean age 12.3 years) at presentation. The majority of patients were from rural environment – 21/28 (75%).

The primary tumors were staged using plain radiography, technetium-99 bone scans, computed tomography (CT), and magnetic resonance imaging (MRI) – Fig. 1. Bone scintigraphy and CT scans of the lungs were used to investigate the presence of metastases. The latest AJCC classification of bone sarcomas (Tumor-Node-Metastasis [TNM] system) takes into account the 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 the 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). (8)

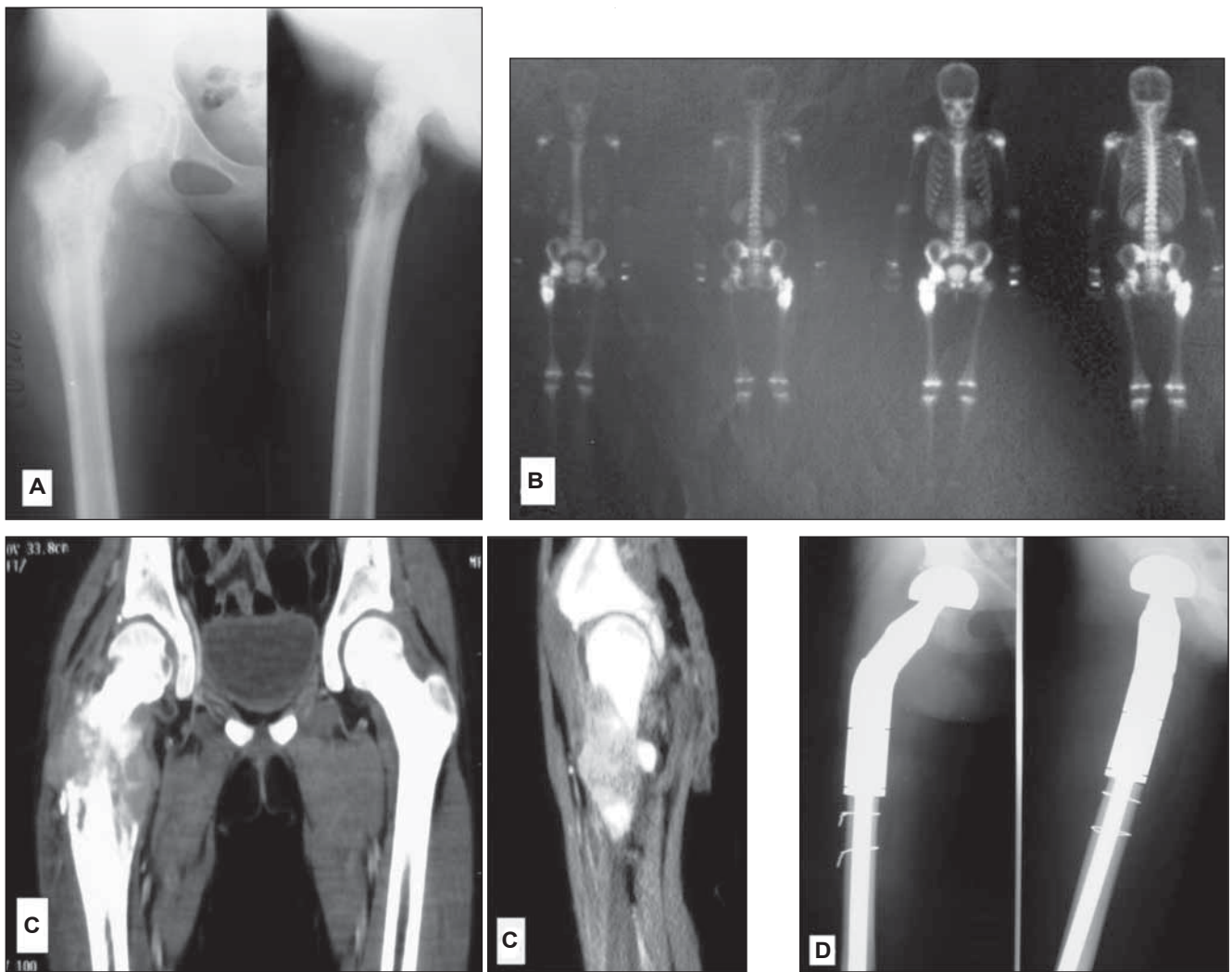


FIGURE 1. A 10 years old patient diagnosed with Ewing sarcoma in the proximal third of the right femur with infiltration of surrounding soft tissues. **A.** Preoperative radiological exam; **B.** Whole body scintigraphy scan; **C.** MRI; **D.** Postoperative radiological exam.

All investigations 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 to 6 months or more frequently if clinically indicated.

RESULTS

Duration of symptoms before presentation ranged from 0.5 month to 3 years. The time until diagnosis was long; in 17.85% (5/28) it was less than 3 months, in 50% (14/28) it was between 3-6

months and in 32.14% (9/28) 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 factor. The most common presenting symptom was local pain, frequently associated with trauma, followed by swelling, functional disability and pathologic fracture in four cases.

Patient characteristics are depicted in Table 1. The primary tumor was located in an extremity in 19 patients (67.85%) and in the trunk including the pelvis in 9 (32.14%). Lower limb was the most common primary tumor location: femur – 5, tibia – 4, calcaneus – 3, fibula – 2 and foot – 1. In the upper limb, the humerus was most common affected – 3 cases. We noted the predilection for the distal femur and proximal tibia or fibula – 7/28 cases, corresponding to the most active growth plates during the childhood and adolescent growth spurt.

TABLE 1. Patient characteristics

Variable	No. of patients (n= 28)
Gender	
Female	9
Male	19
Age	
< 5	1
5-9	9
10-14	9
15-19	9
Site of primary tumour	
Lower limb	15
Upper limb	4
Chest wall	3
Pelvic ring	2
Scapular ring	2
Vertebra	2
Volume of primary tumour	
< 100	15
100-200	6
> 200	7
Site of metastasis	
Lung	7
Bone	1

The mean tumor volume was 197.96 cm³ (range 8-1,200 cm³). At presentation, 8 out of 28 patients (28.57%) had metastatic disease, predominantly in the lungs – 7 cases. The majority of patients (20/28 – 71.42%) had localized disease at the time of diagnosis: 16 patients – stage IIA, 3 patients – stage IIB and one in stage III.

An overview of treatment modalities is given in Table 2. Chemotherapy treatment was accomplished according to the European protocol – EWING 99 in 89.28% – 25/28 patients. Except for three cases, the local treatment was performed after neoadjuvant chemotherapy and consisted of surgery alone or surgery combined with radiation. Neoadjuvant chemotherapy corresponded to VIDE regimen which includes administration of vincristine, ifosfamide, doxorubicin and etoposide. The purpose of preoperative chemotherapy was to eradicate any micrometastases that exist at the time of diagnosis and to reduce the volume of the tumor in order to facilitate its excision. Of the seven cases with lung metastases at diagnosis, 2 cases had remitted metastasis at the time of local therapy.

-Local therapy was individually planned for each patient after discussions between the surgeon and paediatric oncologist. Tumor site, tumor size and resectability, the patient's age and individual preference were considered. For local control, all the patients diagnosed with Ewing sarcoma underwent surgery with curative intent. The surgical margins were large in 22 patients – 78.57% and radical in 6 patients – 21.42%. The type of surgery

TABLE 2. Primary treatment modalities and treatment outcome

Treatment	No. of patients (n=28)	No. of patients alive (n=20)
Surgery + Radiotherapy	1	1
CT→Surgery→CT	21	4
CT→Surgery+ Radiotherapy→CT	4	2
Surgery→CT	1	1
Surgery	1	1
CT = Chemotherapy		

depended on the location and extension of the tumor, 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 7 patients we performed amputation and in 21 patients resection with endoprosthesis or reconstruction with autograft/allograft.

The adjuvant chemotherapy was administered to 26/28 (92.85%) patients and consisted of VAI regimen (vincristine + actinomycin + ifosfamide) for 9 patients and VAC-IE regimen (vincristine + doxorubicin + cyclophosphamide alternating with ifosfamide + etoposide) for 17 patients.

With a mean follow-up of 51.5 months (range 10-118 months) overall and 65.7 months (range 24-118 months) for the survivors, the final status of the study subjects was 9 dead of disease, 17 (60.71%) continuously disease-free and 2 patients alive with disease.

DISCUSSION

In recent years, molecular techniques have been commonly used to diagnose ES because it often exhibits specific chromosomal translocations. Reverse transcription polymerase chain reaction and fluorescent in situ hybridization are very useful methods for detecting fusion genes. (9) The EWS-FLI1 fusion gene, which is caused by the t(11;22)(q24;q12) translocation, is the most common type of fusion gene: 85% of ES tumors that exhibit the EWS gene rearrangement were found to possess this type of translocation (10). EWS-ERG, which is caused by the t(21;22)(q22;q12) translocation, is observed in 10 % of cases. (11) ES represents a paradigm for understanding and investigating sarcoma biology and the search for the identification of tumor specific therapeutic targets is the focus of current research.

The treatment of Ewing sarcoma has evolved over the last decades – systemic treatments have become more intensive and local control measures

more aggressive. As we advance toward the new generation of studies, a critical evaluation of our current understanding of the treatment of this malignancy must be performed, and the relative contribution of each of the therapeutic component should be analyzed.

There are few Romanian studies that have investigated the results of treatment for Ewing sarcoma in children and adolescent because of the relative rarity of the disease and the lack of well-organized study groups. In this study, we present the outcomes of Ewing sarcoma children and adolescent, who underwent surgery at Maria Sklodowska Curie Emergency Hospital for Children, in addition to intensive, multidrug chemotherapy and/or radiotherapy. We believe that the present results closely reflect the actual prognosis of Romanian Ewing sarcoma patients treated with contemporary methods, although the number of patients was admittedly small.

There was a long period of time before establishing the diagnosis (82.14% of patients with duration of symptoms longer than 3 month) which, additionally, to large tumor volume, lead to unfavorable prognosis. In the future, we must succeed decrease the interval between appearance of symptoms and start of treatment to improve prognosis and outcome.

In our patients, the most common sites of Ewing sarcoma were the long bones of the extremities, with a predilection for the inferior limbs. These findings are different from other reports, that find the most common primary sites of Ewing sarcoma are the pelvis followed by the femur, tibia and the remainder of both the long bones of the extremities and flat bones of the axial skeleton. (3,9)

Poor prognostic factors for Ewing sarcoma in children and adolescents are large tumors (volume ≥ 150 ml), primary tumor of the pelvis, metastases at presentation, advanced age and distant recurrences. (12,13) Advanced age as a poor prognostic factor may either be related to biological aspects of more aggressive disease or a lower dose intensity of chemotherapy to be delivered.

Dramatic improvements in survival have been achieved for children and adolescents with cancer. Between 1975 and 2010, childhood cancer mortality decreased by more than 50%. (7) For Ewing sarcoma, the 5-year survival rate has increased over the same time from 59% to 78% for children younger than 15 years and from 20% to 60% for adolescents aged 15 to 19 years. (7) In our series,

the survival rate are lower, even if most patients were under 15 year, but can be explain by large tumors volume and almost a third of patients with metastases at presentation.

Despite improvement in the treatment outcome of Ewing's sarcoma during the past decades, almost 40% patients ultimately die of this disease. It is clear that for optimal efficacy of combined modality therapy with a curative intention, a multidisciplinary approach by experienced medical oncologists, radiologists, pathologists 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. (14)

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 young patients with Ewing sarcoma could achieve treatment outcomes comparable to those from other countries from Europe. It is necessary to perform a prospective multicenter clinical study to investigate the results of treatment for Romanian children and adolescents with ES to define the basic guidelines for use of multidisciplinary treatment strategies.

CONCLUSIONS

With regard to the low incidence of this tumor, we therefore strongly advocate referral of a child or adolescent with Ewing sarcoma to a specialized pediatric oncology center and participation in international trials. After treatment, ES patients must be carefully followed up for tumor relapses, growth-related musculoskeletal complications and secondary malignancies.

Even though our series contained a small number of surgical patients treated at a single institution, the results suggest that Romanian young patients with Ewing sarcoma appear to have a prognosis comparable to that of Western countries if they receive contemporary and multidisciplinary treatment.

We suggest implementation of educational measures so that general physicians and pediatric orthopedic surgeons become more aware of this pathology and send potential patients to reference centers immediately. This would improve time intervals of diagnostic procedures and avoid delays.

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