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Original Article

Survival and prognostic factors in pediatric osteosarcoma: A 5-year single-center experience in Central Java, Indonesia

Muhammad Riza[1], Harsono Salimo[1], Brian Wasita[2], Mujaddid Idulhaq[3], Rhyan Darma Saputra[3,4], Vitri Widyaningsih[5], Soestrisno[6], Fairuz Zahidah[1], Janur Wayanshakty[1]

Abstract

Background The advent of chemotherapy with multimodal treatment has improved the survival rate of osteosarcoma. However, the survival rate of patients with osteosarcoma in low- and middle-income countries (LMICs) remains lower than in high-income countries (HICs).

Objective To assess prognostic factors associated with survival rate of pediatric patients with osteosarcoma in Moewardi Hospital, Surakarta.

Methods This retrospective study was performed in pediatric osteosarcoma patients at Moewardi Hospital, Surakarta from 2018 to 2022. We described patients' clinical presentations and assessed prognostic factors. Survival rate was calculated using Kaplan-Meier survival analysis. Prognostic factors were analyzed using univariate and multivariate Cox regression methods.

Results Of the 82 patients included in the study, 40 (48.8%) were male and 42 (51.2%) were female. Most subjects (75.6%) were diagnosed with osteosarcoma at the age of >10 years, 45 patients (54.9%) had primary tumors in the femur, and 16 patients (19.5%) had limb salvage surgery. The mean event-free survival duration was 13.6 (95%CI 9.7 to 17.5) months. The mean duration of overall survival was 22.7 (95%CI 17.3 to 28.1) months, with a 44.1% survival probability. Type of surgery was a significant prognostic factor (P=0.018), with limb salvage having better survival probability (93.3%) than amputation (19.8%).

Conclusion The overall survival rate of osteosarcoma patients at our center is still lower than in other regional centers. Limb salvage surgery was a significant prognostic factor for survival, while gender, location of primary tumor, histological subtype, and metastasis at the time of diagnosis were not. **[Paediatr Indones. 2024;64:10-6; DOI: 10.14238/pi64.1.2024.10-6**].

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

Osteosarcoma is the most common malignant bone tumor in children and adolescents. It accounts for approximately 4.4 cases per million children annually.[1] Mortality rates of osteosarcoma have decreased primarily due to the introduction of multiagent chemotherapy. However, there is a noticeable gap in treatment outcomes for osteosarcoma between high-income countries (HICs) and low- and middle-income countries (LMICs), and even between various centers within the same country. Mortality rates in many centers within the Asia-Pacific region vary from 20% to 70%.[2-5] Several factors contribute to this finding, including delayed diagnosis, suboptimal treatment, toxicity-induced deaths, lack of compliance, inadequate infrastructure to administer complex protocols, and abandonment of treatment.[6]

Using data from the *Surveillance, Epidemiology, and End Results* (SEER) program database, the overall

From Department of Child Health[1] and Department of Anatomical Pathology[2], Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital; Department of Orthopedics and Traumatology, Universitas Sebelas Maret[3] and Prof. Dr. R. Soeharso Orthopedics Hospital[4]; Department of Public Health, Faculty of Medicine[5] and Department of Obstetrics and Gynecology[6], Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital, Surakarta, Central Java, Indonesia.

Corresponding author: Muhammad Riza. Department of Child Health, Faculty of Medicine, Universitas Sebelas Maret/Dr. Moewardi Hospital. Jalan Samanhudi 22 Surakarta 57142. Email: m_riza@staff.uns.ac.id.

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duration of survival among 3,085 osteosarcoma patients aged four to nine years between 1973 and 2012 was 64.2 (95%CI 59.1 to 69.3) months. In the United States, the overall duration of survival in 10–15-year-old osteosarcoma patients was 66.4 (95%CI 63.5 to 69.3) months.[7] A retrospective cohort study in the Netherlands between 1978 and 2017 showed that the overall survival rate among non-metastatic patients with skeletal high-grade osteosarcoma aged 0–16 years was 78.5%. Meanwhile, the overall survival rate was 21.7% in the metastatic group.8

A study from 2015 to 2019 in the national referral hospital in Indonesia showed that of 89 children with osteosarcoma, the mean event-free survival duration was 10.3 (95%CI 7.7 to 12.8) months and the mean duration of overall survival rate was 28 (95%CI 24.2 to 31.9) months. The study also showed differences in mean survival duration between treatment modality groups, in which the group that received therapeutic modalities consisting of chemotherapy, surgery and radiotherapy had a better survival duration compared to chemotherapy or surgery alone.[9]

Since the advent of chemotherapy, overall cure rates have dramatically improved by more than 50% to 70% in HICs. However, these rates are far higher than in LMICs.[6] Many factors are prognostic of patient survival, but the clinical prognostic features of osteosarcoma and other independent factors have not been fully described.[10,11]

Our institution, Moewardi Hospital, Surakarta, is a tertiary care referral and research center for the Central Java Region in Indonesia. We aimed to determine the survival rate and prognostic factors of children with osteosarcoma treated at our center over a five-year period (2018-2022).

Methods

Medical records of pediatric patients with a confirmed diagnosis of osteosarcoma from January 2018 to December 2022 at Moewardi Hospital, Surakarta were retrieved. We collected data from medical records including clinical presentation, exact anatomical site, histological subtype, type of surgery, presence of metastasis, and outcome from the pediatric cancer database of the Department of Child Health, Moewardi Hospital, Surakarta. Subjects were classified into 2 groups based on age at diagnosis: <10 *vs.* ≥ 10 years. We recorded disease outcome (survived or died) and assessed gender (male or female), location of primary tumor (humerus, femur, tibia/fibula, and others), histological subtype (conventional or other), type of surgery (limb salvage or amputation), and metastases at the time of diagnosis (present or absent) as potential prognostic factors for survival. We analyzed each potential prognostic factor for possible associations with disease outcome.

Osteosarcoma was diagnosed by history-taking, physical examination, CT scan or MRI, and histopathological examination. Surgical excisions and biopsies were done in the Department of Orthopedics and Traumatology and the Department of Anatomical Pathology. For complicated cases, multidisciplinary team discussions were held involving the orthopedic surgeon, pathologist, and pediatric hemato-oncologist to determine the tumor stage, management plan, and prognosis.

Patients with localized disease received a first-line chemotherapy regimen of doxorubicin 25 mg/m2 on day 1 and cisplatin 100 mg/m^2 on days 1-3, given for 3-4 cycles within 7-10 weeks. In cases of metastatic disease or patients who had a poor degree of tumor necrosis (<90%) after surgery, a second line of chemotherapy using doxorubicin, cisplatin (doses were the same as those first-line protocols), and ifosfamide (2650 mg/m^2) at cycles 2 and 4. An intravenous infusion of mesna (1600 mg/m2) was given concomitantly to reduce the side effect of ifosfamide. After completing neoadjuvant chemotherapy, the patient would have limb salvage surgery or limb ablation and amputation.

Overall survival duration was defined as the time interval from the date of diagnosis to the date of death or last follow-up. Overall survival probability was the proportion of patients who survived at the end of the follow-up period. Event-free survival duration was defined as the time interval from the date of diagnosis to the date of the first event (recurrence, metastasis, loss to follow-up, or death). Event-free survival probability was the proportion of patients who were free of events at the end of the follow-up period.

The survival rate was calculated using Kaplan–Meier survival analysis with log-rank test. Prognostic factors were analyzed using univariate and multivariate

Cox regression method, with variables in the model weighted equally to provide a hazard ratio for the given analysis. A P value of <0.05 was considered to be statistically significant. *SPSS version 25 (IBM,* Armonk, New York) was used for statistical analysis.

Results

During the five-year study period, 91 children were confirmed to have osteosarcoma. Nine patients were excluded due to incomplete data; thus, 82 patients were included in our study. There were 42 (51.2%) female patients. At the time of diagnosis, 62 (75.6%) patients were older than 10 years. Mean age at the time of diagnosis was 13 years.

Most tumors were located in the femur (45 patients; 54.9%). The most common histological subtype of osteosarcoma was conventional osteosarcoma (59.8%), and 21 (25.6%) patients had metastatic involvement (**Table 1**). The mean time interval between the date of the last chemotherapy and surgery was 15 weeks. Five subjects had an interval of more than 15 weeks, but all of them survived.

Kaplan-Meier curves (**Figure 1**) showed a mean event-free survival duration (time between diagnosis and the first event) of 13.6 (95%CI 9.7 to 17.5) months, with an 18.8% survival probability. Mean overall survival duration (time between diagnosis and the last follow-up or death) was 22.7 (95%CI 17.3 to 28.1) months, with a 44.1% survival probability.

Table 1. Baseline characteristics of subjects

Characteristics	(N=82)
Gender, n (%)	
Male	40 (48.8)
Female	42 (51.2)
Age, n (%)	
≤10 years	20 (24.4)
>10 years	62 (75.6)
Location of primary tumor, n (%)	
Humerus	9 (11.0)
Femur	45 (54.9)
Tibia/fibula	21 (25.6)
Other	7 (8.5)
Histological subtype, n (%)	
Conventional	48 (58.5)
Other	34 (41.5)
Metastasis, n (%)	
Yes	21 (25.6)
No	61 (74.4)
Type of surgery, n (%)	
Limb salvage	16 (19.5)
Amputation	17 (23.2)

Table 2. Survival probability of pediatric osteosarcoma prognostic factors

Variables	Survival cumulative probability, %	Median overall survival time (range), months	P value*
Gender			
Male	38.6	21.7 (13.6-29.7)	0.879
Female	47.9	20.1 (14.1-25.9)	
Age			
≤10 years	38.8	18.2 (9.1-27.3)	0.076
>10 years	40.6	20.1 (14.8-25.5)	
Location of primary tumor			
Humerus	35.6	16.9 (4.3-29.6)	0.946
Femur	43.9	22.3 (14.9-29.7)	
Tibia/fibula	30.1	17.4 (8.3-26.5)	
Others	45.7	21.5 (6.1-27.0)	
Histological subtype			
Conventional	43.4	22.1 (14.7-29.6)	0.716
Others	44.5	22.5 (15.0-30.0)	
Metastasis			
Yes	17.3	12.7 (9.3-16.1)	0.422
No	56.7	26.0 (20.0-31.9)	
Type of surgery			
Limb salvage	93.3	38.5 (33.8-43.1)	0.018
Amputation	19.8	14.9 (11.7-18.1)	

*Log-rank test

We also drew Kaplan-Meier survival curves based on gender, age, location of primary tumor, histological subtype, metastasis, and type of surgery. Survival rates were significantly different between the types of surgery. Limb salvage had a higher survival rate than amputation [93.3% *vs.* 19.8%, respectively; (P=0.018)]. Mean survival time of patients who received limb salvage surgery was 38.5 months, compared to 14.9 months in patients who underwent amputation (**Table 2**).

Discussion

The overall survival rate in our study was 22.7 (95%CI 17.3 to 28.1) months and the cumulative survival probability was 44.1%. Our results were similar to those in Dharmais Hospital, the national cancer referral hospital in Indonesia, where 41 children with osteosarcoma had an overall survival rate of 23 months with a 29.4% cumulative survival probability. The Dharmais study also showed no significant differences in survival probability by age, gender, metastasis status, tumor site, or stage.[12] A study of 89 children with osteosarcoma in Cipto Mangunkusumo Hospital, Jakarta from 2015 to 2019 showed a better mean overall survival duration [28 (95%CI 24.2 to 31.9) months].[9] The higher survival duration may be due to the larger sample size possibly because their sample size.

The survival rate obtained in our study was lower than in other Southeast Asian countries. A

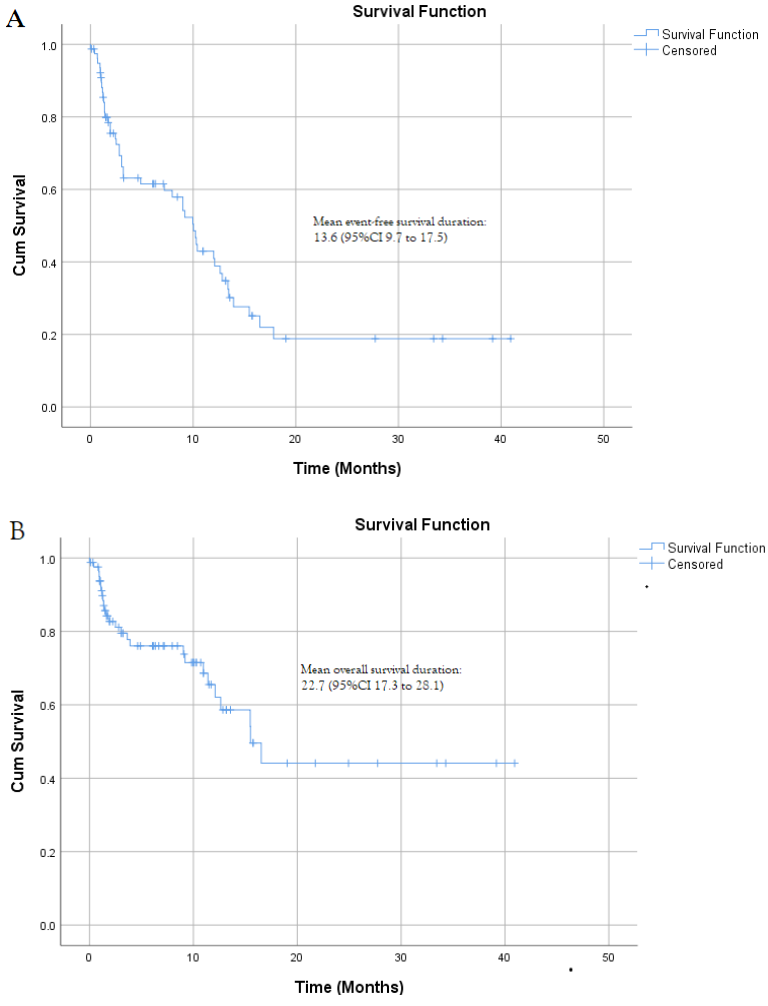

Figure 1. Kaplan-Meier curves of (A) event-free survival; (B) overall survival

multinational study conducted in three Southeast Asian countries (Thailand, Singapore, and the Philippines) found that both overall and event-free survival varied among the three countries. Overall and event-free survival rates in Thailand (70.9% and 59.5%, respectively) and Singapore (65.8% and 52.1%, respectively) did not differ significantly; both used a methotrexate (MTX) chemotherapy regimen-based protocol. However, the Philippines used non-high-dose MTX (non-HD-MTX) as the backbone chemotherapy protocol and had 20.3% overall and 15.3% event-free survival rates. MTX and non-MTX-based regimens have a five-year overall survival of 68% and 39.4%, respectively (P=0.001) and an event-free survival of 55.8% and 29.7%, respectively (P=0.003).[4]

Yasin et al. in Malaysia reported a 5-year overall survival rate of 56.31% (95%CI 46.20 to 65.24), with a median time-to-event of 3 years. Using MTX-doxorubicin-cisplatin based on the EUROMAS-1 study, they also reported that factors significantly associated with survival outcome included metastatic status, percentage of necrosis, tumor size, Enneking stage, local recurrence, completion of treatment, and whether or not the patient received surgical treatment. Gender, age grouping, tumor location, pathological fracture, and histological subtypes were not associated with survival outcome.[3]

Wiromrat et al. in Thailand reported a 5-year overall survival rate of pediatric osteosarcoma of 27.6% (95%CI 15.8 to 40.8%). The median survival duration was 1.6 (95%CI 1.2 to 2.1) years.[13] These values were lower than those observed in our study. However, another Thai study, in which pediatric osteosarcoma patients were treated with a carboplatin-based chemotherapeutic protocol, a mean (SD) 3-year disease-free survival rate and 3-year overall survival rate of 20.2% (SD 7.7%) and 47.1% (SD 9.5%), respectively, slightly higher than the values found in our study.[14] This may be due our the longer follow-up period.

Most international collaborations have demonstrated that the most effective chemotherapy regimens incorporate high-dose MTX as one of the agents.[3] However, LMICs predominantly use non-HD-MTX protocols. The choice of therapy is particularly important because HD-MTX administration brings additional complexities. This is because HD-MTX has a narrow therapeutic index with unpredictable and non-dose-dependent toxicities.[6]

Several factors that contribute to better survival in HICs are related to earlier diagnosis and treatment (including time of surgery), reconstruction principles, and limiting treatment abandonment. A study in Peru noted the impact of delayed diagnosis and treatment on survival of children with osteosarcoma in LMICs. Delay in chemotherapy due to any cause was independently associated with poor prognosis.[16] Furthermore, time of surgery was also associated with poor survival. Surgery was usually performed 3-4 weeks after completing chemotherapy. Another study found that for each week of delay in surgery after completion of neo-adjuvant chemotherapy, the risk of of local recurrence is increased by 1.14.[15] Chemotherapy delays may result from wound healing problems secondary to poor nutrition, difficulties in patient transportation from locations far from cancer centers, and other common logistical challenges.6 In our study, Five subjects had an interval of more than 15 weeks between the date of last chemotherapy and surgery, but all of them survived. Thus, delayed procedures did not contribute to survival in our study.

Reconstruction techniques vary in LMIC and contribute to poor survival. The majority of patients in LMICs cannot afford sophisticated prostheses utilized in HICs. As a result, unique prosthetic designs made of inexpensive, readily available materials are frequently used.[16] Furthermore, the popularity of biological reconstruction techniques in LMICs can be attributed to their affordability, longevity, capacity to avoid several revision procedures, and lifestyle considerations. With an endoprosthesis, the patient will never be able to sit or squat cross-legged and will require numerous costly surgical adjustments throughout their life.[17] The majority of proximal humeral tumors manifest at a stage that renders the axillary nerve and the deltoid insertion unsalvageable for surgeons. Therefore, restoring elbow and hand functionality is the main goal of reconstruction after proximal humerus excision. This is accomplished in the LMIC setting by anchoring a K-nail cement spacer into the glenoid using a prolene mesh, which yields good functional results.[18]

However, in LMICs, treatment abandonment is a serious issue that might contribute to lower survival.[19] According to a study in Philippines, without trained personnel who guide patients through the healthcare

system (navigator), treatment abandonment rates for the patient without navigator was significantly higher compared to those patient with navigator (50% *vs.* 6%, P=0.0001).[20] Protocols that are centered around outpatient care might be more receptive to shorter, easier-to-understand. In order to reduce treatment abandonment, it is also imperative to enhance the ratio of qualified oncologists and sarcoma care facilities per unit population.[21]

Osteosarcoma survival has been associated with other patient-related factors, such as age, gender, tumor site, stage, and metastasis.[22,23] Nevertheless, we did not find any association between these variables and survival probability. An interesting finding was our significantly increased osteosarcoma survival probability when limb salvage was the treatment choice compared to amputation. However, age at diagnosis, sex, tumor site, and histological subtypes were not found to be significantly associated with recurrence or survival.

In patients who underwent limb salvage surgery, mean survival duration was 38.5 (95%CI 33.8 to 43.1) months, with a 98.3% survival probability. The mean survival time for those who underwent amputation was 14.9 (95%CI 11.7 to 18.1) months, with a 19.8% survival probability. Limb-sparing surgery in patients with primary malignant sarcoma of the extremities has now been established. Faisham et al. reported that the survival of those treated with limb salvage surgery was better than those who underwent amputation (58% *vs.* 13% respectively, in five years). The amputation group had larger tumors or more extensive systemic metastases precluding limb salvage surgery. Amputation conferred only a marginal advantage against local recurrence. However, it is generally the treatment of choice for large tumors and patients with a poorer estimated prognosis.[22]

In conclusion, the survival rate of childhood osteosarcoma in Indonesia remains low. This problem needs to be addressed by a better management strategy, such as improving cancer awareness for early detection. In our study, patients who had no metastases at diagnosis and underwent limb salvage procedures had better survival rates. Even though limb salvage was not an independent factor, this type of surgery may be considered to improve survival and prevent disease recurrence.

Conflict of interest

None declared.

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References

1. Mirabello L, Troisi RJ, Savage SA. Osteosarcoma incidence and survival rates from 1973 to 2004: data from the Surveillance, Epidemiology, and End Results Program. Cancer. 2009;115:1531-43. DOI: https://doi.org/10.1002/cncr.24121
2. Wang W, Yang J, Wang Y, Wang D, Han G, Jia J, *et al.* Survival and prognostic factors in Chinese patients with osteosarcoma: 13-year experience in 365 patients treated at a single institution. Pathol Res Pract. 2017;213:119-25. DOI: https://doi.org/10.1016/j.prp.2016.11.009
3. Yasin NF, Abdul Rashid ML, Ajit Singh V. Survival analysis of osteosarcoma patients: a 15-year experience. J Orthop Surg. 2020;28. DOI: https://doi.org/10.1177/2309499019896662
4. Monsereenusorn C, Alcasabas AP, Loh AHP, Soh SY, Leung KWP, Dhamne C, *et al.* Predictors and treatment outcomes of pediatric osteosarcoma in diverse socioeconomic backgrounds in Southeast Asia: a retrospective multicenter study. Asian Pacific J Cancer Prev. 2022;23:631-40. DOI: https://doi.org/10.31557/APJCP.2022.23.2.631
5. Pruksakorn D, Phanphaisarn A, Pongnikorn D, Daoprasert K, Teeyakasem P, Chaiyawat P, *et al.* Age-standardized incidence rates and survival of osteosarcoma in Northern Thailand. Asian Pacific J of Cancer Prev. 2016;17:3455-8. DOI: https://doi.org/10.14456/apjcp.2016.116/APJCP.2016.17.7.3455
6. Mailankody S, Kumar VS, Khan SA, Banavali SD, Bajpai J. Resource-appropriate selection of osteosarcoma treatment protocols in low- and middle-income countries. Pediatr Blood Cancer. 2022;69:e29540. DOI: https://doi.org/10.1002/pbc.29540

7. Nie Z, Peng H. Osteosarcoma in patients below 25 years of age: an observational study of incidence, metastasis, treatment and outcomes. Oncol Lett. 2018;16:6502-14. DOI: https://doi.org/10.3892/ol.2018.9453
8. Evenhuis RE, Acem I, Rueten-Budde AJ, Karis DSA, Fiocco M, Dorleijn DMJ, *et al.* Survival analysis of 3 different age groups and prognostic factors among 402 patients with skeletal high-grade osteosarcoma. Real world data from a single tertiary sarcoma center. Cancers (Basel). 2021;13:486. DOI: https://doi.org/10.3390/cancers13030486
9. Sjakti HA, Putri IA, Windiastuti E. Survival rate of pediatric osteosarcoma in Indonesia: a single center study. Paediatr Indones. 2022;62:27-31. DOI: https://doi.org/10.14238/pi62.1.2022.27-31
10. Lin YH, Jewell BE, Gingold J, Lu L, Zhao R, Wang LL, *et al.* Osteosarcoma: molecular pathogenesis and iPSC modeling. Trends in Mol Med. 2017;23:737-55. DOI: https://doi.org/10.1016/j.molmed.2017.06.004
11. Gianferante DM, Mirabello L, Savage SA. Germline and somatic genetics of osteosarcoma - connecting aetiology, biology and therapy. Nature Reviews Endocrinology. 2017;13:480-91. DOI: https://doi.org/10.1038/nrendo.2017.16
12. Aisyi M, Syarif AH, Anggraeni NA, Perdana AB, Rezky H, Kosasih A, *et al.* Survival analysis in pediatric osteosarcoma. Indones J Cancer. 2019;13:21. DOI: https://doi.org/10.33371/ijoc.v13i2.622
13. Wiromrat P, Jetsrisuparb A, Komvilaisak P, Sirichativapee W, Kamsa-ard S, Wiangnon S. Incidence and survival rates among pediatric osteogenic sarcoma cases in Khon Kaen, Thailand, 1985-2010. Asian Pacific J of Cancer Prev. 2012;13:4281-4. DOI: https://doi.org/10.7314/APJCP.2012.13.9.4281
14. Choeyprasert W, Natesirinilkul R, Charoenkwan P, Sittipreechacharn S. Carboplatin and doxorubicin in treatment of pediatric osteosarcoma: a 9-year single institute experience in the northern region of Thailand. Asian Pacific J of Cancer Prev. 2013;14:1101-6. DOI: https://doi.org/10.7314/APJCP.2013.14.2.1101
15. Poudel RR, Tiwari V, Kumar VS, Bakhshi S, Gamanagatti S, Khan SA, *et al.* Factors associated with local recurrence in operated osteosarcomas: a retrospective evaluation of 95 cases from a tertiary care center in a resource challenged environment. J Surg Oncol. 2017;115:631-6. DOI: https://doi.org/10.1002/jso.24602
16. Vasquez L, Silva J, Chavez S, Zapata A, Diaz R, Tarrillo F, *et al.* Prognostic impact of diagnostic and treatment delays in children with osteosarcoma. Pediatr Blood Cancer. 2020;67. DOI:https://doi.org/10.1002/pbc.28180
17. Mailankody S, Kumar VS, Khan SA, Banavali SD, Bajpai J. Resource-appropriate selection of osteosarcoma treatment protocols in low- and middle-income countries. Pediatr Blood Cancer. 2022;69:e29540. DOI: 10.1002/pbc.29540.
18. Kundu ZS, Gogna P, Gupta V, Kamboj P, Singla R, Sangwan SS. Proximal humeral reconstruction using nail cement spacer in primary and metastatic tumours of proximal humerus. Strategies Trauma Limb Reconstr. 2013;8:149-54. DOI: https://doi.org/ 10.1007/s11751-013-0172-9
19. Ganguly S, Kinsey S, Bakhshi S. Childhood cancer in India. Cancer Epidemiol. 2021;71: 101679. DOI: https://doi.org/10.1016/j.canep.2020.101679
20. Gaston CL, Taleon K, Bersales K, Dimayuga C, Estanislao J, Fajardo P, *et al.* The Effect of a Patient Navigator on Treatment Abandonment and Follow-up for High Grade Osteosarcoma Patients in the Philippine General Hospital. Asian Pacific Journal of Cancer Prevention. 2021;22:2873-7. DOI: https://doi.org/ 10.31557/APJCP.2021.22.9.2873.
21. Bajpai J, Puri A, Shah K, Susan D, Jambhekar N, Rekhi B, *et al*. Chemotherapy compliance in patients with osteosarcoma. Pediatr Blood Cancer. 2013;60:41-4. DOI: https://doi.org/10.1002/pbc.24155
22. Faisham WI, Mat Saad AZ, Alsaigh LN, Nor Azman MZ, Kamarul Imran M, Biswal BM, *et al*. Prognostic factors and survival rate of osteosarcoma: a single-institution study. Asia Pac J Clin Oncol. 2017;13:e104-10. DOI: https://doi.org/10.1111/ajco.12346
23. Vasquez L, Tarrillo F, Oscanoa M, Maza I, Geronimo J, Paredes G, *et al.* Analysis of prognostic factors in high-grade osteosarcoma of the extremities in children: a 15-year single-institution experience. Front Oncol. 2016;6:22. DOI: https://doi.org/10.3389/fonc.2016.00022