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ORIGINAL ARTICLE

Health related quality of life and late side effects of long-term survivors of Ewing's sarcoma of bone

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Summary

Purpose: *The data examining the Health Related Quality of Life (HRQOL) after definitive treatment for Ewing's sarcoma (EWS) is sparse. The objective of this study was to assess the HRQOL and late side effects in EWS of bone survivors treated in the past 2 decades.*

Methods: *Seventeen long-term (≥ 5 years) EWS survivors (age range, 11-27 years) treated from 1990 to 2004 completed the EORTC-QLQ-C30. We compared the HRQOL of our data set with a reference group of cancer survivors and also with the general population. Musculoskeletal late treatment toxicity was also evaluated. The Mann-Whitney and Wilcoxon tests were used for analyses.*

Results: *EWS survivors of our series reported significantly better global, physical, role and cognitive HRQOL and less symptoms of fatigue, pain and insomnia than the normative sample of cancer survivors. Moreover, the HRQOL was equivalent to the general population, with the exception of social functioning. Additionally, patients with tumor location in the extremities did not report significant HRQOL differences compared with those with tumor at other locations. Common chronic grade 2 side effects were generalized muscle weakness (23%) and decreased joint range of motion (23%). Only one patient experienced musculoskeletal chronic grade 3 toxicity.*

Conclusion: *Our findings suggest that EWS survivors treated in the modern era do not experience lower HRQOL than other cancer survivors. Rather, the HRQOL appears to be equivalent to the general population. Further and larger studies are needed to confirm these results.*

Key words: Ewing's sarcoma, pediatric oncology, quality of life, side effects

Introduction

The goal in treating patients with cancer is to cure their disease while rendering a meaningful quality of life. Since 1970 there has been dramatic progress in the treatment of pediatric and adolescent bone tumors with combination multi-agent chemotherapy, new surgical and radiotherapy techniques, and the expertise provided by centralized pediatric cancer studies and services [1-4]. At the same time, recognition of late physical and psychological effects together with the longer life expectancies has raised questions about HRQOL, with increasing appreciation of the importance of the patient's perspective [5]. This study examined the broader impact of disease on everyday life and included physical, psychological and social implications as well as disease- and treatment- related symptoms [6-9].

Much research suggests that HRQOL in long-term survivors of childhood cancers is comparable with that of the general population. However, there are differences depending on tumor group, as well as suggestions that HRQOL in survivors of some cancers, including brain and bone tumors, is relatively poor compared with the general population or survivors of other malignancies [10-14]. EWS of the bone is the second most common primary malignant bone tumor in children worldwide [15] and the most common bone malignancy in Spain [16]. EWS is considered a systemic disease with

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the majority of patients requiring multimodal therapy [17]. The advent of novel surgical and radiation technology such as 3-dimensional (3D) conformal radiotherapy (RT) has raised questions about the HRQOL of EWS survivors treated in the modern era.

The current study thus had 3 primary aims/hypotheses: 1) to determine the HRQOL of EWS survivors treated in the past 2 decades, with the hypothesis that the majority of survivors will not experience a significant decrease in HRQOL compared with other cancer survivors; 2) to compare the HRQOL with the general population, the hypothesis being that EWS survivors will have equivalent HRQOL; and 3) to determine musculoskeletal late side effects, with a focus on determining whether patients treated in the modern era experience severe chronic morbidity.

Methods

Patient selection

This retrospective analysis was approved by the institutional review board of Virgen del Rocío University Hospital. From 1990 to 2004, 46 patients less than 17 years old with a diagnosis of EWS of the bone were treated at our institution. Of the 23 EWS survivors, 2 were not available for follow-up (Figure 1). Among the remaining 21 subjects, 4 declined participation. Ultimately 17 long-term (≥ 5 year) survivors of EWS were available for analysis. This time period was selected based on the advent of novel local treatment techniques, such as 3D conformal RT, at Virgen del Rocío University Hospital.

Chemotherapy

From 1990 to 1995, 4 patients were treated according to the Memorial Sloan-Kettering Cancer Center P6 protocol [18], with cycles 1, 2, 3, and 6 including cyclophosphamide, adriamycin, and vincristine, and cycles 4, 5, and 7 including ifosfamide and etoposide. Tumor resection was after cycle 3 and RT followed completion of all chemotherapy. The most recent (period, 1995-2004; n = 13) and common scheme used was according to the Spanish Society of Pediatric Oncology (SEOP) protocol [17]. The SEOP protocol included 6 induction cycles of vincristine, adriamycin (alternating with dactinomycin before 2001), ifosfamide and etoposide. Surgery, when indicated, was performed 3 weeks after induction chemotherapy. Consolidation chemotherapy included vincristine, dactinomycin and cyclophosphamide for a total of 1 (if they were going to undergo megatherapy with autologous stem cell transplantation) or 8 cycles. Since 1995, end-intensification with megatherapy using high-dose chemotherapy and stem cell rescue was delivered to 7 patients after consolidation chemotherapy according to our bone marrow transplant protocol.

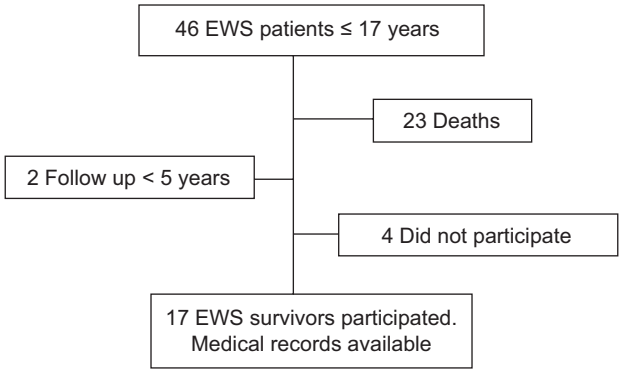

Figure 1. Flow diagram of Ewing's sarcoma patients (EWS) treated at Virgen del Rocio University Hospital from 1990 to 2004.

Surgery

Eight patients underwent surgical resection of the tumor alone, 5 received RT alone, and 4 were treated with both surgery and RT. The intent of radical surgery was removal of all gross tumor and, if feasible, with negative margins. Maximal resection was followed by reconstruction. Laminectomy was performed in 3 out of the 4 cases with the primary location in the spine due to cord compression. Patients with a tumor location in the extremities or pelvis (n = 5) were treated with limb sparing surgery. In contrast, patients with the tumor in the bones of the foot (n = 3) underwent amputation. Two patients had an amputation of a toe, and a foot and ankle amputation was performed in the third case.

Radiotherapy

RT was delivered to 9 patients using megavoltage technology (6-18 MV photons). Patients treated before 2000 (n = 3) had treatment planned with 2-dimensional (2D) non conformal techniques. Patients treated in 2000 or later were treated with 3D conformal techniques targeting the primary lesion at diagnosis plus a 4 cm craniocaudal margin and 2 cm in the other axes except in cases in which this margin would result in overdosing of an adjacent critical structure (such as epiphysis, spinal cord or ovary). The dose of RT ranged from 45 Gy to 55.8 Gy, delivered daily at fraction sizes of 1.8-2 Gy.

Measurement of HRQOL and late side effects

The European Organisation for Research and

Treatment of Cancer (EORTC) quality of life (QoL) questionnaire is an integrated system for assessing the HRQOL of cancer patients participating in international clinical trials. The core questionnaire (QLQ-C30) [19], is composed of both multi-item scales and single-item measures. These include 5 functional scales (physical, role, emotional, cognitive and social functioning), 9 symptom scales/items (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties); and a global health status score. Each of the multi-item scales includes a different set of items - no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. For the 5 functional scales and the global QoL scale, item responses were recorded so that a higher score represents a better level of functioning. On the other hand, a high score on the symptom scales/items represents a high level of symptomatology [20]. This measure has been used by researchers internationally including the United States, Germany, Norway, Austria, and Denmark, and can be used to discriminate between subgroups of cancer patients. When necessary, the questionnaire was completed with the assistance of the patient's parents.

Additionally, late side effects were evaluated by the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 [21]. Late side effects were defined as those that first occur at least 6 months after last protocol therapy was over. Six representative musculoskeletal and connective tissue disorders were selected for evaluation (Table 1).

Follow-up

After completing treatment, patients were followed up at approximately 1-3 months post-therapy and then every 3 months for 5 years, and annually thereafter. The follow up evaluations consisted of a history and physical examination and a computerized axial tomography scan at an interval of 3-6 months, at the treating physician's discretion.

Statistical analyses

All data analyses were done using the SPSS (version 19.0) statistical software. The domains of the QLQ-C30 of our sample were compared with two different populations using the Mann-Whitney and Wilcoxon test. The first population represented the cancer survivors under the age of 50, in whom reference average scores for the EORTC-QLQ-C30 were obtained from Scott et al.

Table 1. Late side effects evaluated in the study according the Common Terminology Criteria for Adverse Events v. 4.0.

	Grade			
Adverse event	*1*	*2*	*3*	*4*
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	
Joint range of motion decreased	≤25% loss of range of motion; decreased range of motion limiting athletic activity	>25-50% decrease in range of motion; limiting instrumental activities of daily living	>50% decrease in range of motion; limiting self care activities of daily living; disabling	
Growth suppression	Reduction in growth velocity by 10-29% ideally measured over the period of a year	Reduction in growth velocity by 30-49% ideally measured over the period of a year or 0-49% reduction in growth from the baseline growth curve	Reduction in growth velocity of ≤50% ideally measured over the period of a year	
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental activities of daily living	Weakness limiting self care activities of daily living; disabling	
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental activities of daily living	Severe localized edema and intervention indicated; limiting self care activities of daily living	
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated

[22]. The second group represented a general population of 200 caucasian subjects (111 males and 89 females) with a median age of 19 years (range 14-31) who had reported no history of cancer in their lifetime and were obtained by the primary care provider. Additionally, we studied the impact of the tumor location (extremities vs. other locations) and local treatment (combined modality vs. single modality) on QoL outcomes.

Results

Patient characteristics are presented in Table 2. The median age at diagnosis was 10 years (range 2-14), with a male/female sex ratio of 9:8. At assessment, the median age for the entire group of patients was 19 years (range 11-27) with a median follow-up from the end of therapy of 9 years (range 6-19).

Table 2. Characteristics of patients treated for Ewing's sarcoma of bone

Patient No./Sex	*Age at diagnosis (years)*	*Clinical presentation*	*Site of disease at diagnosis (primary/ distant)*	*Laterality*	*Stage*	*Treatment protocol*	*Year of treatment*	*Local treatment*	*Bone marrow transplant*	*Last follow-up, Time from diagnosis (years)*
1/M	7	Swelling	Ilium/Lung	Right	IVA	MSKCC P6	1990	RT	No	NED (18.8)
2/F	2	Swelling	Rib	Right	IIB	MSKCC P6	1993	Surgery*	No	NED (15.9)
3/M	10	Swelling	Distal toe phalanx	Left	IIA	MSKCC P6	1995	Surgery†	No	NED (13.5)
4/F	11	Functional disability	Femur	Left	IIB	MSKCC P6	1996	Surgery‡	No	NED (12.4)
5/F	10	Swelling	Astragalus	Left	IIA	SEOP	1996	Surgery†	Yes	NED§ (12.7)
6/M	13	Swelling	Ilium	Right	IIB	SEOP	1998	RT	Yes	NED (11.2)
7/M	13	Functional disability	Ilium	Right	IIA	SEOP	1999	Surgery‡ +RT	No	NED (10.5)
8/M	10	Pain	Rib	Left	IIA	SEOP	2000	Surgery* +RT	Yes	NED (9.3)
9/F	9	Pain	Middle toe phalanx	Right	IIA	SEOP	2000	Surgery†	No	NED (9)
10/M	7	Pain	Ilium	Right	IIB	SEOP	2000	RT‡	Yes	NED (8.8)
11/F	3	Neurologic symptoms	Thoracic vertebrae	–	IIA	SEOP	2000	Surgery#	No	NED§ (8.8)
12/M	3	Pain	Lumbar vertebrae	–	IIA	SEOP	2000	RT	Yes	NED (8.7)
13/M	2	Neurologic symptoms	Lumbar vertebrae/Bone	–	IVB	SEOP	2003	Surgery#	Yes	NED (12.4)
14/F	8	Pain	Rib	Left	IIB	SEOP	2003	Surgery* +RT	No	NED (5.9)
15/F	14	Swelling	Fibula	Right	IIA	SEOP	2004	Surgery* +RT	No	NED (5.6)
16/M	11	Neurologic symptoms	Lumbar vertebrae	–	IIB	SEOP	2004	Surgery# +RT	Yes	NED (5.6)
17/F	11	Swelling	Humerus	Right	IIB	SEOP	2004	Surgery‡	No	NED (4.9)

M: male, F: female, MSKCC: Memorial Sloan-Kettering Cancer Center, SEOP: Spanish Society of Pediatric Oncology, RT: radiation therapy, NED: no evidence of disease, *resection, †amputation, ‡ allograft, #laminectomy, §distant recurrence within 2 years from diagnosis treated with salvage chemotherapy

HRQOL assessment

Global health status and functional scales score

High HRQOL scores were observed for the entire group of patients (Table 3). When patients were divided into 2 groups on the basis of tumor location, there were not significant HRQOL differences between patients with tumor location in the extremities vs. those with tumors located at other sites (Figure 2A). Patients who underwent multimodality local treatment had lower score for all scales compared with those who received single modality treatment (Figure 2B), though these latter results did not show statistical significance.

Symptom and single items scales score

All patients experienced low scores for all symptom items (Table 3). No patient reported dyspnea despite having undergone thoracic surgery, RT or combination of both in 5 cases. In addition, chronic constipation was not reported. Pain and insomnia had the highest score. No significant differences were observed after clinical and treatment stratification. Again, it was noted that a score indicating increased symptoms was observed for all scales when patients underwent multimodality local treatment compared with those receiving a single modality for local treatment.

Comparisons to reference scores

The study group scored higher on global health status and functional domains (Table 3) than the reference population of cancer survivors, being significant for global health status ($p = 0.001$), physical functioning ($p = 0.004$), role functioning ($p < 0.001$), and cogni-

Table 3. Wilcoxon test comparisons between health-related quality of life scores of sample and normative values

EORTC-QLQ-C30	*Reference Score*		*Sample*		*T (SE)*	*z*	*p-value*
Measure/item	*Mean (SD)*	*Median [IQR]*	*Mean (SD)*	*Median [IQR]*			
Global Health Status/QOL	61.4 (23.4)	66.7 [50-83.3]	91.17 (13.97)	100 [87.49-100]	147 (20.62)	3.420	0.001
Physical functioning	80.2 (20.8)	86.7 [66.7-100]	93.33 (21.21)	100 [100-100]	134 (19.73)	2.914	0.004
Role functioning	68.6 (31.7)	66.7 [50-100]	96.08 (11.07)	100 [100-100]	150 (19.39)	3.790	<0.001
Emotional functioning	69.2 (24.4)	75 [58.3-91.7]	82.35 (26.01)	100 [58.33-100]	99 (20.01)	1.124	0.261
Cognitive functioning	82.9 (21.6)	83.3 [66.7-100]	93.14 (13.26)	100 [91.66-100]	144 (20.01)	3.374	0.001
Social functioning	72.1 (29.5)	83.3 [50-100]	83.33 (22.05)	100 [66.66-100]	96 (20.75)	0.940	0.347
Fatigue	33.9 (26.1)	33.3 [11.1-55.6]	4.57 (14.19)	0 [0-0]	2 (19.39)	–3.841	<0.001
Nausea/vomiting	9.4 (19.1)	0 [0-16.7]	2.94 (8.81)	0 [0-0]	3 (1.12)	1.342	0.18
Pain	27.2 (28.8)	16.7 [0-50]	9.8 (18.69)	0 [0-16.67]	24 (20.25)	–2.592	0.01
Dyspnoea	17.1 (25.8)	0 [0-33.3]	0 (0)	0 [0-0]	0 (0)	NE	1
Insomnia	30.2 (32.2)	33.3 [0-66.7]	7.84 (25.08)	0 [0-0]	18 (19.39)	–3.016	0.003
Appetite loss	19.7 (29.1)	0 [0-33.3]	5.88 (17.62)	0 [0-0]	3 (1.12)	1.342	0.18
Constipation	15.3 (26.5)	0 [0-33.3]	0 (0)	0 [0-0]	0 (0)	NE	1
Diarrhoea	9.0 (19.9)	0 [0-0]	1.96 (8.08)	0 [0-0]	1 (0.50)	1	0.317
Financial difficulties	23.6 (32.0)	0 [0-33.3]	7.84 (22.14)	0 [0-0]	3 (1.06)	1.414	0.157

EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, SD: standard deviation, IQR: interquartile range, SE: standard error, NE: not evaluable

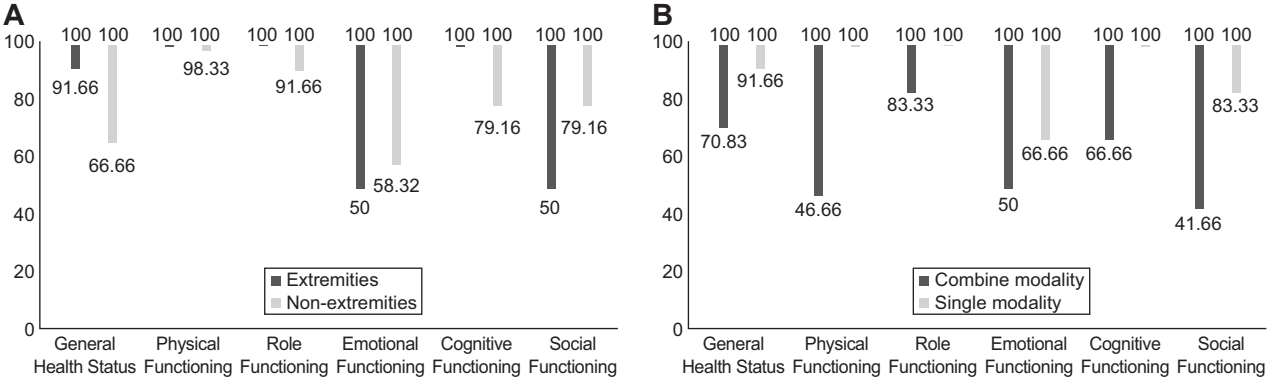

Figure 2. Health-related quality of life (HRQOL) in patients with Ewing's sarcoma of bone according tumor location (**A**) and local treatment (**B**). The HRQOL 25th-75th percentile range score on the domains is transposed to a 0-100 scale. A *high* scale score represents a *better* HRQOL.

tive functioning (p = 0.001). In addition, the study group scored significantly lower for fatigue (p < 0.001), pain (p = 0.01), and insomnia (p = 0.003) on the symptom domains. Finally, when comparing our series with the general population (Table 4), no statistically significant difference for the global health status was seen. In terms of functional domains, the general population group scored significantly higher for social functioning (p < 0.001) and fatigue (p < 0.001). The rest of functional and symptom domains were not significantly lower for the study group.

Late side effects

The most common chronic grade 1/2 complication was radiation musculoskeletal deformity (Figure 3), which occurred in 11 cases (64.7%). All patients scored as grade 2 musculoskeletal deformity (n = 3) underwent surgery. A decrease in joint range of motion was observed in 6 patients: grade 1 in 2 cases and grade 2 in 4. All patients experiencing grade 2 were ≥ 10 years old at diagnosis. Grade 1 chronic generalized muscle weakness occurred in 3 patients and grade 2 in 4. These 4 cases received RT. Grade 1 growth suppression was observed in 4 cases, and grade 2 in 1. The patient who experienced grade 2 growth suppression was a 7-year-old male with a large unresectable ileal tumor and lung metastases at diagnosis and both lesions were treated with 2D RT. No patient experienced grade 4 or 5 toxicity. Only one patient experienced grade 3 late side effects, an 11-year-old with stage IIB disease (No. 16, Table 2) who underwent laminectomy for cord compression (lumbar vertebrae) followed by RT. The patient suffered a disabling fracture in the lumbar area which required surgery for stabilization. As a result of this fracture, the patient's self care activities of daily living were limited and experienced a significant deformity of the vertebral column.

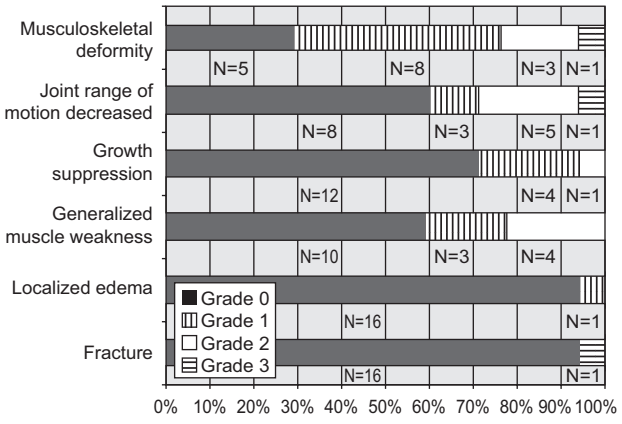

Figure 3. Late side effects in 17 Ewing's sarcoma of bone survivors as percentage of the grade-matched score.

Discussion

The results of this study suggest that in general the HRQOL of childhood survivors of EWS of bone treated in the past 2 decades is at least comparable to other cancer survivors and equivalent, except for the social functioning and fatigue compared with the normal population, confirming previous findings regarding bone tumor survivors [23,24]. Additionally, we did not observe significant HRQOL differences in our series between

Table 4. Mann-Whitney U test comparisons between health-related quality of life scores of sample and the general population

EORTC-QLQ-C30	*General population*		*z*	*p-value*
Measure/item	*Mean (SD)*	*Median [IQR]*		
Global Health Status/QOL	85.58 (13.25)	83.33 [77.08-100]	–1.740	0.082
Physical functioning	98.6 (3.25)	100 [100-100]	–0.292	0.770
Role functioning	96.08 (9.6)	100 [100-100]	–0.311	0.755
Emotional functioning	84.42 (16.57)	91.67 [75-100]	–0.744	0.457
Cognitive functioning	94.08 (10.94)	100 [83.33-100]	–0.135	0.893
Social functioning	97.25 (8.96)	100 [100-100]	–4.570	<0.001
Fatigue	14.11 (13.21)	11.11 [0-22.22]	–3.648	<0.001
Nausea/vomiting	2.58 (7.49)	0 [0-0]	–0.123	0.902
Pain	9.42 (12.79)	0 [0-16.67]	–0.990	0.322
Dyspnoea	4.33 (12.64)	0 [0-0]	–1.474	0.140
Insomnia	8.5 (16.71)	0 [0-0]	–1.068	0.285
Appetite loss	8.5 (17.04)	0 [0-0]	–1.024	0.306
Constipation	4.83 (13.11)	0 [0-0]	–1.580	0.114
Diarrhoea	3.67 (11.47)	0 [0-0]	–0.628	0.530
Financial difficulties	1.67 (8.68)	0 [0-0]	–1.506	0.132

For abbreviations and data for the sample group see footnote of Table 3

patients in relation to tumor location. When comparing patients treated with multimodal therapy for local control, those receiving a single modality reported better HRQOL scores than those treated with combined modality treatment. However, these results were not statistically significant. Finally, only one patient experienced severe (grade ≥ 3) late musculoskeletal toxicity.

Several recent studies have examined the HRQOL on bone tumor survivors treated during childhood [23, 25, 26]. It is notable that EWS survivors of our series reported significant better global, physical, and cognitive HRQOL and decreased symptoms of fatigue, pain and insomnia than the normative sample of cancer survivors. These findings are consistent with Barrera et al. [23] that reported similar results in terms of functional scales using the same normative sample of cancer survivors and the identical HRQOL questionnaire of that in our study. In the multicentric study by Hudson et al. [12], bone tumor survivors experienced significantly higher functional impairment and activity limitations than leukemia survivors. However, the general and mental HRQOL outcomes were not significantly different from either the leukemia group or other categories of cancer survivors.

With regard to the second finding that in general HRQOL is equivalent to the healthy population, our results are consistent with other recent reports [5, 27]. For instance, a Dutch study carried out by Koopman et al. [5] observed that at 8 years after treatment bone tumor survivors showed significantly better cognitive functioning and less negative emotions than the control group. Moreover, bone tumor survivors showed better social functioning than the control group. Despite the high median score reported by EWS survivors of our study for this domain, it is likely that the reason we observed a lower score compared with the general population is because all participants of the reference group reported the maximum score for this domain. The Dutch study also observed that the previously reported lower HRQOL on motor functioning and autonomy at 3 years after treatment had approached normal limits by 8 years. These results are in contrast to other earlier studies [11,14] such as Ginsberg et al. [11], who found that 13.6% of EWS survivors reported moderate to extreme adverse general health compared with 5.1% of their siblings. However, this study included participants treated between 1970 and 1986, so the results may not be relevant to current treatment modalities. The use of more limb sparing operations, smaller radiation fields (1-2 cm margin rather than whole bone or muscle compartment) and conformal techniques (3D, intensity-modulated, limited area RT) potentially decrease morbidity in patients being treated with modern techniques [28]. The British Childhood Cancer Survivor Study (BCCSS) [14] reported that survivors of bone tumors scored significantly below the expected levels in regards to physical health. This study included individuals diagnosed with childhood cancer between 1940 and 1991. When adjusting by age of respondents, those diagnosed at an earlier age (16-24 years) reported less physical impairment than older patients.

With respect to the HRQOL according to tumor location, our findings did not show significant differences between those patients with a tumor located in the extremities compared to other sites. Prior literature is discordant with respect to these findings [6,23,27,29]. For instance, Nagarajan et al. [27] evaluated the function and HRQOL in 528 osteosarcoma (80%) or EWS (20%) survivors from the Childhood Cancer Survivor Study (CCSS) with a primary tumor location in the lower extremity using the Toronto Extremity Salvage Score (TESS) and the Quality of Life for Cancer Survivors (QOL-CS) instrument. Overall the survivors reported excellent function and HRQOL and interestingly, survivors who underwent amputation were not more likely to have lower function and HRQOL scores and self-perception of disability than those who underwent a limb-sparing procedure. Additionally, Robert et al. [29] did not find HRQOL differences between survivors who underwent amputation and those with limb-salvage surgery. They observed that lower limb functionality, rather than the nature of the surgical resection, was the primary predictor of HRQOL. In our series, only patients with a tumor location in the foot underwent amputation, such that the preserved functionality of treatment was responsible for maintaining relatively high HRQOL scores. A multicenter study [6] in the Netherlands using the Short Form-36 (SF-36) demonstrated that bone tumors in the lower extremities had comparable levels of HRQOL within the social, emotional, and cognitive domains, when compared to healthy controls. However, patients reported significantly worse scores than healthy controls within the physical function domains. The follow-up period of this study ranged from 1 to 5 years, and representation of various stages of the rehabilitation process varied largely, and thus it is possible that a fraction of the patients had not yet reached their optimal levels of HRQOL and that further improvement could come in the years ahead.

In terms of late side effects, only one patient (5%) in our series experienced severe (grade ≥ 3) musculoskeletal toxicity. The low rate of severe chronic toxicity observed is contrary to other published studies [11,13]. For example, Ginsberg et al. [11] reported a 15% rate of severe chronic conditions at 5 or more years after diagnosis in EWS survivors using the same toxicity

criteria. Nevertheless, the percentage of musculoskeletal impairment was not specified amongst the chronic conditions reported. Mansky et al. [13] found musculoskeletal limitations in a cohort of 32 sarcoma survivors (87.5% EWS family of tumors) using different methods including strength testing and goniometric measurement of joint range of motion for the assessments of the musculoskeletal functioning. This study included patients treated from 1965 to 1998 with an age range of 7.1 to 34.2 years old. It is likely that the treatment time as well as other methodological and clinical factors such as the higher age at diagnosis could in part explain the divergences between these findings and ours.

We acknowledge several limitations in our study. First, there were inherent methodological shortcomings of the study that affect the applicability of these findings, such as the small sample size from a single center, and inclusion of different tumor locations. Second, the HRQOL assessment does not have questions that specifically address bone tumors, which also limits these findings. Third, it is possible that the patients' intense and life-threatening life experiences may result in a varied perspective on life, rather than strictly a function of the treatment techniques utilized. Finally, our series contains patients located at different chronological stages at the time of evaluation (age range, 11 to 27 years old) which may have influenced the results, especially for those patients at earlier ages.

Notwithstanding these limitations, our study provides data on the impact on QoL in patients mostly treated with modern techniques for EWS of the bone. Our findings suggest that the HRQOL and morbidity of EWS patients treated in the past decades may approach that of the normal population, which would be very significant in terms of these therapies that reduce long-term toxicity [23]. Multicentric studies with a larger sample of patients treated in the modern era are needed to confirm these results.

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