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Review Article

Prevalence of low bone mineral density and risk of fractures in osteosarcoma and Ewing's sarcoma survivors: A scoping review

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HIGHLIGHTS

- >50 % of osteosarcoma / Ewing's sarcoma long-term survivors have a bone mass deficit.
- A frailer physique and younger age at diagnosis are associated with lower bone mass.
- Available data are insufficient to decide if those survivors face an increased risk of fractures.
- There is an unappreciated knowledge gap in our understanding of bone health status in those survivors.

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ABSTRACT

Background: The clinical outcomes of patients with pediatric cancer have significantly improved over the past few decades. However, the treatments are often highly intensive and can advertently pose a risk for developing various health conditions, including bone mass loss and fragility fractures. Since patients with bone malignancies, such as osteosarcoma (OS) and Ewing's sarcoma (ES), require musculoskeletal surgery as well as chemotherapy, OS/ES survivors are potentially at even greater risk of developing these musculoskeletal conditions than those with other types of cancer. However, these issues in OS/ES survivors are often overlooked by clinicians treating childhood cancers. Thus, this scoping review was designed and conducted to better understand the bone health conditions in OS/ES survivors.

Design: We conducted a literature search and included the studies that describe bone mineral density in association with bone health in OS/ES survivors for analysis. Data regarding patients' demographic, diagnosis, bone mineral density, laboratory examinations, and incidence of fractures were extracted and evaluated.

Results: We found that almost half of OS/ES survivors have bone mass deficit and that several factors (such as a frailer physique and younger age at diagnosis) are potentially associated with low bone mass in OS/ES survivors. On the other hand, due to a paucity of information currently available, we could not determine whether long-term OS/ES survivors would ultimately regain bone mass or be at a greater risk of fragility fractures.

Conclusions: This scoping review reveals a previously unappreciated knowledge gap in our understanding of bone health conditions in OS/ES survivors and raises awareness among clinicians and care providers of this condition that OS/ES patients may encounter after successful treatment.

1. Introduction

Owing to the development of effective therapeutic modalities and diagnostic measures, the clinical outcomes of pediatric cancers have markedly improved over the past few decades, with a five-year survival rate exceeding 60–80 % in most cancer types [1,2]. However, these therapies are often highly intensive and lengthy, taking longer than a year from diagnosis to completion of treatment. Consequently, a large proportion of patients are inadvertently inflicted with varying degrees of physical and mental impairments, including cardiovascular, pulmonary, musculoskeletal, and metabolic disorders, which ultimately lead to a decreased quality of life and shorter life expectancy [3,4]. As the number of childhood cancer survivors (CCS) increases, and they reach middle and old age, it has now become one of the central issues for clinicians

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and care providers to understand and prevent the cumulative burden of chronic health conditions in these patients [4,5].

Osteosarcoma (OS) and Ewing's sarcoma (ES) are the most common, yet overall, highly rare, malignant bone tumors. OS and ES most frequently affect juveniles and young adults, with incidences of approximately 4.4 and 2.9 cases per million per year, respectively [6–9]. In both malignancies, standard treatment consists of neoadjuvant (pre-operative) chemotherapy, surgery (and/or radiation in certain ES cases), and adjuvant chemotherapy. The regimens of chemotherapy differ between the two; in OS, high-dose methotrexate, doxorubicin, cisplatin, and ifosfamide are most commonly used; whereas, in ES, vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide are commonly used. The choice of surgery for these bone tumors varies significantly depending on the site and extent of the tumor. When the major nerves and arteries are spareable, limb salvage surgery with a combination of prosthesis replacement or biological reconstruction is usually chosen [10,11]. However, amputation of the affected limb is often performed if limb salvage surgery is not possible. In either case, patients with OS or ES have to undergo not only intensive chemotherapy but also musculoskeletal surgery, which can result in a lasting disability in daily activity and mobility. Therefore, it is possible that chronic musculoskeletal complications and conditions in OS/ES survivors are different from those in other types of childhood cancer, as they do not involve musculoskeletal surgery [12]. However, most studies investigating chronic health conditions in CCS have focused on acute lymphoblastic leukemia (ALL), the most common malignancy in childhood [1,13], indicating that there is an underappreciated knowledge gap regarding chronic health conditions in OS/ES survivors.

Thus, in this scoping review, we aimed to map our current understanding of bone health conditions in OS/ES survivors through a review of published literature. Specifically, we focused on the bone mineral density (BMD) status and risk of fractures in OS/ES survivors.

2. Materials and methods

2.1. Research questions

We followed the recommendations of the Preferred Reporting Items for Scoping Reviews [14]. This scoping review aimed to address the following questions: "How often do OS/ES survivors develop osteopenia/osteoporosis?", "Do OS/ES survivors have any characteristic laboratory data concerning bone metabolism?", "What factors are associated with BMD deficit in OS/ES survivors?", and "How much impact does a decrease in BMD have on fracture risk in OS/ES survivors?".

2.2. Literature search and study selection

We searched PubMed, Scopus, and Web of Science on August 6, 2022. The inclusion criteria were publications published in peer-reviewed English journals that described the BMD status in association with bone health conditions in OS/ES survivors. Case reports, case series with fewer than five cases, review articles, and meeting abstracts were excluded. An outline of the search strategy is presented in Supplementary Table S1. Bibliographical data were imported into EndNote X9 (Clarivate, London, UK) and duplicates were manually removed. The titles and abstracts of all publications were reviewed by one author (KH), and publications that did not describe the bone health conditions of OS/ES survivors were excluded. Next, full texts of potentially relevant publications were reviewed. Publications that did not meet the defined criteria or shared patient data with other publications were excluded.

2.3. Data extraction

Data were extracted using a standardized data collection form in Microsoft Excel (Redmond, WA). The data items included the following: article information (first author, year of publication, and affiliation/country), aim/clinical questions of the study, patient data (number of patients, diagnosis, and inclusion criteria), timing of evaluation, age at evaluation, methods of BMD evaluation, results of BMD analysis, bone metabolic markers, factors associated with BMD, factors not associated with BMD, prevalence of fracture, and additional information that were potentially relevant to the present study. The ratio (%) was calculated based on the data provided in the publication when applicable.

3. Results

3.1. Search results

The flowchart of the search procedure is presented in Fig. 1. Our search yielded 339 unique hits following the removal of duplicates. After assessing the titles and abstracts, 18 publications were identified as relevant, and the full texts of these publications were obtained and further reviewed. Eight publications were excluded; three publications contained patient data that potentially overlapped with other publications from the same research group, three had no data on BMD, and one had only three patients. Consequently, 11 publications were included in this review. The list of the publications and extracted data is shown in Supplementary Table S2.

3.2. Characteristics of included studies

The publications were from Europe ($N = 6$), Korea ($N = 3$), and the USA ($N = 2$). The number of patients included in each study ranged from nine to 207 (median, 47). BMD evaluation and laboratory tests were performed during treatment or within 1 month of treatment completion in four studies [15–18] and at least 1 year after treatment completion in seven studies [12,19–24]. In the former publications, the mean/median age of patients ranged from 12.8 to 15.0 year, and in the latter, from 26 to 37.6 year.

Two publications were retrospective longitudinal studies [15,17]; however, these studies included only nine patients each, and the follow-up period was less than 1 year. One study investigated the changes in BMD before and after the completion of chemotherapy in OS patients [17], and another investigated the efficacy of pamidronate therapy in OS patients who had completed the therapy [15]. The rest (nine publications) were cross-sectional studies. One study included patients with sarcomas other than OS or ES (rhabdomyosarcoma and non-

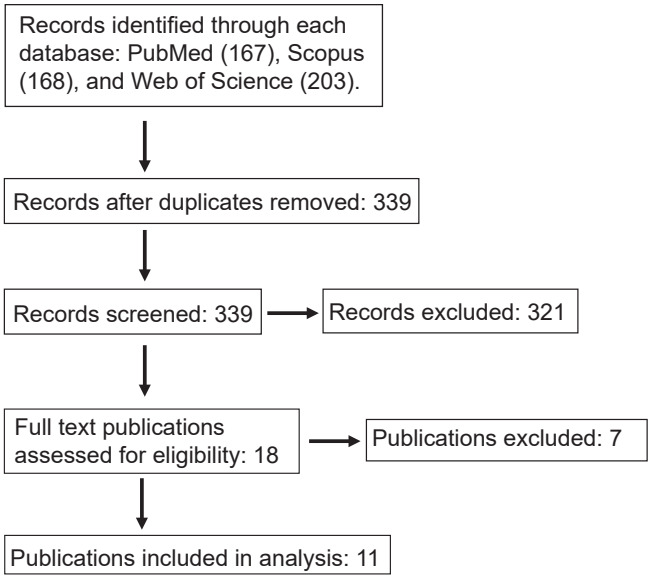

Fig. 1. Publication selection flowchart based on the Preferred Reporting Items for Systematic Review and meta-Analyses guidelines.

rhabdomyosarcoma) [22]; however, since the difference in the diagnosis was not associated with a difference in BMD, the study was included in the analysis. Dual-energy X-ray absorptiometry (DEXA) was used to evaluate the BMD in all studies but one in which quantitative computed tomography was used [22].

3.3. Prevalence of osteoporosis and osteopenia

Diagnosis of osteoporosis and osteopenia in OS/ES survivors (at least 1 year after the completion of therapy) was described in six studies [12,19–21,23,24]. In three studies [19,20,24], osteoporosis and osteopenia in adults were determined according to the WHO osteoporosis definition [25], where a T-score < -2.5 was diagnosed as osteoporosis, $-2.5 \leq T$-score < -1 as osteopenia, and $-1.0 \leq T$-score as normal. One study [12] used the Common Terminology Criteria for Adverse Events, ver. 4.03 (the Division of Cancer Treatment and Diagnosis, National Cancer Institute), in which grade 1 and grade 2 bone loss correspond to the WHO definition of osteopenia and osteoporosis, respectively. Four studies [19–21,23] that included skeletally immature patients used the following definitions: Z-score < -2.0, osteoporosis; $-2.0 \leq$ Z-score < -1.0, osteopenia; and $-1.0 \leq$ Z-score, normal. In general, bone loss in skeletally immature patients is better described as low bone density compared with the age-matched population; however, for simplicity and consistency, we incorporated these definitions into the present study.

Fig. 2A summarizes the results of the six studies. The anatomical sites used for DEXA were either the lumbar spine (L1–L4 or L2–L4) or femur (femoral neck or total femur). The unaffected side of the femur was evaluated in patients with lower-limb tumors. In two studies, both the lumbar spine and unaffected femur were separately described [21,23]. The prevalence of osteoporosis and osteopenia differed markedly among the studies. The average prevalence of osteoporosis and osteopenia calculated by adjusting the number of subjects included in each study was 20.5 % and 34.3 %, respectively (when the data of both the lumbar spine and femur were presented, the former was used for analysis). Therefore, these studies indicate that almost half of the OS/ES survivors had either osteoporosis or osteopenia (T-score or Z-score < -1).

BMD at the completion of chemotherapy was evaluated in three studies [16–18]. In two studies [16,17], BMD was evaluated on the completion of adjuvant chemotherapy and in one [18], after neo-adjuvant chemotherapy. As summarized in Fig. 2B, the prevalence of osteoporosis and osteopenia varied widely among studies. The adjusted prevalence of osteoporosis and osteopenia (determined based on lumbar BMD) according to the number of patients was 2.8 % and 26.9 %, respectively.

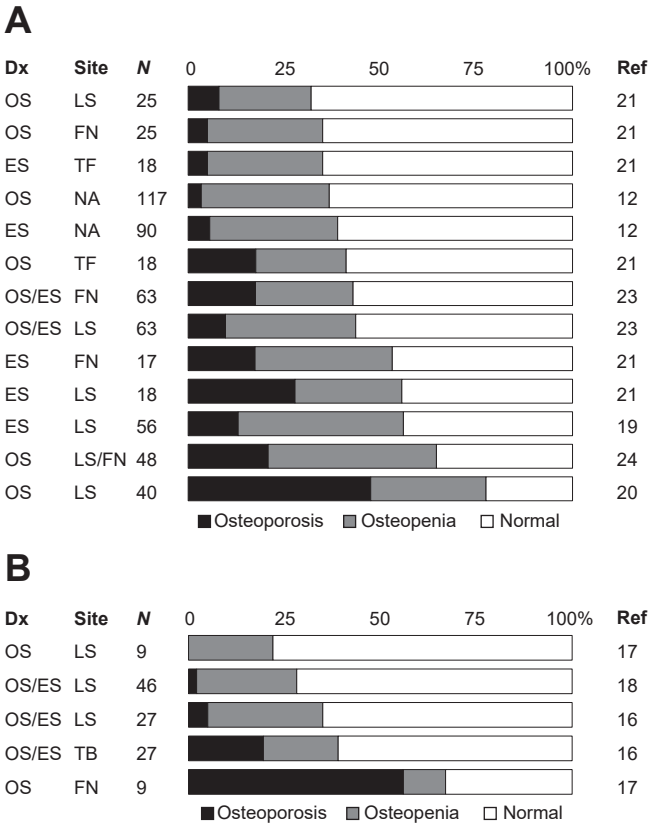

Fig. 2. Prevalence of osteoporosis and osteopenia in OS/ES survivors. Diagnosed at least one year after the completion of treatment (A), or during or within one month after the treatment (B). Please note that data are presented separately according to the diagnosis (OS or ES) or the site of DEXA scanning (lumbar spine or femur) in some studies [12,16,17,21,23]. Dx, diagnosis; Site, the site of DEXA scanning; *N*, the number of subjects; LS, lumbar spine; FN, femoral neck; TB, total body; NA, not available; TF, total femur; Ref, reference number.

3.4. Bone metabolic markers

Laboratory data were evaluated in three studies [16,21,23]; however, no bone metabolic markers were associated with BMD or recurrently identified in sarcoma patients in these studies. In contrast, serum vitamin D levels were found to be significantly lower in OS/ES survivors than in the reference value or control subjects in two studies [16,23]. In accordance, a relatively high proportion of OS/ES survivors had a vitamin D deficiency (78 %–88 %) [16,21].

3.5. Factors associated with BMD in OS/ES survivors

The factors associated with BMD (and not associated) were investigated in ten studies [12,16–24]. Tables 1 and 2 summarize the factors described in more than one publication. Factors that reflect a frailer physique (lower body mass index (BMI), lower height, lower body weight, or smaller lean mass) and a younger age at diagnosis are most frequently noted as risk factors for a lower BMD [16,19–24]. In contrast, a longer follow-up period after the completion of treatment was found to be associated with a higher BMD in two studies [19,23]. The potential association between gender and BMD was inconclusive. Two studies showed that male survivors had a lower BMD or a higher prevalence of osteopenia/osteoporosis than female survivors [20,23]. However, three studies showed a negative correlation between gender and BMD [19,21,22].

While methotrexate was thought to severely impair bone metabolism (a condition known as methotrexate osteopathy) [26,27], the presence of high-dose methotrexate therapy or differences in chemotherapeutic regimens were not associated with the BMD status in six studies [16,19–23]. Furthermore, there was no significant association between tumor size or location and BMD [19,20].

3.6. Association between fracture risk and BMD in OS/ES survivors

The incidence of fractures in OS/ES survivors was described in seven studies [17,19–24]. Among the six cross-sectional studies with a follow-up period longer than 3 years [19–24], the fracture incidence varied from 30.0 % to 70.8 % (Fig. 3). The average incidence rate among these six studies was 40.4 % (141 cases out of 349 cases). In one longitudinal

Table 1
Factors associated with BMD.

Factors	References
BMI / weight/height / lean mass (smaller, the lower BMD)	[16,19–24]
Age at diagnosis (lower, the lower BMD)	[20,22,23]
Gender	[20,23]
Follow-up duration (longer, the higher BMD)	[19,23]

Table 2
Factors unassociated with BMD.

Factors	References
Use of high-dose MTX/difference in chemotherapeutic regimens	[16,19–23]
Tumor size/location	[19,20]
Gender	[19,21,22]

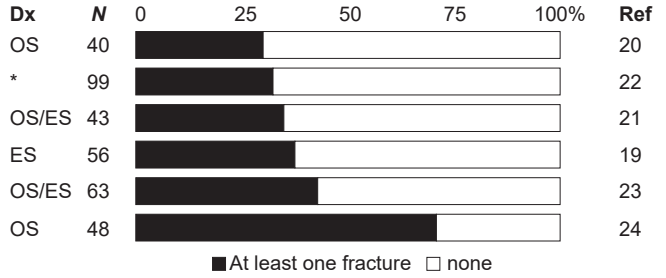

Fig. 3. Prevalence of fractures by the time of evaluation in OS/ES survivors. Dx, diagnosis; *N*, the number of subjects; *, OS, ES, rhabdomyosarcoma, and non– rhabdomyosarcoma; Ref, reference number.

study [17], one of the nine patients had a fracture 5 months after finishing the treatment.

Two studies provided information on the site of fractures, which indicated that fractures occur more often in the lower limbs than in the upper limbs (lower limb fractures in 14 of 21 and six of seven, respectively) [19,21]. Information on the site of fractures in association with the tumor sites was not provided in any of the studies, except in one study that mentioned that all fractures occurred in the affected limb [20].

Three studies investigated the potential association between BMD status/levels and the incidence of fractures [19,20,23]; however, none of these studies showed a significant association. We also performed a statistical analysis (chi-square test) using the data presented in the study by Holzer et al. [24] and found no significant correlation between BMD status and the incidence of fracture (data not shown).

4. Discussion

In this scoping review, we aimed to elucidate our current understanding of bone health conditions in OS/ES survivors, focusing on BMD status and its potential association with fracture risk. Data collected from the publications indicate that the prevalence of osteoporosis and osteopenia may be higher in long-term OS/ES survivors (>50 %) than in other CCS and that BMD status may not be associated with a risk of fracture in OS/ES survivors. On the other hand, it was not clear whether OS/ES survivors regain bone mass or face an increased risk of fracture after the completion of treatment. It is tempting to assume that a certain subpopulation of OS/ES survivors (e.g., those who had mega-prosthesis replacement surgery or suffered from implant failures) are more likely to develop BMD deficits and inflict fractures; however, there was not enough information to test these hypotheses. Taken together, this study indicates that there is a relatively large knowledge gap in our understanding of bone health status in OS/ES survivors.

4.1. BMD deficit in OS/ES survivors

This scoping review found that the prevalence of osteopenia ranged from 24.0 % to 43.8 %, and that of osteoporosis ranged from 5 % to 47.5 % in OS/ES survivors (Fig. 2A). Our estimate based on these data indicated that the prevalence of osteopenia and osteoporosis was approximately 34.3 % and 20.1 %, respectively, suggesting that approximately half of the OS/ES survivors had a certain degree of BMD deficit. In contrast, our estimate of the prevalence of osteopenia and osteoporosis upon treatment completion was approximately 30 % (Fig. 2B).

In case of ALL, patients undergoing treatment lose bone mass as severely as, if not more severely than, patients with OS/ES. However, it has been shown that patients with ALL regain bone mass within a few years after the completion of treatment [28,29]. A cohort study by Gurney et al. [30] which involved 845 patients with a history of ALL, showed that the prevalence of osteoporosis and osteopenia at a median age of 31 years was 5.7 % and 23.8 %, respectively (evaluated by lumbar vertebrae DEXA). Similarly, a study by den Hoed et al., which included 166 ALL survivors, showed that 32 % of the patients had a BMD less than −1 standardized deviation score. While we cannot draw any definite conclusion, these results may suggest that the recovery of BMD in OS/ES survivors does not occur as readily as in ALL survivors, or that bone mass continues to decrease after the completion of treatment, potentially due to surgery that could compromise mobility.

4.2. Laboratory data in OS/ES survivors

This scoping review identified no recurrent bone metabolic markers in OS/ES survivors, indicating that bone metabolism several years after the completion of treatment is essentially static in most cases and that there is no overt bone resorption or bone formation. Nevertheless, given that laboratory data were available in only three studies [16,21,23], this issue remains inconclusive. However, these studies showed that vitamin D deficiency is prevalent in OS/ES survivors. Vitamin D deficiency is also frequent in ALL survivors and could be one of the underlying mechanisms for low BMD in CCS in general [31]. These observations may indicate that vitamin D supplementation is beneficial in improving bone health in CCS; however, this hypothesis remains to be elucidated [31–34].

4.3. Factors associated with BMD in OS/ES survivors

The factors that are found to be potentially associated with BMD in this scoping review mostly overlap with those found in ALL survivors [35]. Given that muscle loss and poor nutritional status both lead to BMD deficits, it may not be surprising that BMI, weight, height, and lean mass were all, to some degree, associated with BMD in OS/ES survivors. It is also conceivable that skeletally immature patients who fail to accumulate bone mass during the growth period due to treatment would ultimately result in a BMD deficit. The association between a long follow-up period and a higher BMD suggests that bone mass recovers, albeit slowly, after the completion of treatment in OS/ES survivors. The potential association between gender and BMD is not conclusive, but because males need to accumulate more bone mass than females, and male gonads are more sensitive to chemotherapeutic agents than female gonads, the negative effects of chemotherapy on bone metabolism could be aggravated in male CCS.

Considering the well-documented negative impact of methotrexate on bone health [26,27], the lack of association between the use of methotrexate and BMD was intriguing. It is possible that other chemotherapeutic agents have similar negative effects on bone metabolism, and the effects of methotrexate are undermined. Furthermore, although it is tempting to assume that patients who had a tumor in the weight-bearing bone (lower limbs, pelvis, or spine) or who underwent prosthesis replacement surgery would have a more severe BMD deficit due to the impairment in mobility, we found no evidence to support these assumptions.

4.4. BMD deficit and fracture risk in OS/ES survivors

Overall, clinical information on fractures was highly heterogeneous among the studies, and we could not systemically analyze the nature of fractures (e.g., pathological fracture due to bone tumor, fragility fracture due to systemic bone loss after treatment, pathological fracture due to complications of the surgery, or fracture unrelated to treatment or

tumor), fracture sites (e.g., upper limb, lower limb, or vertebrae; or affected limbs or unaffected limb), or patient background (e.g., gender, age at incidence, etc.). Moreover, because the information on fracture incidence was based on a questionnaire in most studies, the data were not necessarily highly objective or reliable. Additionally, although it is likely that ES survivors who underwent local radiation therapy would have an increased risk of fractures, this issue was discussed only in one study [19]. Of note, contrary to the previous publications which suggest an increased risk of fractures within the radiation fields [36–38], this study did not find a positive association between radiation therapy and an increased risk of fractures. Thus, this issue remains to be addressed.

An increased risk of fracture has been reported in patients with ALL during treatment and shortly after the completion of treatment [39–41]. However, the incidence of fractures among long-term survivors remains poorly understood. A study by Wilson et al., which involved 7414 CCS of mixed diagnoses (median follow-up period from diagnosis, 22.7 years) and their siblings (2374 subjects), showed no significant difference in the prevalence of having at least one fracture between these two groups (approximately 35 % and 39 %, respectively) [42]. The results of this study may indicate that the fracture incidence in OS/ES survivors, which this review suggests is approximately 40 %, is not necessarily higher than that in CCS with other types of cancer.

Consistent with other studies [41,43], we found no significant association between low BMD and increased risk of fracture in OS/ES survivors. Low BMD is a well-established risk factor for fracture; however, its predictive value for fracture is age-dependent and significantly increases with advancing age [44]. Accordingly, a study has shown that the incidence of fracture remains relatively low until the age of 50 in women and 65 in men and significantly increases thereafter [45]. Therefore, it is possible that even though we do not see an increase in fracture incidence in CCS in middle age, these patients may face a higher risk of fracture when they reach old age than their age-matched counterparts.

4.5. Limitations

As discussed above, compared to the number of publications (and the number of patients included in each study) exploring this issue in patients with ALL [13,34], there were only a limited number of publications with a relatively small number of patients exploring this issue in OS/ES survivors. Furthermore, the publications included in this review were highly heterogeneous in terms of study design and patient population. Given that various potential confounders could affect the bone health status in OS/ES survivors, such as tumor site (upper limbs, lower limbs, spine, or pelvis), choice of surgery (amputation or limb-salvage procedure), use of prosthesis, presence or absence of radiation therapy, and duration from the completion of treatment, the amount of published data is not sufficient to provide reasonable answers to the questions we initially raised. Further studies with a larger patient population are required to address these issues.

5. Conclusions

Considering that OS/ES survivors who were treated at around the time of the introduction of effective chemotherapies (1970–1980) will now reach old age, investigating whether these long-term survivors are at a greater risk of inflicting fractures and if intervention at an early stage could circumvent this undesired condition is important. Most critically, clinicians and care providers of patients with OS/ES need to raise awareness of the potential chronic bone health issues that these patients may encounter after successful treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jbo.2022.100464.

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