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Original Article

Survival rates of pediatric osteosarcoma in Indonesia: a single center study

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Abstract

Background Over the years, the survival rate of children with osteosarcoma has increased with improved management. However, survival tends to be lower in low-middle-income countries.

Objective To report the survival rate of children with osteosarcoma in a single center in Indonesia and to evaluate the outcomes of treatment modalities currently used.

Methods We performed a retrospective analysis of the medical records of pediatric osteosarcoma patients in Cipto Mangunkusumo Hospital, Jakarta, from 2015 to 2019. Patients were categorized based on age group, sex, primary tumor location, treatment modalities, disease metastasis, and disease outcome.

Results We included 83 children with osteosarcoma, with a median age of 13 (median 4-17). Mean estimated overall survival and event-free survival were 28 (95%CI 24 to 32) months and 10 (95%CI 8 to 13) months, respectively. Overall survival duration between treatment modality groups was significantly different ($P<0.05$). The mean estimated overall duration of survival was 9 (95%CI 3 to 15) months for chemotherapy, 18 (95%CI 14 to 22) months for chemotherapy with surgery, and 21 (95%CI 14 to 27) months for chemotherapy with surgery and radiation.

Conclusion The survival rate of childhood osteosarcoma in Indonesia remains low. The current treatment option currently used in our center may contribute to the low rate of survival. **[Paediatr Indones. 2022;62:27-31 ; DOI: 10.14238/pi62.1.2022.27-31].**

Keywords: *childhood osteosarcoma; survival rate; low-middle income countries*

Osteosarcoma is the most common primary bone malignancy in children and accounts for 3-5% of pediatric cancers. The incidence of osteosarcoma is distributed bimodally across the lifetime, with an initial peak between the ages of 10 and 14 years during the pubertal growth spurt and a second peak after the age of 60 years.[1]

Osteosarcoma is defined by the presence of malignant mesenchymal cells producing osteoid or immature bone. It may occur in primary and secondary forms.[2] Osteosarcoma is frequently located at the metaphyseal section of long bones, such a distal femur, proximal tibia, and proximal humerus.[3]

Metastatic disease is the major cause of osteosarcoma-related death. Based on its location, metastasis is classified as either pulmonary or extrapulmonary. Lung involvement occurs in approximately 80% of cases, but bone metastasis is associated with worse prognosis.[4] Approximately 15-20% of patients present with lung metastases at initial diagnosis, whereas 40% develop metastases

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in later stages.[5] The estimated five-year event-free survival of children with metastatic disease is less than 30%.[6]

The aim of this study was to determine the survival rate of children with osteosarcoma treated in our center over the last five years. We also aimed to evaluate the outcomes of treatment modalities currently being used.

Methods

We performed a retrospective observational study on pediatric patients diagnosed with osteosarcoma from 2015 to 2019 in Cipto Mangunkusumo Hospital, Jakarta. Patients were identified from the Pediatric Cancer Database of the Department of Child Health and through a search of electronic medical records. Patients were classified based on age at diagnosis, sex, primary tumor location (humerus, tibia/fibula/femur, pelvis, or other), clinical staging, treatment modalities used (chemotherapy only, chemotherapy and surgery, or chemotherapy with surgery and radiotherapy), metastases at diagnosis (present or absent), site of metastasis (pulmonary or extrapulmonary), and disease outcome (survived, lost to follow-up, relapsed, or died).

Osteosarcoma was diagnosed by history taking, physical examination, and supporting examinations. From the patient's history, we recorded symptoms that may lead to an osteosarcoma diagnosis, including progressive pain in the extremities for three to six months prior to diagnosis or a history of fracture(s). We also recorded CT scan and MRI results to determine tumor staging, histopathological diagnoses from tissue biopsy specimens, and bone scan results to detect skeletal metastases.

Surgical excisions and/or biopsies were done in the Department of Orthopedics and Traumatology. For some difficult cases, multidisciplinary team discussions were held involving the orthopedic surgeon, pathologist, radiologist, pediatric hemato-oncologist, and internal medicine specialists to determine tumor staging, management plan, and prognosis.

The chemotherapy protocol used for treating children with osteosarcoma was derived from the *Werkgroep Kindertumoren, Emma Kinderziekenhuis Academic Medical Center* (WKT, EKZ, AMC, 1989) protocol and consisted of three drugs: cisplatin 60 mg/m^2, ifosfamide 3000 mg/m^2, and doxorubicin 25 mg/m^2/day given for three days every three weeks (total cumulative dose 375 mg/m^2). Neoadjuvant therapy was given for three cycles. Following chemotherapy, patients underwent surgery (limb salvage surgery or limb amputation) and/or extracorporeal irradiation, depending on the mass size, location, and characteristics. The patient was then given adjuvant chemotherapy with the same regimen as before for 3 cycles. Radiotherapy was done when the incisional site of resection was too close to the tumor or when pathology results were positive for tumor cells in the incisional site. The dose of radiotherapy given was 50.4-55.8 Gy.

Event-free survival was defined as the duration of the period from the date of diagnosis to the date of the first event (recurrence, metastasis, loss to follow-up, or death). Overall survival was defined as the duration of the period from the date of diagnosis to the date of death or final follow-up. Data were analyzed using *SPSS version 22* (*IBM*, Armonk, New York). Survival curves were generated using the Kaplan-Meier method.

Results

Eighty-nine children were diagnosed with osteosarcoma from 2015 to 2019. Six patients were excluded due to incomplete data. Of 83 patients included in the study, 48 (57.8%) were male and 35 (42.2%) were female. Fifteen patients were below 10 years of age and 68 were 10 years of age or older; subjects' median age was 13 years. The most common sites of the primary tumors were in the lower extremities: the femur in 42/83 (50.6%) subjects and the tibia/fibula in 33/83 (39.8%). The rest had primary tumors in the upper extremities (4/83; 4.8%) and other regions. Forty-seven patients underwent chemotherapy and surgery; 15 received a combination of chemotherapy, surgery, and radiation, 15 had chemotherapy only, and four did not receive any treatment. Metastatic disease at diagnosis was found in 13 patients. More than half of the study population (61%) had metastatic disease, with the lung as the most common site of metastasis (57%) (**Table 1**).

The mean event-free survival duration (time between diagnosis and first event) was 10.3 (95%CI 7.7 to 12.8) months. The mean duration of overall survival (time between diagnosis and last follow-up or death) was 28 (95%CI 24.2 to 31.9) months. Mean survival duration was 9 (95%CI 2.8 to 15.2) months

in the chemotherapy group, 17.8 (95%CI 13.5 to 22.2) months in the chemotherapy and surgery group, and 20.7 (95%CI 14.5 to 27) months in the chemotherapy, surgery, and radiotherapy group (**Figure 1**).

Discussion

The overall survival rate of all childhood cancers has improved from 30% to more than 80% in high-income countries.[7] Improvements in survival outcome of childhood sarcoma are a result of improvement in treatment modalities, including surgery and chemotherapy regimens.[8]

Table 1. Baseline characteristics of subjects

Parameters	(N=83)
Age, n (%)	
< 10 years	15 (18.1)
≥ 10 years	68 (81.9)
Sex, n (%)	
Male	48 (57.8)
Female	35 (42.2)
Primary tumor, n (%)	
Humerus	4 (4.8)
Femur	42 (50.6)
Tibia/fibula	33 (39.8)
Others	4 (4.8)
Treatment modalities, n (%)	
Chemotherapy	15 (18.1)
Chemotherapy & surgery	47 (56.6)
Chemotherapy, surgery, & radiation	15 (18.1)
Surgery	2 (2.4)
No treatment	4 (4.8)
Metastases at diagnosis, n (%)	
Yes	70 (84.3)
No	13 (15.7)
Site of metastases, n (%)	
Lung	48 (57.8)
Other extremities	1 (1.2)
Other	2 (2.4)
No metastasis	32 (38.6)
Staging, n (%)	
IB	1 (1.2)
IIA	2 (2.4)
IIB	13 (15.7)
IIIA	2 (2.4)
IV	51 (61.4)
No staging done	14 (16.8)
Outcomes, n (%)	
Died	30 (36.1)
Relapsed	1 (1.2)
Lost to follow-up	32 (38.6)
Survived	20 (24.1)

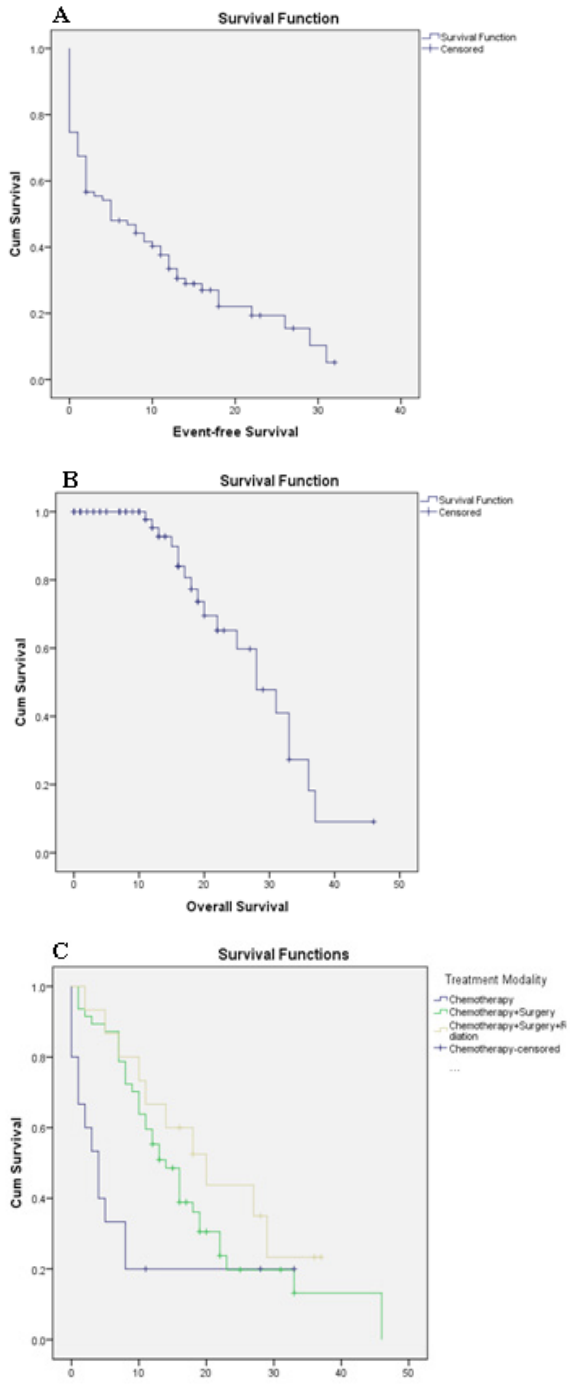

Figure 1. Kaplan-Meier curves of A. event-free survival; B. overall survival; C. overall survival in different treatment modality groups (chemotherapy; chemotherapy and surgery; chemotherapy, surgery, and radiation)

More than 80% of childhood cancers occur in low-middle income countries. Unfortunately, children are often neglected in cancer control planning efforts, despite a disproportionately high number of person-years of life lost, due to missed opportunities to diagnose and treat cancer in low- and middle-income countries (LMICs).[9,10]

In Thailand, the survival rates of osteosarcoma in children have been reported to be lower than those in other Western and Asian countries. The overall survival rates at 5 and 10 years were 35% and 33.6%, respectively, with non-methotrexate chemotherapeutic protocols.[11] In another center in northeast Thailand, the 5-year survival rate of pediatric osteosarcoma was 27.6%.[12] These studies were similar to our study, in that non-methotrexate chemotherapeutic protocols were preferred and the studies were done in a low-middle income country in Southeast Asia.

Patients with delayed diagnosis and treatment have been reported to have a shorter mean survival duration (8.3 months) compared to those treated in a timely manner with good compliance (15.2 months).[11] In our study center, 13 (16%) subjects had metastatic osteosarcoma at initial diagnosis. The limited capacity of health care facilities for childhood cancer management has resulted in a long queue of patients waiting for diagnosis and treatment. Most health care facilities capable of childhood cancer management are located in big cities, consequently, children from remote areas experience further treatment delays related to transfers and referrals.

Death (36%) and loss to follow up (39%) were two of the most frequent outcomes of the patients in our study. Many factors contributed to low patient compliance. A study in Peru reported that the most common cause for delay in completing chemotherapy was medical (neutropenia and sepsis). Other obstacles to treatment included a lack of available beds or surgical material, insurance problems, and social issues.[13] In some regions, due to cultural beliefs or financial limitations, parents tended to seek alternative medicine or traditional healers.[14]

Although the 6-year event-free survival of patients with non-metastatic disease has improved from 11% to 61%, the outlook for children with metastatic disease remains poor, with an estimated event-free survival of <30% at 5 years.[6] A meta-analysis showed that the 5-year survival rate of patients with tumor metastasis at initial diagnosis was lower than patients without metastasis (OR 0.2; 95%CI 0.11 to 0.39).[15] The poor survival rate of pediatric osteosarcoma demonstrated in our study coincided with a high number of children with metastatic disease. Another factor lay in the chemotherapeutic protocol used in our center; as we had no available tool to detect methotrexate levels in the body, we chose non-methotrexate regimen treatment protocols.

In our single-center study, both event-free survival and overall survival of childhood osteosarcoma were poor. Raising public awareness on early detection of childhood cancer and increasing cancer detection capability in primary health care centers are needed to reduce the delayed diagnosis of cancer. In addition, establishing more childhood cancer management centers and diagnostic work-up tools would help resolve the long waiting times. Further studies are needed to improve childhood cancer management and prolong patient survival duration.

Conflict of interest

None declared.

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