original report

Health-Related Quality of Life and Survival Outcomes of Pediatric Patients With Nonmetastatic Osteosarcoma Treated in Countries With Different Resources

abstract

Purpose Health-related quality of life (HRQOL) improves throughout treatment of patients with nonmetastatic osteosarcoma. We compared HRQOL for patients in the United States and Chile treated on an international trial (OS99) with polychemotherapy and surgery, and we assessed the relationships among HRQOL measures, event-free survival (EFS), and overall survival (OS).

Materials and Methods Patients with newly diagnosed, localized osteosarcoma and their parents completed three HRQOL instruments (PedsQL v.4, PedsQL Cancer v.3, and Symptom Distress Scale [SDS]). Data were collected at four time points throughout therapy. Repeated measures models were used to investigate the effect of treatment site on instrument scores. The log-rank test examined the impact of treatment site on survival outcomes, and Cox proportional hazards regression models evaluated baseline HRQOL measures as predictors of EFS and OS.

Results Of 71 eligible patients, 66 (93%) participated in the HRQOL studies in the United States (n = 44) and Chile (n = 22). The median age was 13.4 years (range, 5 to 23 years). Clinical characteristics were similar between treatment sites. US patients reported better scores for physical ($P = .030$), emotional ($P = .027$), and school functioning ($P < .001$). Chilean patients reported poorer scores for worry ($P < .001$) and nausea ($P = .007$). Patient and parent nausea scores were similar between patients treated in the United States and Chile by the end of therapy. Differences in symptom distress were not observed between the countries. Neither HRQOL measures nor treatment site were associated with EFS or OS.

Conclusion Although significant differences in HRQOL were observed between countries, outcomes were similar, and HRQOL measures were not associated with prognosis.

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INTRODUCTION

Osteosarcoma is the most common primary bone malignancy of children and adolescents; its age-adjusted incidence is 4.4 per million.[1] Survival rates for nonmetastatic osteosarcoma of the extremity have improved with the advent of multimodal therapy that includes aggressive surgery and chemotherapy.[2-4] This advancement has facilitated the study of health-related quality of life (HRQOL) outcomes, which provide greater comprehension of the physical, psychological, and social implications of disease- and treatment-related sequelae. Patients with osteosarcoma are at risk for numerous complications of care, including significant nausea from platinum-based chemotherapy, pain related to both disease and surgery, and debilitation of physical performance related to tumor location, subsequent surgical resection, and extended recovery and rehabilitation. Better understanding of HRQOL outcomes may identify opportunities to improve treatment-related morbidities, facilitate decision making, establish effective communication strategies, and improve satisfaction with care for patients and their families.[5,6]

We have previously reported results of a multi-institutional clinical trial for the management nonmetastatic osteosarcoma in newly diagnosed

patients.[4] HRQOL was measured at diagnosis and at several time points during and after therapy[7]; most domain results improved over time during treatment, and there was good agreement between patient and parent reports.[8] The study was conducted at two pediatric cancer centers in the United States and at one center in Chile as part of international collaborative efforts to provide care to patients in developing countries.

Given potential differences in available resources and delivery of care between countries, we hypothesized that HRQOL outcomes would differ between sites. In addition, HRQOL outcomes have had demonstrated prognostic significance for survival in adult patients with cancer.[9,10] However, the impact of HRQOL on survival outcomes for pediatric patients with cancer has not been well studied. Therefore, this study aimed to compare patient- and parent-reported HRQOL outcomes between two countries (United States and Chile) with potential disparities in supportive care measures and to evaluate the association of HRQOL outcomes with event-free survival (EFS) and overall survival (OS).

MATERIALS AND METHODS

Protocol Treatment

Patients with newly diagnosed nonmetastatic osteosarcoma were treated on a prospective clinical protocol (OS99; NCT00145639) that included 12 cycles of chemotherapy (composed of doublets of carboplatin, ifosfamide, and doxorubicin) administered every 3 weeks with hematopoietic growth factor support for a total of 35 weeks.[4] After four cycles of neoadjuvant chemotherapy, surgery for local control was completed at each institution by limb-sparing procedure or amputation and was followed by eight additional cycles of chemotherapy. Central pathology review was performed at St Jude Children's Research Hospital; imaging studies were centrally reviewed for selected patient cases. The study was approved by the institutional review board of all participating institutions (ie, St Jude Children's Research Hospital, Memphis, TN; Washington University, St Louis, MO; and Luis Calvo McKenna Hospital, Santiago, Chile). Patients received treatments in an outpatient infusion center or an inpatient setting; 65% of treatments were administered in outpatient settings. Supportive care guidelines were included in the study protocol to be followed by each institution.

Study Design and Instruments

Patient and parent reports were solicited during face-to-face interviews at four time points: diagnosis (before or during cycle 1 of chemotherapy), week 12 (before definitive surgery), week 23 (following cycle 8 of chemotherapy), and after the completion of therapy (a median of 20 weeks after the last chemotherapy cycle). Patients age 5 years or older who spoke English or Spanish and had parental permission were eligible to participate in HRQOL studies. Patients and parents completed the PedsQL Inventory v. 4.0 and the PedsQL Cancer Module v. 3.0. Patients age 8 years or older also completed the Symptom Distress Scale (SDS). For US patients younger than 8 years, instruments were administered verbally by a research associate; patients age 8 years and older and all parents completed instruments independently. Chilean patients and parents completed Spanish language versions of each instrument; all questionnaires in Chile were administered verbally by a study psychologist who was bilingual in English and Spanish.

The PedsQL Inventory v. 4.0 is a 23-item generic instrument that measures domains of physical, emotional, social, and school functioning that have been experienced during the past 30 days. Age-specific (ie, 5 to 7 years, 8 to 12 years, and $\geq$ 13 years) forms are available for patient reports, and they have accompanying parent forms. Responses for patients age 5 to 7 years are scored using a three-point Likert-type scale, whereas the scoring format for patients age 8 years or older uses a five-point Likert-type scale. Item ratings are reverse coded and linearly transformed so that higher scores indicate better HRQOL.[11,12] This instrument has acceptable internal consistency, known groups, and construct-validity estimates when used with pediatric samples that include well, acutely ill, or chronically ill children.[12-15] Cronbach α values for patient reports at baseline ranged from 0.45 (social functioning) to 0.88 (physical functioning), and those for parent reports ranged from 0.58 (social functioning) to 0.90 (physical functioning). Because of unacceptably low Cronbach α values (< 0.70) for the social functioning domain of patient and parent reports at all four data time points, this domain was excluded from analysis.

The PedsQL Cancer Module v. 3.0 is a 27-item instrument that measures domains of pain and hurt, nausea, cognition, procedural anxiety, treatment anxiety, worry, perceived physical appearance, and communication. This instrument also has satisfactory internal consistency, known groups, and construct-validity estimates.[16] Item formats and scores are similar to those in the PedsQL Inventory v. 4.0. Cronbach α values for

patient reports at baseline ranged from 0.45 (perceived physical appearance) to 0.90 (procedural anxiety), and those for parent reports ranged from 0.65 (perceived physical appearance) to 0.98 (procedural anxiety). Because of unacceptably low Cronbach α values for patient reports of physical appearance across all four data time points, this domain was excluded from analysis.

The SDS measures intensity (single item) and distress (summed items) of 10 cancer-related symptoms on a five-point Likert-type scale. Internal consistency, face validity and content, and construct validity of the SDS have been established for use in pediatric patients with cancer.[17,18] The internal consistency estimate at baseline for this study was 0.79 and ranged from 0.66 to 0.73 at other data points.

Statistical Methods

Domain scores for the PedsQL instruments were calculated for both patient and parent reports at each time point with the standard approach specified by the instrument developers, in which higher scores indicated better HRQOL.[11,12] Because of exclusion of the social functioning domain from analysis, total and psychosocial health scores for the PedsQL Inventory v. 4.0 could not be calculated. The total SDS score was calculated as the sum of the item scores answered divided by the number of items answered, multiplied by 10 to

Table 1. Clinical and Treatment Characteristics of Patients Treated During Participation in OS99 HR-QOL Studies

Characteristic	No. (%) of Patients			*P*
	Overall (N = 66)	From United States (n = 44 [67%])	From Chile (n = 22 [33%])	
Age, years (median [range])	13.4 (5-23)	13.4 (5.8-23)	13.7 (5-16.9)	.38
Age group, years				
5-7	6 (9)	3 (7)	3 (14)	.68
8-12	21 (32)	15 (34)	6 (27)	
⩾ 13	39 (59)	26 (59)	13 (59)	
Sex				
Male	36 (55)	22 (50)	14 (64)	.43
Female	30 (45)	22 (50)	8 (36)	
Ethnicity				
White	28 (42)	28 (64)	—	< .001
Black	11 (17)	11 (25)	—	
Hispanic	27 (41)	5 (11)	22 (100)	
Primary site				
Femur	43 (65)	30 (68)	13 (59)	.62
Tibia	16 (24)	9 (20)	7 (32)	
Fibula	2 (3)	1 (2)	1 (5)	
Humerus	2 (3)	2 (5)	—	
Ulna	1 (2)	1 (2)	—	
Rib	1 (2)	1 (2)	—	
Mandible	1 (2)	—	1 (5)	
Limb-salvage surgery in 64 extremity tumors	53 (83)	38 (88)	15 (71)	.155
Histologic response in 61 patients*				
< 90% tumor necrosis	20 (33)	16 (39)	4 (20)	.26†
⩾ 90% tumor necrosis	37 (61)	23 (56)	14 (70)	
PD prior to surgery	3 (5)	2 (5)	1 (5)	
Death prior to surgery	1 (2)	—	1 (5)	

Abbreviations: HR-QOL, health-related quality of life; PD, progressive disease.

*Five patients had delayed surgery beyond the time stipulated by protocol (greater than four cycles of preoperative chemotherapy).

†Comparison of good histologic response (⩾ 90% tumor necrosis) with poor histologic response (< 90% tumor necrosis or PD before surgery).

maintain the score range of 10 to 50. For individual items, scores of 3 or higher were classified as meriting clinical intervention.[18]

Comparison of age distributions between US and Chilean patients was performed with the exact Wilcoxon rank sum test (as a continuous variable) and the exact Kruskal-Wallis test (as a categoric variable). Distributions of sex, surgery type, and histologic response to preoperative chemotherapy by country of enrollment were evaluated with the Fisher exact test. Repeated measures models were used to investigate the effect of country of enrollment on PedsQL Inventory v. 4.0 and PedsQL v. 3.0 domain scores as well as on the SDS total score. Models were fit separately for patients and parents; models included terms for site and time as well as an interaction term when a significant interaction between site and time was observed. The log-rank test was used to examine the impact of country of enrollment on EFS and OS. Cox proportional hazards regression models were used to examine baseline HRQOL instrument scores for the total cohort of patients and parents as predictors of EFS and OS.

RESULTS

Patient Characteristics

Seventy-one of the 72 patients enrolled on the OS99 trial were eligible to participate in HRQOL studies. Sixty-six patients (93%) and 67 parents (94%) completed one to three of the HRQOL instruments at one to four of the prespecified time points during the study period (Data Supplement). Total group comparisons for all instruments were previously reported.[8] All Chilean patients, compared with 90% of US patients, participated in the HRQOL studies ($P = .32$). Clinical and treatment characteristics were similar between countries except that ethnicity differed as expected, because the two countries had different population compositions (Table 1). The median age was 13.4 years (range, 5 to 23 years). There were no significant differences between the US and Chilean populations for rates of limb-sparing procedures for extremity tumors or histologic response to preoperative chemotherapy.

PedsQL Inventory 4.0

Scores for patients and parents on the PedsQL Inventory 4.0 are listed in Table 2. Significant

Table 2. Estimated Mean Domain Values for Responses in the United States and Chile on PedsQL 4.0 at All Time Points

Response by Topic and Country	Mean (SE) Value				*P*		
	Diagnosis	Week 12	Week 23	After Therapy	Study Site	Time	Study Site–Time
Patient self report							
Physical functioning							
US	48 (4)	52 (4)	57 (4)	69 (4)	.0303	< .001	NS
Chile	33 (5)	48 (5)	42 (5)	63 (5)			
Emotional functioning							
US	60 (3)	70 (4)	72 (4)	78 (4)	.0271	< .001	NS
Chile	48 (4)	59 (4)	64 (4)	69 (4)			
School functioning							
US	70 (3)	75 (4)	75 (3)	76 (3)	< .001	.0083	.0347
Chile	51 (4)	49 (6)	43 (6)	67 (5)			
Parental proxy report							
Physical functioning							
US	53 (3)	49 (4)	43 (4)	57 (4)	.4575	< .001	.0032
Chile	32 (6)	53 (6)	44 (6)	60 (6)			
Emotional functioning							
US	56 (3)	64 (4)	63 (4)	72 (4)	.0087	< .001	NS
Chile	44 (5)	44 (5)	62 (5)	60 (5)			
School functioning							
US	72 (4)	70 (5)	66 (4)	72 (4)	< .001	.059	NS
Chile	50 (5)	55 (6)	37 (7)	65 (6)			

NOTE. Higher scores indicate better HR-QOL.
Abbreviations: HR-QOL, health-related quality of life; NS, no significant interaction observed.

Table 3. Estimated Mean Domain Values for Responses in United States and Chile on PedsQL 3.0 at All Time Points

Response by Topic and Country	Mean (SE) Value				*P*		
	Diagnosis	Week 12	Week 23	After Therapy	Study Site	Time	Study Site–Time
Patient self report							
Pain and hurt							
US	56 (4)	78 (4)	74 (4)	68 (4)	.7813	< .001	NS
Chile	49 (5)	78 (5)	76 (5)	81 (5)			
Nausea							
US	67 (3)	55 (3)	49 (3)	78 (4)	.0066	< .001	.0071
Chile	51 (6)	31 (6)	42 (6)	81 (6)			
Procedural anxiety							
US	57 (5)	72 (5)	71 (5)	77 (5)	.2940	< .001	NS
Chile	67 (6)	73 (7)	80 (7)	85 (7)			
Treatment anxiety							
US	73 (4)	84 (4)	88 (4)	87 (4)	.4405	< .001	NS
Chile	70 (4)	91 (5)	91 (5)	94 (5)			
Worry							
US	56 (4)	65 (4)	72 (4)	74 (4)	< .001	< .001	NS
Chile	25 (6)	22 (7)	38 (7)	50 (7)			
Cognitive problems							
US	79 (3)	79 (3)	81 (3)	80 (3)	.0511	.8769	NS
Chile	71 (4)	72 (4)	72 (4)	76 (4)			
Communications							
US	71 (3)	79 (4)	82 (4)	85 (4)	.3250	.0064	NS
Chile	71 (6)	71 (6)	79 (6)	76 (6)			
Parental proxy report							
Pain and hurt							
US	50 (4)	81 (5)	60 (4)	65 (4)	.4722	< .001	NS
Chile	42 (6)	69 (6)	65 (6)	68 (6)			
Nausea							
US	67 (4)	49 (4)	45 (4)	81 (4)	.0012	< .001	NS
Chile	44 (7)	29 (7)	33 (7)	77 (7)			
Procedural anxiety							
US	54 (4)	71 (5)	73 (5)	80 (5)	.8391	< .001	NS
Chile	66 (7)	59 (7)	76 (7)	82 (7)			
Treatment anxiety							
US	64 (4)	72 (4)	76 (4)	80 (4)	.2731	.0006	NS
Chile	56 (7)	66 (7)	66 (7)	82 (8)			
Worry							
US	57 (4)	62 (4)	66 (4)	76 (4)	< .001	< .001	.0034
Chile	19 (6)	30 (6)	55 (6)	55 (6)			
Cognitive problems							
US	68 (4)	74 (4)	78 (4)	76 (4)	.3413	.1001	NS
Chile	66 (5)	70 (5)	70 (6)	71 (6)			

(Continued on following page)

Table 3. Estimated Mean Domain Values for Responses in United States and Chile on PedsQL 3.0 at All Time Points (Continued)

Response by Topic and Country	Mean (SE) Value				*P*		
	Diagnosis	Week 12	Week 23	After Therapy	Study Site	Time	Study Site–Time
Physical appearance							
US	73 (4)	69 (4)	70 (4)	78 (4)	.0462	.1631	NS
Chile	57 (5)	62 (6)	68 (8)	67 (6)			
Communications							
US	62 (4)	73 (5)	74 (4)	77 (5)	.1051	.2863	NS
Chile	65 (7)	58 (7)	64 (7)	60 (8)			

NOTE. Higher scores indicate better HR-QOL.
Abbreviations: HR-QOL, health-related quality of life; NS, no significant interaction observed; SE, standard error.

differences in physical, emotional, and school functioning were observed between the United States and Chile; scores also improved overall across time points for physical and emotional functioning. Score differences in each domain between countries were independent of changes in ratings over time. Parent reports demonstrated significant differences between countries for emotional functioning, but an interaction was observed between sites over time. Chilean parents reported poorer physical functioning at diagnosis, but values at later time points were similar to US scores. Parent reports of emotional functioning were poorer in Chile, but both sites observed improvement over time. Although Chilean patients and parents consistently reported lower scores for school functioning at diagnosis and throughout therapy, mean scores significantly improved after completion of treatment.

PedsQL Cancer Module v. 3.0

Table 3 demonstrates estimated mean domain scores for patients and parents on the PedsQL Cancer Module v. 3.0 and associated *P* values. Significant differences between the two countries were observed for nausea and worry. Although patients in Chile reported worse nausea at diagnosis and week 12, values significantly improved and were similar to US patient scores after surgery. US patient reports of worry were better than those of Chilean patients throughout treatment. Parent scores also reflected differences in perceptions of nausea and worry and in perceived physical appearance. Although US parents reported less perceived worry overall, scores for Chilean parents improved dramatically from diagnosis to completion of therapy. Parent nausea scores in Chile were worse overall than those in the United States, but scores in both countries improved after surgery; a significant interaction was not observed.

SDS

Mean total SDS scores were not significantly different between US and Chilean patients ($P = .170$). In both countries, total symptom distress and the number of symptoms that merited clinical intervention improved with time ($P < .001$; Data Supplement). There was no statistical difference between US and Chilean patients in the number of symptoms that merited clinical intervention ($P = .30$), although the mean number of symptoms that required intervention in Chile was slightly higher at week 12 (2.3 *v* 1.8), at week 23 (2.7 *v* 2.0), and after therapy (1.4 *v* 1.0; Data Supplement).

HRQOL and Outcomes

The mean (± standard error) 5-year EFS and OS rates were 65.0% (± 7.5%) and 78.4% (± 6.8%), respectively; patient outcome did not differ by the country of enrollment. The mean (± standard error) 5-year EFS rate was 65.5% (± 8.0%) for patients treated in the United States and was 61.5% (± 19.1%) for patients treated in Chile ($P = .98$; Fig 1). The mean (standard error) 5-year

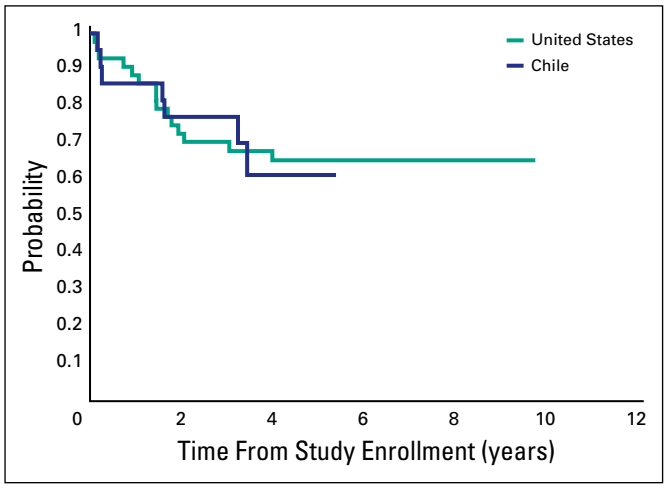

Fig 1. Event-free survival over time, demonstrated as a Kaplan-Meier curve for patients by country (United States *v* Chile).

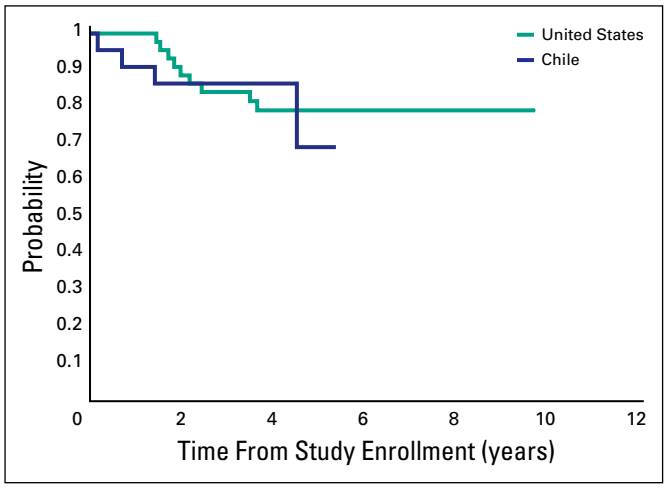

Fig 2. Overall survival over time, demonstrated as a Kaplan-Meier curve for patients by country (United States *v* Chile).

OS was 79.1% (± 7.1%) for US patients and was 69.1% (± 19.2%) for Chilean patients ($P = .83$; Fig 2).

Individual domains for patients and parents on the PedsQL modules, SDS total score, and number of distress items at baseline were evaluated for associations with EFS and OS for all eligible patients (Table 4). Parent reports of perceived physical appearance were statistically associated with OS (hazard ratio, 0.976; $P = .0258$); however, given that results were not adjusted for multiple comparisons and that the hazard ratio value was nearly 1, this finding was likely not clinically significant. None of the other evaluated scores predicted EFS or OS.

DISCUSSION

Previous studies of quality of life in patients with bone tumors evaluated physical function changes[19,20]; differences between amputation and limb-sparing surgery[21]; and long-term survivorship issues that included educational attainment, marital status, and employment.[22] This study presented a unique opportunity to compare HRQOL scores reported by pediatric patients treated prospectively on the same protocol in two countries of different resources, and to our knowledge, this study is the first to evaluate the prognostic significance of HRQOL in a pediatric cancer population. Although the importance of HRQOL measures are well established for children and adolescents with cancer, their implementation has focused historically on long-term survivors and extended effects of therapy. More recently, HRQOL has been evaluated prospectively for pediatric brain tumors in patients who underwent proton radiotherapy,[23] and HRQOL-based objectives have been embedded in longitudinal collaborative studies of standard-risk acute lymphoblastic leukemia.[24] To date, however, no reports have assessed the prognostic value of HRQOL measures for survival of patients with pediatric cancer.

Assessments of HRQOL in adult studies have served as a complement to classic measures, have provided insight about disease burden and treatment efficacy, and may have affected clinical decision making. Numerous studies have shown that aspects of baseline HRQOL, independent of clinical variables, are prognostic in adult cancers. A meta-analysis of 30 randomized controlled trials from the European Organization for Research and Treatment of Cancer showed that physical functioning, pain, and appetite loss increased the predictive accuracy of prognosis of OS when included in multivariable models with sociodemographic and clinical characteristics.[9] When considered by tumor site, at least one HRQOL domain provided additive prognostic information for survival.[10] Although scant data exist specifically for sarcomas, HRQOL measures were included in the Pazopanib Explored in Soft-Tissue Sarcoma (PALETTE) study, a randomized phase III trial of pazopanib versus placebo for adults with progressive soft tissue sarcoma. No differences were observed between treatment arms, but general health status for the entire cohort was associated with OS.[25] Our results did not reveal an association of HRQOL with survival in children and adolescents with osteosarcoma. We hypothesize that analysis of a cohort with only localized disease and relatively favorable outcomes may have decreased the likelihood of demonstrated associations of HRQOL and survival. Previous adult studies have shown no association between HRQOL and survival in early-stage melanoma or breast cancer, but strong correlations have been observed in patients with advanced, metastatic disease.[26-28] Given the prevalence of adult studies that demonstrate positive correlations of HRQOL measures with advanced disease, additional studies of HRQOL in pediatric patients with high-risk tumors are warranted to better define the value of HRQOL as a predictive measure.

Several differences in HRQOL outcomes were demonstrated between patients treated in the United States and those treated in Chile. As previously reported, several domains, including physical and emotional functioning, demonstrated improvement over time for both the US and Chilean patients.[8] Although school functioning scores were significantly lower in Chile throughout therapy, drastic improvement was observed after

Table 4. Results of Models to Examine HR-QOL and Symptom Distress As Predictors of EFS and OS for All Eligible Patients

Instrument and Variable	*P*	
	EFS	OS
PedsQL Inventory v. 4.0 (patient report)		
Physical functioning	.6547	.6944
Emotional functioning	.2024	.6511
School functioning	.8033	.8311
PedsQL Inventory v. 4.0 (parent report)		
Physical functioning	.6654	.1690
Emotional functioning	.1155	.8277
School functioning	.2489	.6994
PedsQL Cancer Module v. 3.0 (patient report)		
Pain and hurt	.8184	.8348
Nausea	.6474	.7119
Procedural anxiety	.1898	.7553
Treatment anxiety	.9303	.8274
Worry	.5339	.6169
Cognitive problems	.5224	.5898
Communication	.2549	.9312
PedsQL Cancer Module v. 3.0 (parent report)		
Pain and hurt	.7004	.9499
Nausea	.6990	.9691
Procedural anxiety	.2111	.4352
Treatment anxiety	.4107	.3840
Worry	.7679	.2590
Cognitive problems	.1919	.2121
Physical appearance	.5306	.0258*
Communication	.2493	.6424
Symptom Distress Scale		
Total score	.4674	.6170
No. of distress items	.7009	.7572

Abbreviations: EFS, event-free survival; HR-QOL, health-related quality of life; OS, overall survival.
*Associated hazard ratio, 0.976 and 95% CI, 0.955 to 0.997.

completion of therapy. In addition, the findings in this study demonstrated no differences in survival outcomes between patients treated in the United States and in Chile. Some observed differences of HRQOL domain scores may be attributed to access to specialized care. Patients and parents in Chile may have experienced decreased ancillary support, because hospital-based programs for social, educational, and psychological support were in early stages of development and implementation during the study treatment period. Differences in availability of school services during therapy also may explain a significant contrast in scores for school functioning between countries; as patients in Chile returned home after completion of treatment and resumed normal social/school routines, school functioning domain scores improved and approached US levels. Discrepancies in nausea scores are more difficult to explain, because the protocol included supportive care guidelines; antiemetic administration data were not available, which prevented additional analysis. Differences between countries were observed in both patient and parent reports for nausea, worry, and emotional functioning domains, so these results may be related to differences in socioeconomic and educational backgrounds of patients and families, which would influence the responses to diagnosis and the expectations of symptoms and prognosis. Proximity to care was not felt to contribute to reporting differences, because patients in both countries who resided long distances from the treating hospital were provided local domiciliary housing with ready access to supportive care services. Despite differences in HRQOL, survival outcomes between countries were similar and continued to demonstrate the success of a twinning strategy used to improve patient outcomes in developing countries.[29] This largely is due to the robust efforts of the Chilean national cooperative pediatric oncology organization, PINDA (National Pediatric Program for Antineoplastic Agents).

Some limitations of this study must be considered. At the time of study, Spanish versions of the instruments had not been validated for Chile; all questionnaires in Chile were administered by a psychologist who was bilingual in English and Spanish. Validated instruments are in use now for national Chilean protocols. We could not evaluate social functioning, which has shown a correlation with survival in some adult tumors.[30,31] In addition, because of the small sizes of the subgroups, we could not examine interactions between study sites and patient age or sex. HRQOL studies can suffer from multicolinearity, given the number of individual variables within testing batteries that are implemented in models. The data in this study were not adjusted for multiple comparisons, but only one variable (parental perception of physical appearance) demonstrated significance in regression modeling. The minimal change in hazard ratio was not likely to yield clinical significance for our population. This study experienced attrition of participation in HRQOL studies among the US cohort; the majority of these patients experienced progression of disease and left the study before all of the timed evaluations were completed. Results of some prior studies

have suggested that the use of parent proxy reports can overestimate impairment of the patient.[32-34] However, for the majority of domains evaluated within this analysis, agreement of patient and parent reports was observed, which is consistent with a previous publication.[8] Like many HRQOL instruments, those used in this study have not been modeled to determine minimally important differences that estimate the clinical significance of findings. Future HRQOL studies will use instruments, such as the PROMIS measures, that include modeling for minimally important differences.[35]

In summary, significant differences in HRQOL outcomes were observed between patients with osteosarcoma treated on an international clinical trial in the United States and Chile, but HRQOL and the site of treatment did not affect survival outcomes. These findings highlight the ability to achieve equivalent survival outcomes in developing countries through international partnership, and they support the implementation of expanded ancillary services for medical care, psychosocial interventions, and educational services for patients and families to improve HRQOL outcomes for patients with cancer who are treated in developing countries.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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