Primary bone sarcomas in KSA: A Saudi tumor registry review

Wazzan S. Aljuhani, MD a, Abdullah M. Alanazi, MBBS b and Mohammad A. Alghafees, MBBS b, *

Original Article

Objectives: To report the incidence and differences in tumour type, site of origin, and mortality across gender, regions, age, and the different characteristics of tumour types.

Methods: This retrospective cohort study included all patients diagnosed with primary bone sarcomas from January 1, 2013, to December 31, 2017. Frequencies and percentages were generated for categorical variables. Means and standard deviations were calculated for quantitative variables. A chi-squared test was used to detect differences among categorical variables. Student-t, ANOVA, and Tukey tests were used to detect differences among quantitative variables. Lastly, we calculated the incidence of each tumour type.

Results: A total of 451 patients were included in the study. The most common tumour type was osteosarcoma (248 patients, 55%). The three-year survival rate was 82.30%. Significant differences were noted in origin site, grade, basis of diagnosis, and lateralisation across tumour types.

Conclusions: In our study, the observed bone sarcoma incidence rates were lower than the ones reported in the literature.
Introduction

A sarcoma is a heterogeneous group of neoplasms that arises from mesenchymal cells and can affect any anatomical site, whether it is soft tissue or bone. Primary bone sarcomas have a variety of histologic subtypes, mainly osteosarcoma, chondrosarcoma, Ewing’s sarcoma, and other less common bone sarcomas.

Bone Sarcomas are among the rarest malignancies that affect humans. According to the American Cancer Society, primary bone cancers account for less than 0.2% of all cancers. Osteosarcoma is the most common subtype, accounting for almost 35% of the bone sarcoma cases, followed by chondrosarcoma (25%) and Ewing’s sarcoma (16%). In Europe, the 2012 RARECARE Project had collected data from 1995 until 2002 and stated that the incidence of all sarcomas was 5.6 per 100,000 per year, of which soft tissue sarcoma makes up 84% (4.7 per 100,000) and bone sarcoma makes up 15% (0.8 per 100,000).

The geographic incidence of tumours usually uncovers the influence that the environment, race, and culture exert upon the prevalence of cancers. Therefore, due to the absence of local studies, this study of bone sarcomas is presented to highlight the incidence and detect differences based on tumour type, site of origin, and mortality across gender, regions, and age, and differences in the characteristics of tumour types between January 1, 2013, and December 31, 2017. Such studies would help develop selective screening protocols and facilitate treatment strategies and surveillance treatment pathways.

Materials and Methods

Study design and participants

This retrospective cohort study included all the patients that were diagnosed with primary bone sarcomas from January 1, 2013, to December 31, 2017. Patients who were diagnosed with soft tissue sarcomas or metastatic bone sarcomas were excluded from the study.

Data collection method

The data were collected from the Saudi Cancer Registry (SCR). The SCR collects tumour data from all private, military, and health ministry hospitals in KSA through five regional offices, and data analysis and periodic reporting occur at the main office in Riyadh. All of the patients who were diagnosed with bone sarcomas in the specified period except the ones that did not meet the inclusion criteria were enrolled. The included variables were gender, age, patient’s region, tumour’s site of origin, tumour’s histological subtype, tumour’s behaviour, tumour’s grade, tumour’s extent, tumour’s laterality, the basis of diagnosis, and survival status.

Statistical analysis

All the data were managed using Microsoft Excel 2019 (Microsoft Ltd., WA, USA) and analysed using SPSS version 23.0 (IBM Corporation, NY, USA). Frequencies and percentages were generated for categorical variables. Means and standard deviations were calculated for quantitative variables. A chi-squared test was used to test the presence of significant differences among categorical variables. T-test and ANOVA test were utilised to identify significant differences among quantitative variables. The Tukey post-hoc test was used to detect where the exact differences lay. The incidence rate was calculated for each type of tumour per million for each year separately and then the average over the five years was calculated and reported. The country’s population size for each year was acquired from the National Authority for Statistics in KSA and was used to calculate the incidence rate.

Results

The total incidence of bone sarcomas in KSA between 2013 and 2017 was 451. Figure 1 shows the tumour type-specific incidence for each year. The incidence rate was 7.82 cases per 1,000,000 per five years for osteosarcoma, 4.75 cases per 1,000,000 per five years for Ewing sarcoma, and 1.35 cases per 1,000,000 per five years for chondrosarcoma. The yearly incidence rate was 1.56 cases per 1,000,000 per year for osteosarcoma, 0.95 cases per 1,000,000 per year for Ewing sarcoma, and 0.27 cases per 1,000,000 per year for chondrosarcoma. No significant differences were observed within the incidence rates of tumours across the years.
Table 1 shows the demographical data of the patients. The mean age of the patients was 22.34 ± 16.85. Of these, 274 (60.8%) patients were aged 18 years and younger, 53 (11.8%) were aged between 19 and 24 years, 92 (20.4%) were aged between 25 and 59 years, and 32 (7.1%) were aged 60 years and older. Males constituted 256 (56.80%) of the participants and 195 (43.20%) were female. The largest proportion of patients was from the central region 143 (31.70%); the least proportion was from the northern region (39 [8.60%]). Nine (2%) of the patients did not have a registered place of residency. Among the 451 patients, 371 (82.30%) survived for more than three years, and 80 (17.70%) did not.

Table 2 demonstrates the details of bone sarcoma characteristics. From the 451 patients, 248 (55%) had osteosarcomas, 160 (35.5%) had Ewing sarcoma, and 43 (9.5%) had chondrosarcoma. In terms of the origin site of the tumour, long bones of lower limbs were the most common site, with 234 (51.9%), followed by bones of the skull and face and pelvic bones, sacrum, and coccyx, with both categories having a frequency of 52 (11.5%). When assessing the grade of tumours, it was revealed that 265 (58.8%) did not have a record of the grade. The data on tumour degree of extension showed that most of the patients had localised tumours [239 (53%)] and 97 (21.5%) had distant metastasis. The lateralisation state of tumours displayed that 197 (43.70%) had left lateralisation, and 164 (36.40%) had right lateralisation. With regard to the basis of diagnosis, the vast majority was diagnosed based on the histology of the primary tumour 423 (93.8%).

Table 3A compares the type of tumour, site of origin, and three years’ survival, across gender. A significant difference ($p = 0.034$) between males and females was present only in the type of tumour. More males were affected by osteosarcoma, and more females were affected by Ewing sarcoma. Table 3B displays the differences between type of tumour, site of origin, and three years’ survival among patients from different places of residency; no significant difference was found. Table 3C describes the relationship
between age and type of tumour, site of origin, and three years’ survival. A significant difference in age was present in these characteristics ($p < 0.001$ in type of tumour, $p = 0.002$ in site of origin, and $p = 0.001$ in three years’ survival). The Tukey post-hoc test revealed that in terms of the types of tumour groups, there was a significant difference in the mean age between osteosarcomas and Ewing sarcoma ($p = 0.03$), osteosarcoma and chondrosarcoma ($p < 0.001$), and Ewing sarcoma and chondrosarcoma ($p < 0.001$). As for the difference in age between the different sites of origin, the Tukey post-hoc test revealed a significant difference in the mean age only between the long bones of the lower limbs and bones of the skull and face ($p = 0.01$).

Table 4 demonstrates the differences of characteristics among the types of tumours. A significant difference in the site of origin between the three types of tumours was present ($p < 0.001$). Although in all types, the most common site was the long bones of lower limbs, Ewing sarcomas showed considerably higher rates of occurrence in the vertebral column and pelvic bones, sacrum, and coccyx. Chondrosarcomas have shown considerably higher occurrence in the bones of the skull and face, rib, sternum, and clavicle. A significant difference between the three types was also found in the grade of the tumour ($p < 0.001$). The majority of chondrosarcoma patients had first- and second-grade tumours, while the majority of both osteosarcoma and Ewing sarcoma patients had third- and fourth-grade tumours. A significant difference between the types of tumours was also observed in terms of the base of diagnosis and lateralisation ($p < 0.001$ and $p = 0.014$), respectively. Higher rates of diagnosing chondrosarcoma through medical imaging were observed. The different patterns of lateralisation were present among the three types of tumours. No significant difference was found among the types of tumours in terms of extension or three years’ survival.

Table 4: Tumor Details ($n = 451$).

| Type of Tumor            | n | %  |
|--------------------------|---|----|
| Osteosarcoma             | 248 | 55 |
| Ewing sarcoma            | 160 | 35.5 |
| Chondrosarcoma           | 43  | 9.5 |

| Origin Site of Tumor     | n  | %  |
|--------------------------|----|----|
| Long bones of upper limb | 55 | 12.2 |
| Short bones of upper limb| 2  | 0.4 |
| Long bones of lower limb | 234| 51.9 |
| Short bones of lower limb| 13 | 2.9 |
| Bones of the skull and face| 52 | 11.5 |
| Vertebral column         | 22 | 4.9 |
| Rib, Sternum, and Clavicle| 18 | 4  |
| Pelvic bones, Sacrum, and Coccyx| 52 | 11.5 |
| Unknown primary site     | 3  | 0.7 |

| Grade        | n  | %  |
|--------------|----|----|
| Grade I      | 14 | 3.10 |
| Grade II     | 25 | 5.50 |
| Grade III    | 74 | 16.40 |
| Grade IV     | 73 | 16.20 |
| Unknown      | 265| 58.8 |

| TNM Extension                                       | n  | %  |
|-----------------------------------------------------|----|----|
| In Situ                                             | 1  | 0.2 |
| Localized                                           | 239| 53 |
| Regional: Direct Extension                          | 67 | 14.9 |
| Regional: Lymph Node                                | 5  | 1.1 |
| Regional: Direct Extension & Lymph Node             | 5  | 1.1 |
| Distant Metastasis                                   | 97 | 21.5 |
| Unknown                                             | 37 | 8.2 |

| Lateralization                                       | n  | %  |
|-----------------------------------------------------|----|----|
| Not paired                                          | 81 | 18.00 |
| Right                                               | 164| 36.40 |
| Left                                                | 197| 43.70 |
| Bilateral Involvement                                | 1  | 0.2 |
| Paired at site of origin                            | 8  | 1.8 |

| Bases of diagnosis                                   | n  | %  |
|-----------------------------------------------------|----|----|
| Unknown                                             | 14 | 3.10 |
| Medical Imaging                                     | 7  | 1.60 |
| Cytology and hematology                             | 3  | 0.70 |
| Histology of metastases                             | 4  | 0.90 |
| Histology of primary tumor                          | 423| 93.8 |
Table 3: A. Gender-Based Comparison of Type of Tumor, Site of Origin and Mortality. B. Site of Residency Based Comparison of Type of Tumor, Site of Origin and Mortality. C. Age-Based Comparison of Type of Tumor, Site of Origin and Mortality.

| Variable                  | Gender | P-Value |
|---------------------------|--------|---------|
|                           | Male (n = 256) | Female (n = 195) |
|                           | n     | %      | n    | %     |         |

**Type of Tumor**
- Osteosarcoma: Male 130 (51.20%), Female 118 (60.80%) 0.034 *
- Ewing sarcoma: Male 102 (40.20%), Female 55 (28.40%)
- Chondrosarcoma: Male 22 (8.70%), Female 21 (10.80%)

**Origin Site of Tumor**
- Long bones of upper limb: Male 28 (11.00%), Female 27 (13.90%) 0.068
- Short bones of upper limb: Male 2 (0.80%), Female 0 (0.00)
- Long bones of lower limb: Male 126 (49.60%), Female 108 (55.70%)
- Short bones of lower limb: Male 8 (3.10%), Female 5 (2.60)
- Bones of skull and face: Male 28 (11.00%), Female 24 (12.40)
- Vertebral column: Male 19 (7.50%), Female 3 (1.50)
- Rib, Sternum, and Clavicle: Male 9 (3.50%), Female 9 (4.60)
- Pelvic bones, Sacrum, and Coccyx: Male 34 (13.40%), Female 18 (9.30)

**3 Year Survival**
- Dead: Male 42 (16.50%), Female 37 (19.10%) 0.485
- Alive: Male 212 (19.10%), Female 157 (80.90%)

| Variable                  | Cite of Residency | P-Value |
|---------------------------|-------------------|---------|
|                           | Central Region (n = 143) | Eastern Region (n = 67) | Northern Region (n = 39) | Western Region (n = 138) | Southern Region (n = 55) |
|                           | n     | %      | n    | %     | n    | %     | n    | %     | n    | %     |         |

**Type of Tumor**
- Osteosarcoma: Male 83 (58.00%), Female 31 (47.00%), Male 83 (60.10%), Female 31 (47.00%), 0.554
- Ewing sarcoma: Male 48 (33.60%), Female 27 (40.90%), Male 44 (31.90%), Female 27 (40.90%), 0.370
- Chondrosarcoma: Male 12 (8.40%), Female 8 (7.70%), Male 11 (8.00%), Female 8 (7.70%), 0.150

**Origin Site of Tumor**
- Long bones of upper limb: Male 17 (11.90%), Female 8 (12.10%), Male 10 (7.20%), Female 8 (12.10%), 0.150
- Short bones of upper limb: Male 2 (1.40%), Female 0 (0.00%), Male 0 (0.00%), Female 0 (0.00%), 0.00
- Long bones of lower limb: Male 78 (54.50%), Female 28 (42.40%), Male 82 (59.40%), Female 31 (42.40%), 0.350
- Short bones of lower limb: Male 4 (2.80%), Female 5 (7.70%), Male 2 (1.40%), Female 5 (7.70%), 1.90
- Bones of skull and face: Male 14 (9.80%), Female 3 (4.50%), Male 9 (6.10%), Female 3 (4.50%), 1.90
- Vertebral column: Male 6 (4.20%), Female 2 (3.20%), Male 8 (5.80%), Female 2 (3.20%), 0.08
- Rib, Sternum, and Clavicle: Male 8 (5.60%), Female 5 (7.60%), Male 6 (4.30%), Female 5 (7.60%), 1.90
- Pelvic bones, Sacrum, and Coccyx: Male 14 (9.80%), Female 6 (10.60%), Male 13 (9.00%), Female 6 (10.60%), 0.059

**3 Year Survival**
- Dead: Male 33 (23.10%), Female 11 (16.70%), Male 21 (15.20%), Female 11 (16.70%), 0.059
- Alive: Male 110 (76.90%), Female 55 (83.30%), Male 119 (84.80%), Female 55 (83.30%), 0.059

| Variable                  | Age | P-Value |
|---------------------------|-----|---------|
|                           | Mean | SD     |         |

**Type of Tumor**
- Osteosarcoma: Male 21.3, Female 17.46, 0.001 *
- Ewing sarcoma: Male 46.51, Female 12.14
- Chondrosarcoma: Male 21.3, Female 17.46

**Origin Site of Tumor**
- Long bones of upper limb: Male 20.35, Female 12.5, 0.002 *
- Short bones of upper limb: Male 20.35, Female 12.5
- Long bones of lower limb: Male 20.35, Female 12.5
- Short bones of lower limb: Male 17.31, Female 12.5
- Bones of skull and face: Male 29.38, Female 19.31
- Vertebral column: Male 27, Female 21.93
- Rib, Sternum, and Clavicle: Male 31.72, Female 24.62
- Pelvic bones, Sacrum, and Coccyx: Male 23.25, Female 13.47

**3 Year Survival**
- Dead: Male 28.25, Female 21.70, 0.001 *
- Alive: Male 21.07, Female 15.35

* Significant at level ≤ 0.05.
The study aimed to highlight the descriptive epidemiology of primary bone sarcomas in KSA. The incidence rate was 7.82 cases per 1,000,000 per five years for osteosarcoma, 4.75 cases per 1,000,000 per five years for Ewing sarcoma, and 1.35 cases per 1,000,000 per five years for chondrosarcoma. The yearly incidence rate was 1.56 cases per 1,000,000 per year for osteosarcoma, 0.95 cases per 1,000,000 per year for Ewing sarcoma, and 0.27 cases per 1,000,000 per year for chondrosarcoma. A significant difference between males and females was present only in the type of tumour. A significant difference in age was present among types of tumours, sites of origin, and three years’ survival. A significant difference among the three types of tumours in terms of site of origin, grade, base of diagnosis, and lateralisation was also present.

Due to a plethora of factors, the geographical incidence of bone tumours differs from one region to another. Collectively, the osteosarcoma, chondrosarcoma, and Ewing sarcoma yearly incidence rates detected were lower than the ones detected globally. It is thought that the reasons behind the lower incidence rate include underreporting by hospitals to SCR, lower population, and risk factors that need to be assessed locally. In comparison to our results, a German study that included 671 patients diagnosed with bone sarcoma assessed an age-standardised cumulative incidence of 2.1 per 100,000. In addition, a British study found the incidence rate to be 8.1 to 9.3 per 1,000,000 in males and 5.4 to 6.8 in females. Moreover, a French study found that the incidence of bone sarcoma was 0.6 per 100,000. In the Netherlands, a study found that the incidence of chondrosarcoma was 0.15 per 100,000 the osteosarcoma incidence was 0.25 per 100,000 and the Ewing sarcoma incidence was 0.15 per 100,000. In Brazil, the median incidence rate of bone cancer was 5.74 per 1,000,000 among children and 11.25 per 1,000,000 among adolescents. In Taiwan, an overall

| Variable                  | Type of Tumor | P-Value |
|---------------------------|---------------|---------|
| Origin Site of Tumor      |               |         |
| Long bones of upper limb  | 26 (10.50)    | 23 (14.60) | 6 (14.00) | < 0.001* |
| Short bones of upper limb | 1 (0.40)      | 1 (0.60)   | 0 (0.00)  |         |
| Long bones of lower limb  | 165 (66.50)   | 56 (35.70) | 13 (30.20) |         |
| Short bones of lower limb | 5 (2.00)      | 7 (4.50)   | 1 (2.30)  |         |
| Bones of skull and face   | 28 (11.30)    | 15 (9.60)  | 9 (20.90) |         |
| Vertebral column          | 5 (2.00)      | 15 (9.60)  | 2 (4.70)  |         |
| Rib, Sternum, and Clavicle| 3 (1.20)      | 7 (4.50)   | 8 (18.60) |         |
| Pelvic bones, Sacrum, and Coccyx | 15 (6.00) | 33 (21.00) | 4 (9.30)  |         |
| Grade                     |               |         |
| Grade I                   | 5 (3.20)      | 0 (0.00)  | 9 (34.60) | < 0.001* |
| Grade II                  | 9 (5.80)      | 1 (16.70) | 15 (57.70) |         |
| Grade III                 | 71 (46.10)    | 3 (50.00) | 0 (0.00)  |         |
| Grade IV                  | 69 (44.80)    | 2 (33.30) | 2 (7.70)  |         |
| TNM Extension             |               |         |
| In Situ                   | 1 (0.40)      | 0 (0.00)  | 0 (0.00)  | 0.546    |
| Localized                 | 127 (55.70)   | 88 (58.30) | 24 (33.30) |        |
| Regional: Direct Extension| 43 (18.90)    | 22 (14.60) | 2 (4.70)  |         |
| Regional: Lymph Node      | 4 (1.80)      | 1 (0.70)  | 0 (0.00)  |         |
| Regional: Direct Extension & Lymph Node | 4 (1.80) | 1 (0.70) | 0 (0.00) |         |
| Distant Metastasis        | 49 (21.50)    | 39 (25.80) | 9 (25.70) |         |
| Bases of Diagnosis        |               |         |
| Medical Imaging           | 2 (0.80)      | 1 (0.60)  | 4 (9.80)  | < 0.001* |
| Cytology/Hematological    | 1 (0.40)      | 2 (1.30)  | 0 (0.00)  |         |
| Histology of metastases   | 0 (0.00)      | 4 (2.50)  | 0 (0.00)  |         |
| Histology of primary      | 235 (97.10)   | 152 (95.00) | 36 (87.80) |         |
| Lateralization            |               |         |
| Not paired                | 33 (13.30)    | 35 (21.90) | 13 (30.20) | 0.014 *  |
| Right                     | 99 (39.90)    | 54 (33.80) | 11 (25.60) |         |
| Left                      | 112 (45.20)   | 69 (43.10) | 16 (37.20) |         |
| Bilateral Involvement     | 1 (0.40)      | 0 (0.00)  | 0 (0.00)  |         |
| Paired at site of origin  | 3 (1.20)      | 2 (1.30)  | 3 (7.00)  |         |
| 3 Year Survival           |               |         |
| Dead                      | 49 (19.80)    | 24 (15.00) | 7 (16.30) | 0.454    |
| Alive                     | 199 (80.20)   | 136 (85.00) | 36 (83.70) |         |

* Significant at level ≤ 0.05.
incidence of 6.70 per 1,000,000 person-years was detected for bone sarcomas. In Finland, a nationwide study detected an annual incidence rate of 1.8 osteosarcomas per 1,000,000. In Croatia, the annual incidence rate was 1.68 cases per 1,000,000 for osteosarcoma and 0.76 per 1,000,000 for chondrosarcoma. However, the yearly incidence rate for Ewing sarcoma was 0.79 per 1,000,000, which is lower than the one observed in our study. In Belgium, the overall annual incidence of bone sarcomas was 0.91 per 100,000.19 In Kuwait, the annual incidence of bone sarcomas was 3.3 cases per 1,000,000 inhabitants. In addition, unlike the presented study, which found osteosarcoma to be the most common tumour observed, the most common tumour detected was Ewing sarcoma. In India, the annual incidence of Ewing sarcoma was 1.6 per 1,000,000 in males and 1.0 per 1,000,000 in females.21

When it comes to the patterns of tumour behaviour, a Nigerian study found that different types of bone tumours have a difference in their geographical incidence, which contradicts our findings. Another study assessing the incidence of bone sarcomas in both the United States and the United Kingdom found that chondrosarcoma varied significantly among regions, which also contradicts the negative findings in the present study. However, the same study also found a significant difference between the types of tumours across ages, which is consistent with our findings.10 Another American study also found a significant difference between the types of tumours across ages, which is also consistent with our findings. Furthermore, a recent Japanese study that investigated the epidemiology and outcomes of bone sarcomas found variations of tumour types across ages. In terms of gender, a European study found that bone sarcomas were more prevalent in males, agreeing with the present study, which found a higher percentage of males diagnosed with bone sarcoma than females.13 A Japanese study found a slight male preponderance in bone sarcomas, which is consistent with our findings.14 Furthermore, agreeing with our findings, a Taiwanese study found a significant difference in tumour types across genders.15 However, a Chinese study found that there was no significant difference across genders when it comes to any type of bone sarcoma, which is inconsistent with our findings.17

Understanding the tumour behaviour in the region can aid in detecting the prognostic factors for survival in bone sarcoma. This would aid in the development of risk and response-based treatment strategies that allow for early decision-making. For instance, a Dutch study that aimed to develop a prognostic model for surviving bone sarcoma found that metastasis at diagnosis, large tumours (volume ≥ 200 ml or largest diameter ≥ 8 cm), primary tumours located in the axial skeleton, and histological response of less than 100% were all associated with survival.16 A British study also found that the critical factor for adverse prognosis was metastases at diagnosis. Among the group that had metastases, the ones with lung involvement had better survival chances. The risk analysis also demonstrated that site, age-group, and the period of diagnosis had a significant influence on risk-free survival chances.24

This study had some limitations. First, due to the retrospective nature of the study, the research team could not directly observe the cases and had to rely on other individuals for accurate recordkeeping. Consequently, the data registered in the Saudi Cancer Registry may be incomplete. Second, the data in the registry only spans from 2013, the year it was founded, to 2017. In terms of the current study’s strengths, first, the study is the first of its kind in the Middle East and would be a good initiative for conducting more extensive studies that investigate factors affecting the prognosis quality and the mortality rates of bone sarcomas. Second, the Saudi Cancer Registry includes cases from all hospitals in the country, whether they are private, military, or health ministry hospitals. Third, the study took raw collected data from the Saudi Cancer Registry and applied statistical methods to detect major epidemiological differences across tumour types and compare them with the ones detected in other studies.

Conclusion

To our knowledge, this study is the first of its kind in our region, that is, KSA, giving a baseline to be compared with other regions globally. It is thought that underreporting to the SCR, lower population, and risk factors for developing bone sarcomas might be the reasons for lower incidence rates; therefore, it is recommended that hospitals should investigate the barriers to reporting tumour cases to the SCR as soon as possible. Significant differences in tumour type, origin site, and three-year survival across age and gender were detected. Significant differences of origin site, grade, the base of diagnosis, and laterality across tumour types were also detected. These data are useful for health leaders to develop strategies such as selective screening and to facilitate treatment strategies ranging from the traditional operative approach to newer approaches that include non-operative and surveillance treatment pathways. In addition, understanding the tumour behaviour pattern in the region will help to develop tailored risk and response-based treatment strategies that allow for early decision-making.

Recommendations

In KSA, there has been an absence of studies that focus on improving the clinical outcomes of bone sarcoma, possibly because few studies focus on such relatively rare malignancies. Future studies are recommended to focus on risk factors associated with poor outcomes and developing response-based treatment strategies that allow for early decision-making.

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Conflict of interest

The authors have no conflict of interest to declare.
Ethical approval

The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center, Ministry of National Guard Health Affairs, Riyadh, KSA, (approval number RC16/223/R, dated 12 February 2017). Patients’ confidentiality was ensured. The patients’ data were collected and used by the research team only. Serial numbers were used instead of medical record numbers to ensure anonymity. Due to the retrospective nature of the study and the use of anonymised patient data, the requirements for informed consent were waived.

Authors’ contribution

WSJ, AMA, and MAG formulated the idea, designed the methods, validated the study, and provided research materials. MAG curated and analysed the data and interpreted and presented the results. WSJ, AMA, and MAG wrote the original draft of the article. WSJ critically revised the original draft for important intellectual content, supervised, and administered the project. All authors approved the final draft and are responsible for the accuracy and integrity of the work and the similarity index of the manuscript.

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