Do Long Term Survivors of Ewing Family of Tumors Experience Low Bone Mineral Density and Increased Fracture Risk?

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Abstract

Background Multimodal treatment regimens for Ewing's sarcoma have led to survival rates approaching 70% of patients with no metastases at diagnosis. However, these treatments have long-term side effects. Low bone mineral density (BMD) and risk of fractures can occur owing in part to chemotherapy and limited mobility from local control of the primary tumor. **Questions/purposes** We performed this study to answer the following questions: (1) Do long-term survivors of the Ewing family of tumors sustain low BMD? (2) Which factors are associated with BMD in these patients? (3) Do they experience fractures? (4) Are BMD and fractures associated with each other?

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Methods We queried our institutional registry to identify all known survivors of Ewing tumors who were treated before 2005. Of 100 such patients, 67 (67%) responded to a postal survey to participate in this study, and an additional 11 (11%) patients were excluded according to prespecified criteria. In the remaining 56 long-term survivors (27 females, 29 males; mean $\pm$ SD age at followup, 32 ± 10 years; mean followup, 15 ± 7 years), BMD was measured by dual-energy x-ray absorptiometry and history of fractures was assessed using a questionnaire. Associations were tested using univariate and multivariate models by stepwise variable selection procedure, including Bonferroni correction.

Results Thirty-one of 56 (56%) patients had a pathologic BMD. Seven (13%) had osteoporosis and 24 (43%) had osteopenia. Factors related to low BMD after Bonferroni correction were the length of time between surgery and followup and the BMI at followup. Twenty-one patients reported 29 fractures. With the numbers available, BMD levels were not associated with fractures.

Conclusions We could not confirm some potentially important predictors for fractures to be associated with clinical events of interest. However, the data are valuable as hypothesis-generating pilot data for future, multicenter prospective studies. If BMD changes cannot explain the propensity of fractures, there may be other bone characteristics like microarchitectural changes of bone to more accurately explain the effect.

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Introduction

The Ewing family of tumors, which includes classic Ewing's sarcoma in addition to primitive neuroectodermal tumors, is the second most common variety of primary malignant bone tumors in children and adolescents. Multidisciplinary treatment including wide tumor resection, neoadjuvant chemotherapy, and local radiation therapy has improved the outcome of these tumors during the last decades [22]. Under current treatment regimens, the overall survival rate is approximately 70% [24]. However, treatments may lead to some long-term side effects, including chronic disorders of the cardiac, pulmonary, and nervous systems [12, 15], and it also can affect bone. Chemotherapy-induced bone loss was reported in adult cancers of the breast [36] and prostate [1].

Under healthy conditions, peak bone mass is reached between the ages of 20 and 30 years [4, 38]. During the period of bone accumulation in childhood and adolescence, a malignant tumor and its treatment can affect bone turnover and decrease bone mineral density (BMD) [18]. Reduced levels of BMD were reported in long-term survivors of childhood cancers, such as leukemia [2, 17], osteosarcoma [18], and a few mixed solid pediatric tumor cohorts [3, 26, 30, 32, 34]. Therefore, in survivors of Ewing tumors, an accumulation of treatment-induced effects may compromise bone [3, 25]. However, the degree to which this is the case in survivors of these tumors during longer periods, and whether this problem might be associated with fractures in patients has, to our knowledge, not been studied. Pathologic fractures at the time of diagnosis of Ewing's sarcoma or after multimodal treatment have been reported [7, 13], but not in a context with BMD changes.

The aim of this cross-sectional study was to assess BMD and fractures in a cohort of young survivors of Ewing tumors to evaluate (1) whether these tumors and their treatment were associated with low BMD, (2) whether any clinical or oncologic measures were associated with either BMD or fractures, (3) whether fractures do occur, and (4) and whether BMD and fractures were associated with each other.

Patients and Methods

Between 1963 and 2005, 183 patients were treated for at our institution. At the time of the study, 83 patients were

known to have died of disease. The remaining 100 patients were informed about the trial by mail and 67 patients responded. Inclusion criteria were diagnosis of a Ewing tumor, completion of a multimodal treatment including chemotherapy and limb salvage surgery, minimum followup of 5 years, and disease-free status at the time of followup. Eleven survivors were excluded because of their refusal to participate in the study, pregnancy, or major illnesses at the time of followup.

Fifty-six survivors (29 males and 27 females) agreed to participate and were included in this cross-sectional study. Their mean age at followup was 32 years (range, 16–61 years), and minimum followup was 5 years (mean, 15 years; range, 5–48 years). A questionnaire was used to obtain demographic and clinical data. Oncologic data were taken from the local bone and soft tissue tumor registry. Surgical resection margins were classified according to Enneking et al. [11], and the response to neoadjuvant chemotherapy was assessed by histologic regression grading according to Salzer-Kuntschik et al. [35] (Table 1).

All 56 patients received multidisciplinary treatment. Neoadjuvant polychemotherapy was administered according to protocols of the Cooperative Ewing's Sarcoma Study (CESS 81, 86, 91) [10], the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS 92) [31], and Euro-EWING 99 [21]. The protocols included vincristine, actinomycin D, cyclophosphamide, and doxorubicin (VACA); vincristine, actinomycin D, ifosfamide, and doxorubicin (VAIA); etoposide, vincristine, actinomycin D, ifosfamide, and doxorubicin (EVAIA); vincristine, ifosfamide, doxorubicin, and etoposide (VIDE); vincristine, actinomycin D, and ifosfamide (VAI); vincristine, actinomycin D, and cyclophosphamide (VAC); and endoxane or T2 and T6 protocols (Table 1).

Ifosfamide was used as a substitute for cyclophosphamide in the CESS 86 protocol in patients with a tumor load greater than 100 mL. The VAIA protocol showed better tumor-free survival than the VACA protocol and was used in combination with etoposide (EVAIA) in the EICESS 92 protocol in high-risk patients. VIDE is the standard protocol in the Euro-EWING 99 protocol for induction, followed by VAC or VAI depending on risk profile for tumor progression [9].

The common approach for limb salvage surgery was resection of the tumor, followed by biologic methods of reconstruction or implantation of megaendoprostheses. A resection with wide margins was achieved in 40 patients, marginal margins in four, and intralesional margins in five. For reconstruction, 15 patients received a Howmedica® Kotz Modular Femoral Tibial Reconstruction System (Stryker Orthopaedics, Mahwah, NJ, USA) (proximal femur, $n = 11$; distal femur, $n = 2$; proximal tibia, $n = 2$), four patients had reconstruction using a custom-made

Table 1. Demographic and oncologic data

Variable	Normal bone mineral density (n = 25)	Osteopenia (n = 24)	Osteoporosis (n = 7)	Total (n = 56)
Sex (female/male) (number of patients)	11/14	12/12	6/1	29/27
Age at surgery (years)*	14 (2–34)	18 (4–52)	21 (5–36)	16 (2–52)
Age at followup (years)*	31 (12–56)	32 (18–61)	37 (25–53)	32 (12–61)
BMI at followup* (kg/m ²)	25 (16–40)	22 (18–33)	25 (19–33)	24 (16–40)
Followup (years)*	16 (5–34)	13 (7–23)	16 (6–48)	15 (5–48)
Diagnosis (number of patients)				
Ewing's sarcoma	22	21	7	50
Primitive neuroectodermal tumor	3	3	0	6
Histologic tumor regression grade [16] (n = 37 patients)				
I–III	13	10	4	27
IV–VI	4	6	0	10
Staging system for malignant tumors [15] (n = 31 patients) Stage 2b	13	14	4	31
Resection margin (n = 49 patients)				
Wide	17	17	6	40
Marginal	2	2	0	4
Intralesional	2	3	0	5
Metastasis (n = 7 patients)	3	3	1	7
Localization of tumor (n = 56 patients)				
Femur proximal	3	6	3	12
Pelvis	4	5	2	11
Spine/rib	3	3	1	7
Fibula	4	2	0	6
Tibia distal	2	3	1	6
Femur distal	4	1	0	5
Tibia proximal	2	2	0	4
Other [†]	3	2	0	5
Surgical method (n = 56 patients)				
Resection only	13	12	2	27
Proximal femur megareplacement	3	5	3	11
Fibula for tibia transfer	2	3	1	6
Pelvic megaprosthesis	0	3	1	4
Distal femur megareplacement	2	0	0	2
Proximal tibia megareplacement	2	0	0	2
Ulna transposition	0	1	0	1
Fibula-prohumeral transfer	1	0	0	1
Revision surgery (n = 27 procedures)				
Number of patients	14	9	4	27
Mean number of surgical interventions per patient	3.4	2	2.4	2.7
Polychemotherapy (n = 56 patients)				
VACA (CESS 81/86)	5	4	0	9
VAIA or EVAIA (CESS 86/91 or EICESS 92)	13	16	3	32
VIDE-VAI/VAC (Euro-EWING 99)	6	4	3	13
Other [‡]	1		1	2
Local radiation (n = 51 patients)				
Yes	15	19	2	36

Table 1. continued

Variable	Normal bone mineral density (n = 25)	Osteopenia (n = 24)	Osteoporosis (n = 7)	Total (n = 56)
No	7	4	4	15

* Values are expressed as mean, with range in parentheses; †toes, forearm, proximal humerus; VACA = vincristine, actinomycin D, cyclophosphamide, and Adriamycin; CESS = Cooperative Ewing's Sarcoma Study; VAIA = vincristine, actinomycin D, ifosfamide, and Adriamycin; EVAIA = etoposide, vincristine, actinomycin D, ifosfamide, and Adriamycin; EICESS 92 = European Intergroup Cooperative Ewing's Sarcoma Study; VIDE = vincristine, ifosfamide, doxorubicin, and etoposide; VAI/VAC = vincristine, actinomycin D, and ifosfamide/cyclophosphamide; ‡endoxane or T2 and T6 protocols.

three-dimensional pelvic endoprosthesis, and one received a Howmedica® Modular Replacement System (Stryker Orthopaedics) for the proximal humerus. Biologic reconstructions in patients were a van Nes rotationplasty (n = 1), a fibula-protibia reconstruction (n = 6), a fibula-prohumeral reconstruction (n = 1), and an ulnar transposition (n = 1). Resection only, without any kind of reconstruction, was performed in 27 patients.

Thirty-six patients received local radiation therapy. Patients with megaprotheses or biologic reconstruction were excluded from receiving radiation therapy unless resection margins were found to be marginal. The dosage of the radiation field was between 45 and 54 Gy in single dosages between 1.8 and 2 Gy five times per week.

Standard laboratory parameters including whole blood cell count, serum calcium, serum phosphate, and bone turnover markers were assessed to exclude secondary osteoporosis.

BMD measurements of the lumbar spine (L1–L4) and the proximal femur of the contralateral side were acquired by dual-energy x-ray absorptiometry (DEXA). The majority of patients were scanned with a Hologic® Discovery A S/N 45313 (n = 48) and Hologic® QDR4500W (n = 2) (Hologic Inc, Bedford, MA, USA). In six patients, measurements were made on a Lunar® Prodigy (n = 2), Lunar® iDXA (n = 3), or Lunar® DPX (n = 1) (GE Medical Systems Germany, Munich, Germany). These measurements are expressed in terms of SDs from a healthy young reference population (T-scores) and from a healthy age- and sex-matched reference population (Z-score) [23]. To correct for the different scans, values were calculated according to Genant et al. [14]. Patients were classified according to the WHO criteria in three groups: patients with T-scores greater than −1 SD were considered normal, with T-scores between −1 and −2.5 SD, they were considered to have osteopenia, and with scores less than −2.5 SD, they were considered to have osteoporosis [23]. In adolescents (15–19 years old), BMD was assessed at the lumbar spine and results are expressed in Z-scores. In this group, a low BMD was assumed at Z-scores less than −2 SD. Because of the high correlation ($r = 0.935$ – 1.0 ; $p < 0.0001$) between T-score,

Z-score, and bone mass in g/cm^2 at a given location, if not explicitly mentioned otherwise, all three of them will be subsumed under the expression BMD, and analysis will be restricted to the Z-scores.

The BMD values of the study participants were compared with those of healthy control subjects [27] using Wilcoxon signed-rank tests.

To identify significant factors for BMD different factors were investigated separately for effects on BMD by linear univariate models; factors found significant at $p = 0.1$ in these separate analyses were eligible for a multivariate model with stepwise variable selection; a Bonferroni correction of the p values to account for multiple hypothesis testing was performed. Significance is reported with respect to the corrected p values.

Linear regression analysis was performed to investigate the effects of age at surgery, age at followup, time between surgery and followup, BMI, and tumor size. Amenorrhea in women was classified in one of five groups according to the duration of the interruption by intervals of 5 months, and chemotherapy protocols were listed in order of time in use (I = CESS 81/86; II = EI CESS 86/91/92; III = Euro-EWING 99). Spearman correlation was used to investigate correlations between these factors and BMD, histologic regression grading, number of surgeries, procollagen Type 1 N-terminal propeptide, and BMD. Effects of sex, absence or presence of metastases, and absence or presence of radiation therapy were investigated using two-sided t-tests. One-way ANOVAs were performed to investigate the effects of localization of the tumor and resection margins.

Differences in the number of fractures among patients with normal BMD, osteopenic BMD, and osteoporotic BMD were investigated with Fisher's exact test. Owing to the exploratory character of the study, correlation coefficients were investigated for each measure of BMD.

All statistical analyses were performed with R 2.15.0 (The R Project for Statistical Computing, Vienna, Austria).

The study was approved by the institutional review board (EK 373/2009) and conducted according to the Helsinki Declaration. Informed consent of all participants was obtained before inclusion in the study.

Table 2. BMD measurements

Variable	Normal BMD (n = 25)		Osteopenia (n = 24)		Osteoporosis (n = 7)		Total (n = 56)	
	Male (n = 11)	Female (n = 14)	Male (n = 12)	Female (n = 12)	Male (n = 6)	Female (n = 1)	Male (n = 29)	Female (n = 27)
Total femur*								
T-score	0.3 (-0.5 to 1.4)	0.07 (-0.6 to 1.5)	-0.94 (-1.6 to -0.1)	-1.25 (-2 to -0.1)	-1.92 (-3.1 to -0.5)	-1.10	-0.74 (-3.1 to 1.4)	-0.61 (-2 to 1.5)
Z-score	0.45 (-0.5 to 1.5)	0.17 (-0.5 to 1.5)	-0.77 (-1.6 to 0.6)	-1.12 (-2 to 1.0)	-1.77 (-3 to -0.1)	-0.80	-0.58 (-3 to 1.5)	-0.48 (-2 to 1.5)
Bone mass (g/cm ²)	1.06 (0.89–1.25)	0.90 (0.61–1.12)	0.91 (0.78–1.05)	0.80 (0.69–0.94)	0.74 (0.56–0.96)	0.81	0.93 (0.56–1.25)	0.86 (0.61–1.12)
Femoral neck*								
T-score	-0.22 (-0.7 to 0.8)	-0.12 (-0.9 to 1.1)	-1.32 (-1.9 to -0.4)	-1.48 (-2.2 to -0.5)	-2.03 (-3.4 to -1.2)	-1.80	-1.11 (-3.4 to 0.8)	-0.84 (-2.2 to 1.1)
Z-score	0.10 (-0.6 to 1.0)	0.05 (-0.6 to 1.1)	-1.05 (-1.8 to 0.3)	-1.27 (-1.9 to -0.3)	-1.67 (-3.1 to -0.4)	-1.40	-0.80 (-3.1 to 1.0)	-0.64 (-1.9 to 1.1)
Bone mass (g/cm ²)	0.88 (0.68 to 1.03)	0.80 (0.52 to 0.97)	0.78 (0.67 to 0.93)	0.69 (0.60–0.84)	0.65 (0.46–0.77)	0.65	0.79 (0.46–1.03)	0.75 (0.52–0.97)
Spine (L1–L4)								
T-score	-0.13 (-0.9 to 1.1)	0.35 (-0.7 to 1.7)	-0.75 (-2.2 to 1.3)	-1.24 (-2.3 to 0.5)	-2.18 (-3.5 to -0.7)	-1.10	-0.81 (-3.5 to 1.3)	-0.51 (-2.3 to 1.7)
Z-score	-0.19 (-1.3 to 1.6)	0.30 (-1.4 to 1.9)	-0.70 (-2.2 to 1.3)	-1.05 (-2.1 to 0.5)	-2.02 (-3.5 to -0.2)	-0.80	-0.74 (-3.5 to 1.6)	-0.37 (-2.1 to 1.9)
Bone mass (g/cm ²)	1.04 (0.79–1.21)	1.04 (0.74–1.24)	1.00 (0.84–1.21)	0.91 (0.79–1.1)	0.85 (0.71–1.02)	0.92	0.99 (0.71–1.21)	0.98 (0.74–1.24)

Values are expressed as mean, with range in parentheses; *no measurement for patients younger than 18 years (n = 52); BMD = bone mineral density.

Results

Bone Mineral Density

Seven of the 56 patients (13%; six males and one female) showed evidence of osteoporosis, 24 (43%; 12 males and 12 females) had osteopenia, and 25 (44%; 11 males and 14 females) had normal BMD. T-scores of the spine ($p = 0.003$) and the femoral neck ($p < 0.001$) were lower in patients than in healthy control subjects [27] (Table 2).

Features Associated With BMD

Patients with longer followups had higher Z-scores for total spine (estimate, 0.06; 95% CI, 0.03–0.10; $p = 0.013$). Patients with low BMI had low Z-scores of the total femur and femoral neck (estimate, 0.09; 95% CI, 0.04–0.14; $p = 0.002$) (Table 3). With the numbers available, patients who were younger at the time of surgery had higher T-scores of the femoral neck in the multivariate model, but not after Bonferroni correction.

With the numbers available, gender, tumor-specific parameters such as tumor size, localization, diagnosis of metastases, and surgical features such as resection margins, numbers of surgical interventions, radiation therapy, different chemotherapeutic protocols, and the duration of secondary amenorrhea had no influence on BMD in the multivariate model.

Fractures

Twenty-one patients (41%) reported 29 fractures (Table 4). In six patients (11%, three male/three female), fractures resulted from low-impact trauma. Low-impact was defined as falling while standing or walking. Fifteen patients reported high-impact fractures, all of which were the result of an accident. Three patients experienced more than one fracture. There was no difference in fracture rates between patients with and without radiation therapy, with the numbers available. The fraction of patients with radiation therapy who had a fracture in the radiation field was 0.2 (95% CI, 0.08–0.36). For patients who had radiation therapy, the fraction of all fractures occurring in the radiation field was 0.39 (95% CI, 0.17–0.64).

BMD and Fractures

The overall percentage of fractures was 38% in patients with normal BMD, 34% in patients with osteopenic BMD, and 50% in patients with osteoporotic BMD. With the

Table 3. Factors associated with low BMD in a multivariate model[§]

Variable	Multivariate p value (p value after Bonferroni correction)			
		Total femur	Femoral neck	L1–L4
Older age at surgery	NS		0.023 [#] (0.161)	NS
Age at followup	NS		NS	NS
Short followup	NS		NS	0.002 (0.013)*
Sex	NS		NS	NS
Chemotherapy protocol	NS		NS	NS
Low BMI	< 0.001 (0.002)**		0.002 0.014*	NS

BMD = bone mineral density; NS = not significant; [§]Z-scores with and without Bonferroni correction; [#]T-scores; *p < 0.05 after Bonferroni correction; **p < 0.01 after Bonferroni correction.

Table 4. Patients with fractures

Variable	Number of patients (male/female)		
	Normal BMD	Osteopenia	Osteoporosis
Low-impact fracture (n = 6)	1 (1/0)	2 (0/2)	3 (2/1)
High-impact fracture (n = 15)	8 (5/3)	6 (5/1)	1 (1/0)
Patients with fractures total (n = 21)	9 (3/6)	8 (3/5)	4 (1/3)
Localization			
Radius	2 (1/1)	0	2 (1/1)
Tibia	4 (1/3)	5 (2/3)	1 (0/1)
Fibula	0	1 (0/1)	0
Humerus	2 (1/1)	0	0
Femur	1 (0/1)	1 (1/0)	0
Spine	0	0	1 (0/1)
Toe	0	1 (1/0)	0

BMD = bone mineral density.

numbers available, there was no difference among groups (p = 0.332).

Discussion

Ewing tumors are the second most frequent malignant bone tumors in childhood and adolescence. Multidisciplinary treatment in patients with Ewing tumors consists of neo-adjuvant chemotherapy and wide tumor resection or, in some cases, radiotherapy for local control. Depending on the localization of the tumor, wide resection is followed by

biologic reconstruction or implantation of megaendoprostheses. Surgical treatment involves long-term rehabilitation and functional impairment, both affecting the bone owing to inactivity. In healthy humans, peak bone mass is reached between the age of 20 and 30 years followed by a slow age-related decrease of BMD. Patients receiving chemotherapy during childhood and adolescence usually cannot reach their genetically determined peak bone mass and have low BMD develop early during life. The questions arise whether patients with Ewing tumors have low BMD and consecutive fractures.

This study is limited because single analyses are based on a small number of patients, although a large group of patients with Ewing tumors was analyzed. The long-term response of patients considered to be alive was only 76%. Survivors of malignant diseases may decline participation in studies for various reasons including general rejection of study participation or owing to professional commitment, not having time for followups, or relocation. The final percentage of 56% of patients who were included in this study poses a selection bias. This resulted in some no-difference findings, but these no-difference findings may have been a function of insufficient statistical power from a small sample size. Larger studies are needed to determine whether some of the differences we were unable to identify as significant are either statistically significant or clinically important. Our study may provide pilot data for such studies, which will need to be multicenter collaborations. Some of our patients may not have reached peak-bone mass. However, considering that the majority of BMD is accumulated in the lumbar spine and femur in individuals between 20 to 30 years old [16, 28], a mean age of 32 years may show that a majority of participants have reached peak bone mass before measurement. We also used a published age- and sex-matched control group for bone status. In addition, the majority of our patients were scanned using one type of DEXA scanner. Some patients refused to return to our institution owing to distance and had their DEXA scans done with other DEXA scanners. The results of these scanners, however, were normalized [16, 28].

Thirty-one of the 56 patients in our study (55%) had a pathologic BMD. This is likely attributable to chemotherapy-associated reduction in BMD. Seven patients had osteoporosis. However, in survivors of highly malignant osteosarcoma, high-dose methotrexate [18], a chemotherapeutic drug used in treatment of osteosarcoma, was shown to cause low BMD. Patients with Ewing tumors receive cyclophosphamide, which is part of the VACA protocol and was reported to reduce osteoblasts and osteoclasts [42] and to suppress bone formation in an animal study [33]. Ifosfamide, part of the VAIA protocol, is known to inhibit bone remodeling and to reduce mineral apposition rates

[41]. Thus, cyclophosphamide and/or ifosfamide may cause treatment-induced bone loss in patients with Ewing tumors. It is not clear why almost 1/2 of our patients did not have pathologic BMD. Patients receiving chemotherapy at a younger age might better compensate for the effects on bone. In this study younger age of patients at the time of receiving chemotherapy was significant for higher BMD at followup in a multivariate model before Bonferroni correction.

We could not confirm some potentially important predictors of low BMD in patients with Ewing tumors. Interestingly, our data show no influence of age at followup on BMD levels. The association of higher BMD levels with younger age at surgery and longer followups may indicate a potential recovery of BMD in these patients. Our no-difference finding whether the influence of chemotherapy changing with time toward improvement in survival rates (CESS 81-92/ Euro-EWING 99) may be a function of insufficient sample size. The most powerful factor indicating low Z-scores of the total femur and femoral neck was BMI at age at followup. This was known for patients with postmenopausal osteoporosis [29] and sarcoma [40], and also applies to young survivors of Ewing tumors. In line with Ruza et al. [34], in patients with Ewing tumors, BMI positively correlated with low BMD. Therefore BMI may be an indicator for assessing BMD in survivors of bone tumors. We found no BMD difference in female patients whose menstruation cycles had been interrupted by chemotherapy in multivariate analysis as was seen in survivors of highly malignant osteosarcomas [18]. This no-difference also may be a function of a too small sample size.

At the time of followup, 21 patients reported a history of 29 fractures. In a healthy cohort between 25 to 45 years of age, a fracture incidence of 1.26 per year was reported [39] (not differentiating between high-impact and low-impact fractures). Comparing these percentages with our results, the fracture incidence for survivors of Ewing tumors was twice as great (2.4 fractures per year). The fracture incidence is increased by 53% (from 1.9 fractures to 2.9 fractures per year) in male survivors and more in female survivors (128%; 0.79 fractures to 1.8 fractures per year). The majority of high-impact fractures were seen in patients with normal BMD. Eighty-three percent of the low-impact fractures were accompanied by reduced BMD, but low-impact fractures also were seen in patients with normal BMD. Patients who reported low-impact fractures were older at the time of surgery. Twenty percent of patients who received radiation therapy had fractures in the radiation field, and 39% of fractures in these patients occurred in the radiation field. However, there was no difference in fracture rates between patients with and without radiation

therapy. Greater local BMD attributable to radiation was measured according to Dhakal et al. [8].

Analyzing the effect of low BMD on fractures, we found no influence of BMD on the number of low- and high-impact fractures. Low BMD has been shown to be a good predictor for fractures in the elderly [20, 37], but not in children and young adults [6]. The effect of BMD on fractures may differ between older patients with idiopathic or postmenopausal osteoporosis and young patients with secondary bone loss attributable to tumor treatment. Younger patients may experience less uncoordinated falls and, independently of their activity levels, at least in men, experience fewer fractures even when falling [5]. Our study did not reveal an effect of low BMD on fractures in survivors of Ewing tumors. This is likely because of small sample size. However, one could speculate that other characteristics of bone which are not assessed by DEXA, like the cortical bone [19] or microarchitectural changes in the trabecular and cortical bone, are involved. Independently of low BMD, the higher fracture rates may justify osteoporotic treatment in survivors of Ewing tumors.

Survivors of Ewing tumors are at a high risk of having low BMD and fractures. Low BMD in our patients was not associated with fractures in young survivors. However, this finding may be the result of insufficient sample size. Indicators of low BMD may be the time between surgery and followup and BMI. With the numbers available, we found no differences in several other possible factors. This study should be considered a pilot study for future prospective, multicenter studies, which are needed to address this important problem. As a consequence, these risk factors must be considered as patients with Ewing tumors are followed. Although we did not see BMD-associated events we strongly recommend additional assessment in cohorts of survivors and treatment of osteoporosis should be considered. The introduction of a healthy control group was used to define a therapeutic gap, which should be addressed by future osteoprotective therapy strategies. Causes for the high proportion of patients who experienced fractures remain unknown.

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