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Local Tumor Control Affects Survival of Patients with Osteosarcoma and Ewing Sarcoma

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Abstract

Osteosarcoma and Ewing sarcoma are the most common primary malignant bone tumors in children. This study aimed to analyze the characteristics of osteosarcoma and Ewing sarcoma patients at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, from 2020 to 2023 and compare the one-year survival rates between patients who underwent complete treatment (surgery for local tumor control and chemotherapy) and those who received chemotherapy alone. This study used a descriptive-analytical observational design with a retrospective approach by reviewing electronic medical records from the Indonesian Pediatric Cancer Registry (IPCAR). A total of 44 osteosarcoma patients and 14 Ewing sarcoma patients who met the inclusion criteria were included. The majority of patients were boys (osteosarcoma=61.3%; Ewing sarcoma=64.3%), with a mean age of 13.5 years for osteosarcoma and 9.1 years for Ewing sarcoma. Osteosarcoma was most commonly found in the femur and tibia (90.9%), whereas Ewing sarcoma was primarily located in the axial region (71.4%). Most patients underwent chemotherapy without local tumor control (osteosarcoma=61.4%; Ewing sarcoma=57.1%). The analysis revealed a significant difference in one-year survival between patients who received local tumor control combined with chemotherapy and those who underwent chemotherapy alone (osteosarcoma p=0.000; Ewing sarcoma p=0.010). In conclusion, local tumor control significantly improves one-year survival in both tumor types.

Keywords: Chemotherapy, Ewing sarcoma, osteosarcoma

Introduction

Bone tumors can be classified as either malignant or benign. A primary malignant bone tumor originates from primitive mesenchymal cells, while a secondary bone tumor originates in other tissues and metastases to the bone. Primary bone tumors contribute to 0.2% of the world's malignancy rate, with many cases exhibiting idiopathic causes. There are several types of primary malignant bone tumors, including osteosarcoma, Ewing sarcoma, and chondrosarcoma. Osteosarcoma is the most common primary bone malignancy in pediatrics, while Ewing sarcoma is the second most common malignant bone tumor, accounting for 10-15% of all malignant bone tumors. It primarily affects children during adolescence.[1–3]

Osteosarcoma exhibits a bimodal age distribution. The first peak is observed in children aged 10-14 years, corresponding to pubertal growth, while the second peak is observed in adults aged >65 years. Furthermore, boys are more commonly affected than girls. At initial diagnosis, approximately 15-20% of patients present with lung metastases, and 40% of patients develop metastases at a later stage. Ewing sarcoma represents the second most common bone malignancy in children, with 90% of cases occurring between the ages of 5 and 25. Like in osteosarcoma, boys are also more commonly affected than girls in Ewing sarcoma.[3–5]

Several studies have been concerned with identifying the causes of osteosarcoma by examining factors such as genetics, epidemiology,

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and the environment. Genetic-related conditions include patients with hereditary retinoblastoma, which is associated with loss of heterozygosity of the RB gene; Li-Fraumeni syndrome, which is associated with lineage mutations of the P53 gene; and Rothmund-Thompson syndrome, which is due to mutations in the RECQL4 gene. Osteosarcoma patients frequently present with symptoms including pain hobbled walking, and an increasing lump on the affected limb over several months. Patients typically seek treatment following a trauma or high-intensity physical activity. On physical examination, there may be limited range of motion, joint effusion, pain on pressing, and the limb may feel warmer. Meanwhile, examination with X-rays typically reveals a sunburst pattern.[3,4]

Risk factors for Ewing sarcoma include parental exposure to pesticides or chemical solvents and increased maternal and paternal age at conception. Approximately 95% of Ewing sarcoma cases are estimated to be caused by abnormalities in mesenchymal progenitor cells. This is triggered by genetic factors, whereby Ewing sarcoma patients exhibit a distinctive chromosomal rearrangement in the form of a non-random translocation, specifically t(11;22) (q24;q12) or t(21;22)(q22; q12), which results in aberrant transcription and coding. Moreover, this mutation increases the cell fusion activity of proteins from the Ewing sarcoma (EWS) gene on chromosome 22, the Friend Leukemia Integration-1 (FLI-1) gene on chromosome 11, or the Erythroblast transformation-specific Related Gene (ERG) gene on chromosome 21. The symptoms of Ewing sarcoma typically manifest as pain that worsens at night, stiffness, and swelling that persists over weeks to months. These symptoms are often accompanied by the development of progressively larger bone lesions. Due to the unspecific symptoms, malignancy can only be diagnosed when the onset has been running for three to nine months, which may delay the timing of appropriate treatment. On radiological examination, the characteristic appearance of an onion peel may be observed, which indicates a periosteal reaction, a common feature of Ewing sarcoma.[3,6,7]

The standard treatment for these malignancies consists of a multimodal approach, including surgery for local tumor control and chemotherapy for systemic disease control. Surgery plays a crucial role in removing the primary tumor and improving survival outcomes. Meanwhile, chemotherapy is essential in eradicating micrometastatic disease and reducing the risk of recurrence. Based on the data in Dr. Hasan Sadikin General Hospital Bandung, despite the established treatment guidelines, 60% patients refuse surgical intervention due to concerns about postoperative morbidity, functional impairment, or financial difficulty. As a result, some patients undergo chemotherapy as their sole treatment modality, potentially affecting their overall prognosis.

Patients with bone tumors experience limitations in performing daily activities and a decrease in physiological function. This shows an urgent problem to decrease the morbidity and mortality rate of childhood malignant bone tumors. One of the initial steps to achieve this is to reveal the real characteristics of childhood malignant bone tumor patients. The incidence of bone tumors has been observed to be higher in certain demographic groups. This study identifies patient characteristics, including age, gender, laterality, histopathological pattern, primary tumor location, treatment, and one-year survival. This study aims to describe the clinical features, histopathological patterns, treatment modalities, and one-year survival outcomes of pediatric patients with osteosarcoma and Ewing sarcoma. It also compares survival rates between patients receiving complete treatment (surgery and chemotherapy) and those receiving chemotherapy alone at Dr. Hasan Sadikin General Hospital, a tertiary referral center in West Java.

Methods

This study was a descriptive analytical observational study using secondary data from electronic medical records available on the Indonesian Pediatric Cancer Registry (IPCAR) website. Patient data were filtered by diagnosis codes for osteosarcoma and Ewing sarcoma, then exported into Microsoft Excel format. Several researchers reviewed the exported data based on the inclusion criteria, namely patients diagnosed with osteosarcoma and Ewing sarcoma at Dr. Hasan Sadikin General Hospital Bandung from 2020 to 2023. The exclusion criteria were patients with incomplete medical record data, patients who did not undergo treatment, and patients lost to follow-up. For this study, a total of 58 research subjects were included. After all the data is collected, the data editing, coding, and verification processes are carried out. Data analysis was done with Stata/SE 16. Analytical and descriptive data were analyzed. Categorical scale information, including gender, age,

laterality, treatment, histopathological pattern, primary tumor location, and one-year survival. All of the data are presented as percentages and frequency distributions. Because more than 20% of the cells have an expected count of less than 5, the Fisher exact test was used to compare the one-year survival between the complete treatment group (who underwent surgery as local tumour control and chemotherapy) and the chemotherapy-only group. This study received ethical approval from the Health Research Ethical Committee of Dr. Hasan Sadikin General Hospital Bandung in May 2024 (approval number: DP.04.03/D.XIV.6.5/213/2024).

Results

Based on data collected from 2020 to 2023, applying exclusion criteria, there were 44 patients diagnosed with osteosarcoma, of which 27 were male and 17 were female (Table 1). Additionally, 14 patients were diagnosed with Ewing sarcoma, comprising 9 males and 5 females (Table 2).

Osteosarcoma was found in many age groups; 3 (6.8%) patients in the 0–5-year age group, 5 (11.4%) patients in the 6–10-year age group, and 9 (20.5%) patients in the 16–18-year age group (Table 1). The most prevalent age group of osteosarcomas was the 11–15-year age group, consisting of 27 (61.4%) patients (Table 1). In Ewing sarcoma, there are 4 (28.6%) patients in the 0–5-year age group, 4 (28.6%) patients in the 6–10-year age group, and 1 (7.1%) patient in the 16–18-year age group (Table 2). The most prevalent age group of Ewing sarcoma was the 11–15-year age group; it consists of 5 (33.7%) patients (Table 2).

Regarding laterality, osteosarcoma and Ewing sarcoma were more prevalent in unilateral involvement; 44 (100.0%) patients of osteosarcoma (Table 1) and 13 (92.9%) patients of Ewing sarcoma had unilateral involvement. Only 1 (7.1%) patient with Ewing sarcoma had bilateral involvement (Table 2).

The histopathological patterns in osteosarcoma patients varied. This study

Table 1 Characteristics of Osteosarcoma Patients

Characteristic	Category	n=44	%
Age (year)	0–5	3	6.8
	6–10	5	11.4
	11–15	27	61.4
	16–20	9	20.5
Gender	Male	27	61.4
	Female	17	38.6
Laterality	Unilateral	44	100
	Bilateral	0	0
Histopathological Type	Conventional Osteosarcoma	41	93.2
	Periosteal Osteosarcoma	2	4.6
	Telangiectatic Osteosarcoma	1	2.3
Primary Tumor Location	Femur	20	45.5
	Tibia	20	45.5
	Fibula	2	4.6
	Humery	2	4.6
Therapeutic Modality	Chemotherapy Only	27	61.4
	Complete Treatment (Chemotherapy + Surgery)	17	38.6
One Year Survival Outcome	Died	28	64.6
	Survived	16	36.4

Table 2 Characteristics of Ewing Sarcoma Patients

Characteristic	Category	n=14	%
Age (year)	0–5	4	28.6
	6–10	4	28.6
	11–15	5	33.7
	16–20	1	7.1
Gender	Male	9	64.3
	Female	5	35.7
Laterality	Unilateral	13	92.9
	Bilateral	1	7.1
Histopathological Type	Classical Ewing Sarcoma	14	100
Primary Tumor Location	Extremity	4	38.1
	Axial		
	Vertebrae	1	28.6
	Others	9	71.4
Therapeutic Modalities	Chemotherapy	8	57.1
	Complete Treatment (Chemotherapy + Surgery)	6	42.9
One Year Survival Outcome	Died	6	42.9
	Survived	8	57.1

found 41 (93.2%) patients with conventional osteosarcoma pattern, 2 (4.5%) patients with periosteal osteosarcoma pattern, and 1 (2.3%) patient with telangiectatic osteosarcoma pattern (Table 1). While in Ewing sarcoma, we only found classical Ewing sarcoma patterns in all (100%) patients (Table 2).

Location of the primary tumor in osteosarcoma was mostly found in the femur and tibia (n=20, 45.5%). The other locations found were in humerus of 2 (4.6%) patients and in the fibula of 2 (4.6%) patients (Table 1). In Ewing sarcoma, the most prevalent primary tumor location was in the axial part other than vertebrae, such as the head, neck, thorax, and abdomen (n=10, 71.4%). The other locations were in extremity of 4 (28.6%) patients and in vertebrae of 1 (7.1%) patient (Table 2).

Most of the osteosarcoma patients (61.4%) underwent chemotherapy alone. In contrast, among Ewing sarcoma patients, 8 individuals (57.1%) received chemotherapy, while the remaining 6 patients (42.9%) underwent chemotherapy combined with surgical intervention. There were various reasons why chemotherapy became the most chosen therapeutic modality, such as the parents rejecting the amputation or the patients coming in an unresectable condition.

The one-year survival rate for osteosarcoma patients was 36.4%, with 16 patients surviving, while 64.6% (28 patients) succumbed to the disease. Among Ewing sarcoma patients, 57.1% (8 patients) survived following therapy, whereas 42.9% (6 patients) died post-therapy.

Osteosarcoma patients who underwent chemotherapy combined with surgery demonstrated a higher one-year survival rate (n=12, 70.6%) compared to those who received chemotherapy alone (n=4, 14.8%) (Table 3). Data

Table 3 One-Year Survival Outcome in Osteosarcoma Patients by Treatment Type

	Survived (n)	Died (n)	p-value
Complete Therapy (Chemotherapy + Surgery)	12	5	0.000
Chemotherapy only	4	23	

Table 4 One-Year Survival Outcome in Ewing Sarcoma Patients by Treatment Type

	Survived (n)	Died (n)	p-value
Complete Therapy (Chemotherapy + Surgery)	6	0	0.000
Chemotherapy only	2	6	

on Ewing sarcoma patients also showed that those who underwent chemotherapy combined with surgery had a higher one-year survival rate (n=6, 100%) compared to chemotherapy alone (n=2, 25%) (Table 4).

Discussion

Osteosarcoma and Ewing Sarcoma are primary malignant bone tumors that predominantly affect pediatric populations. According to this research, the median age for osteosarcoma was 14.75 years, while the median age for Ewing Sarcoma was 9.25 years. Certain academic sources suggest that the peak age of onset of osteosarcoma falls within the range of 10 to 14 years, while Ewing sarcoma typically presents between 12 to 18 years.[6,8,9]

Gender disparities are seen in this study; 61.4% of individuals with osteosarcoma and 64.3% of individuals with Ewing Sarcoma were males. In line with previous studies, both osteosarcoma and Ewing Sarcoma demonstrate a higher incidence among male individuals compared to females. Williams LA et al. in their study found that the ratio of incidence in males and females varied depending on the timing of puberty. This is related to the peak of bone growth related to estrogen. Bone growth at puberty involves the growth hormone (GH)/insulin like growth factor 1 (IGF-1) axis. Research shows that estrogen increases GH secretion in both females and males, while testosterone affects GH secretion by converting it to estrogen through the aromatization process. Differences in the timing of puberty and estrogen levels in males and females affect bone growth and this explains the higher incidence of osteosarcoma and Ewing sarcoma in males during adolescence.[9–12]

Based on the results of this study, 93.2% of osteosarcoma in children at Dr. Hasan Sadikin General Hospital Bandung is conventional osteosarcoma. This is in line with some literature stating that conventional osteosarcoma is the classic type of osteosarcoma and is the most common histopathological pattern of osteosarcoma cases. Osteosarcoma is histologically classified by the World Health Organization (WHO) into central, intramodular, and surface. The central classification includes conventional osteosarcoma, telangiectatic osteosarcoma, small-cell osteosarcoma, and low-grade osteosarcoma. Conventional osteosarcoma is the most common type of osteosarcoma, representing 80% of all pediatric osteosarcoma cases. Conventional osteosarcoma is a high-grade tumor that originates from the intramedullary cavity.[13–15]

The most common primary tumor location of osteosarcoma in this study was the femur and tibia. This is consistent with the literature highlighting the prevalence of osteosarcoma in long bones. The femur, the longest and strongest bone in the human body, provides a conducive environment for the development of osteosarcoma due to its high vascularity and rapid bone growth during adolescence.[3]

On the contrary, Ewing sarcoma could happen in any bone or soft tissue; this uncertain predilection challenges the early detection of this sarcoma. In line with the literature, the primary tumor location of Ewing sarcoma in this study was found in various locations but mostly found in axial bones other than vertebrae. However, early detection and precise location of Ewing sarcoma can significantly impact treatment outcomes and improve survival rates for patients with this aggressive malignancy.[7]

One of the important prognostic factors in osteosarcoma and Ewing sarcoma is the laterality involvement of the disease. Unilateral involvement has a better prognosis. In this research, most of the patients, 44 (100%) osteosarcoma patients and 13 (92.9%) Ewing sarcoma patients, have unilateral involvement; this indicates that most patients had a better prognosis. This is evident in Ewing sarcoma patients, with 8 individuals (57.1%) surviving within one year. However, this is in contrast to osteosarcoma patients, the majority of whom (63.6%) died within one year after treatment. This may be due to the fact that many patients came in with complications and metastases, which delayed diagnosis and treatment. In addition, the fact that some patients' parents took

their patients to traditional treatment centers before coming to the hospital also delayed the diagnosis and treatment.

Patients with osteosarcoma who undergo chemotherapy and surgery have a higher one-year survival rate compared to those who receive chemotherapy alone. This is consistent with the research conducted by Liao et al., which indicates that patients treated with chemotherapy alone have significantly poorer outcomes and limited effectiveness in long-term results compared to those receiving a combination of surgical therapy and chemotherapy. Several studies also state that the administration of chemotherapy, particularly neoadjuvant therapy, increases the 5-year survival rate for osteosarcoma patients to 50-60%, compared to only 20% for surgery alone. Management of osteosarcoma with chemotherapy alone is insufficient to eradicate cancer cells in primary tumors or clinically detected metastases. One study conducted by Jaffe et al. showed that the use of chemotherapy alone as exclusive therapy for osteosarcoma has a low cure rate (10%), with nearly all patients experiencing disease recurrence and almost 50% developing pulmonary metastasis.[16,17]

This observation indicates a critical discussion on the impact of the limited use of treatment modalities on patient outcomes. Furthermore, the study results indicate that most patients with malignant bone tumors underwent only chemotherapy as a therapeutic modality. Chemotherapy can be a crucial component in the treatment of certain cancers, including bone tumors but, chemotherapy alone is insufficient to reliably destroy either the primary tumour or to eradicate clinically detectable metastases. Furthermore, the study results highlight the potential lack of utilization of other treatment modalities, such as surgery or radiation therapy, in the management of malignant bone tumors. This raises concerns about the comprehensiveness of care provided to these patients and whether a multidisciplinary approach involving different treatment modalities could lead to better outcomes.[3,7]

This study has several limitations that should be acknowledged. First, the sample size of 58 patients may not be representative of the entire population of childhood malignant bone tumor patients, potentially limiting the generalizability of the findings. Additionally, the study only included patients from a single institution, which may not capture the diversity of cases seen in different healthcare settings.

In conclusion, this study reveals critical characteristics of childhood malignant bone tumor patients at Dr. Hasan Sadikin General Hospital Bandung, highlighting the majority of osteosarcoma and Ewing sarcoma in male adolescents. Despite a higher incidence of unilateral tumors, the outcomes remain poor, with a significant number of patients experiencing death after 1 year of therapy. The findings highlight the urgent need for improved diagnostic and treatment strategies, as well as comprehensive care that includes various therapeutic modalities beyond chemotherapy. Addressing barriers to treatment access and promoting a multidisciplinary approach could enhance the prognosis and quality of life for these patients. Future research with a larger sample size and multi-center collaboration is recommended to further explore the factors influencing treatment decisions and patient outcomes and how high is the survival rate of patients with other multimodal therapies.

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