

Quality-of-life evaluations in children and adolescents with Ewing sarcoma treated with pencil-beam-scanning proton therapy

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Abstract

Background: With improved survival rates for children with cancer, quality-of-life (QoL) issues have increasingly become the focus of attention. We report the QoL of children with Ewing sarcoma (EWS) treated with pencil-beam-scanning proton therapy (PT).

Methods: A PEDQOL (QoL questionnaire for children 4–18 years) self/proxy questionnaire was used to prospectively assess the QoL of 23 children <18 years with EWS treated with PT. This questionnaire evaluates eight different domains. Children (self-rating) and parents (proxy-rating) filled out the questionnaire at the start of PT (E1), 2 months after treatment (E2), and thereafter once yearly (E_{≥3}).

Results: Compared with healthy controls, parents rated the QoL of their children at E1 significantly worse in all but two (cognition and social functioning-*family*) domains. At E4, significant differences between the two groups only remained in three of eight domains. At E1, children self-rated their QoL significantly worse in the domain Physical functioning ($p = .004$) and significantly better in the domain Body image ($p = .044$) compared to healthy controls, whereas no significant differences were observed at E4. For the longitudinal comparison E1 versus E4, according to parents, Emotional functioning, Cognition and Social functioning-*peers* were slightly decreased 2 years after PT. The children rated Emotional functioning and Body image poorly 2 years after PT.

Conclusions: Children with EWS usually recovered seemingly well to normal QoL levels 2 years after the end of PT. They tended to rate their QoL substantially higher

Abbreviations: E1, evaluation before PT; E2, evaluation 2 months after PT; E3, evaluation 1 year after PT; E4, evaluation 2 years after PT; E5, evaluation 3 years after PT; E6, evaluation 4 years after PT; EWS, Ewing sarcoma; Fam, QoL domain, social functioning-*family*; Fr, QoL domain, social functioning-*peers*; Global, QoL domain, subjective well-being; HUI, Health Utilities Index; ICC, intra-class correlations; KB, QoL domain, body image; KV, QoL domain, physical functioning; N, normative group; OS, overall survival; PEDQOL, QoL questionnaire for children 4–18 years; PedsQL, QoL questionnaire for children <4 years; PSI, Paul Scherrer Institute; PT, proton therapy; QoL, quality of life; SE, QoL domain, autonomy.

Damien C. Weber and Jürgen Beer contributed equally to this work.

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than their parents. However, in the longitudinal analysis at 2 years, children rated their Emotional functioning and Body image scores poorly.

KEYWORDS

children, Ewing sarcoma, proton therapy, proxy- and self-assessment, quality of life, teenagers

1 | INTRODUCTION

Ewing sarcoma (EWS) is the second most common malignant pediatric bone tumor with a peak incidence in adolescence.¹ The incidence of EWS has been stable over decades with an average of 2.93 cases/1,000,000 according to the United States population-based cancer registry Surveillance, Epidemiology, and End Results database.² The continuous refinement of the general treatment approach for patients with EWS substantially increased their survival since 1970. The current multimodal treatment strategy consists of risk-adapted multiagent induction and consolidation chemotherapy with sequential local therapy (surgery and/or radiotherapy), resulting in a 5-year overall survival (OS) for patients with localized disease of 65%–75%.³ The outcome for patients with metastatic disease at diagnosis remains however poor, with the 5-year OS of approximately 30%. Noteworthy, as roughly three-fourths of all EWS patients present with localized disease at diagnosis,¹ most EWS patients today will be long-time survivors. With these changes in survival trends, treatment-related late effects of this growing group of long-term survivors of EWS patients have increasingly become the focus of attention.

The excess mortality and morbidity of long-term survivors of childhood EWS have been well documented.^{4,5} More recently also, the psychosocial late effects of EWS survivors including quality-of-life (QoL) issues were emphasized.^{6–8} Although QoL data are of growing importance for clinical decision-making and guidance for treatment of EWS patients, information concerning QoL in EWS survivors is still limited and highly heterogeneous, complicating robust interpretation of this important metric.⁸ Radiotherapy is one of the main drivers of late treatment-related effects in survivors of childhood cancer.⁹ In this context, newer developments in radiation technology, such as intensity-modulated (photon) radiotherapy or proton therapy (PT), with the characteristic of a more conformal radiation dose distribution and therefore a better sparing of normal tissues, may have the potential to reduce radiation-induced toxicity as recently reviewed by Frisch and Timmermann for the case of PT in the treatment of sarcomas.¹⁰ Reliable QoL data for such modern radiotherapy techniques are particularly sparse.

We report prospectively generated, longitudinal QoL data for pediatric EWS patients treated with PT at a single institution as part of their multimodality treatment. To the best of our knowledge, this is the first report of QoL outcomes for EWS patients treated with pencil-beam-scanning PT only. The clinical results for this cohort of EWS patients have been recently published by our group.¹¹

2 | METHODS

2.1 | Study design and study population

Forty-two pediatric patients with histologically confirmed EWS were treated with PT at Paul Scherrer Institute (PSI) between 2005 and 2016. Noteworthy, PSI does not treat children and adults with conventional photon radiotherapy. As such, no photon control arm could be provided for this QoL/PT analysis. Among them, 78.6% (33/42) were ≤ 18 years and thus eligible (median age: 7 years; range: 1–17 years) for QoL assessment and could participate in terms of questionnaire availability. The nine excluded patients were young adults or adults with age range of 22–66 years. The study flowchart is detailed in the [Supporting Material](#). All these former patients participated in a prospective study on QoL, which is still running since 2005 as joint project with the University of Münster/Bonn. This project was approved by the competent ethics committee (EKNZ 2014–244). The applied tool for the QoL assessment (PEDQOL questionnaire [QoL questionnaire for children 4–18 years]) is available for children aged 5–18 years. Therefore, we excluded 10 patients with PedsQL evaluation being ≤ 4 years of age, leaving a total study population of 23 children with EWS (median age: 10.2 years; Table 1), all of whom were included in the present statistical analysis. Patient characteristics are described in Table 1. The most common primary tumor sites were axial or pelvic ($n = 16$, 70%), and the specific distribution for anatomical sites was as follows: spine, $n = 7$; pelvis-sacrum, $n = 7$; paranasal sinus/nasal cavity, $n = 4$; skull, $n = 3$; lower limb, $n = 1$; skull base, $n = 1$. Few patients presented with tumors > 8 cm in size ($n = 4$, 22%). Four patients (17%) presented with metastases at diagnosis (lung: $n = 3$; lung and bone: $n = 1$).

2.2 | Treatment

The delivery of PT has been previously described.¹¹ For the 23 patients of our cohort, the median delivered radiation dose was 55.8 Gy (RBE) (range 45–69.6). No patient had received photon radiotherapy, either prior or sequentially to PT. Surgery was performed in almost half of the patients ($n = 11$, 48%) (Table 1). All patients received multiagent chemotherapy prior to PT according to the Euro-E.W.I.N.G 99 ($n = 10$), EWING 2008 ($n = 11$), or Cooperative Weichteilsarkom Study Group (CWS) SoTiSar ($n = 1$) protocol, and only one patient (4.3%) was treated outside the framework of the study protocol with VIDE chemotherapy.

TABLE 1 Patient characteristics of 23 patients with Ewing sarcoma (EWS) who were assessed for quality of life

Characteristic	N (%)
Gender	
Female	10 (43%)
Male	13 (57%)
Median age (years) [range]	10.2 [4.8–17.7]
Histological proven EWS	23 (100%)
t(11;22) Chromosomal translocation	
Present	18 (79%)
Absent	1 (4%)
Not reported	4 (17%)
Primary site	
Axial/pelvic	16 (70%)
Other (non-axial/pelvic)	7 (30%)
Skeletal EWS	13 (57%)
Extraskelatal EWS	10 (43%)
Median initial tumor size (cm) [range]	5.9 [1.7–15]
Size ≤8 cm	18 (78%)
Size >8 cm	5 (22%)
Local management	
Surgery, chemotherapy, and proton therapy (PT)	11 (48%)
Biopsy, chemotherapy, and PT	12 (52%)

Four patients (17.4%) received anesthesia for the treatment simulation and PT delivery.

2.3 | Assessment of QoL

The PEDQOL questionnaire, an established, multidimensional, validated instrument for children aged 5–18 years, was used to assess QoL.¹² This instrument comprises 49 age-adapted items related to the following eight domains: autonomy, emotional functioning, body image, cognition, physical functioning, social functioning peer, social functioning family, and subjective well-being. The questionnaire is available in a proxy- and self-rating version and captures the subjective QoL of the diseased children, evaluated by the parent or guardian (proxy-rating) or by the children themselves (self-rating). As a reference time frame for the rating, the user of the questionnaire is asked to consider the last week. The rating-instrument is constructed according to a Likert scale with four answer options per item (never, rarely, often, and always). Summary scores for each domain are calculated based on the individual answers per item. Higher scores suggest better QoL, with 100 representing the maximum score per domain. To include patients with various nationalities, the instrument was used in different languages (German, French, Dutch, English, and Italian). The participation in this study is proposed to parents and their children during the first consultation at PSI. At this consultation, the details of the proton treat-

ment are also explained to the families. The purpose and details of this QoL study was also discussed with families. After obtaining the written informed consent for the study, the parents and their child are requested to complete a baseline questionnaire prior to the start of PT (E1). After the end of PT, parents and their child are prospectively followed by postal mail through our Study and Research Office at PSI. Two months after PT (E2) and thereafter once yearly (E₃) until the child turns 18 years of age, two questionnaires (self and proxy) are sent out together with a prepaid return envelope to increase the feedback rate. One reminder is done in writing or via telephone in case of nonresponse. The completed questionnaires are sent back to PSI. After removing the patient identification from the questionnaires in a pseudonymic anonymization process, they are transferred to the working group for QoL at the university hospital Münster/Bonn (under the leadership of Dr. G. Calaminus) for data management and statistical analyses. For comparison purposes, an independent norm group ($n = 233$) with proxy assessments of healthy children between 5 and 18 years of age was included in the analyses. Likewise, for the self-assessment comparison, an independent reference group ($n = 794$) with self-assessments of healthy children between 5 and 18 years of age was also included.

2.4 | Statistical analyses and norm group

Descriptive statistics were generated for patient characteristics in the whole group and in different subgroups. The reported norm values for the proxy ($n = 233$) and self ($n = 794$) assessments were collected from an independent sample of healthy children between 5 and 18 years from Germany. Differences between patient QoL and the norm group were evaluated using the nonparametric Mann–Whitney U test for independent samples. The Wilcoxon signed-rank test for dependent samples was used for assessments between time points. Statistical tests were based on a two-sided significance level of <5%. Statistical Package for the Social Science (SPSS, Version 22) was used for all analyses.

3 | RESULTS

In the [Supporting Materials](#), the provided [Table S1](#) describes the availability of self and proxy questionnaires at follow-up (FU) time points. For 30.43% (7/23) of patients, a long-term (i.e., 4 years after PT) QoL evaluation at time point E6 after PT was available. This [Table S1](#) shows a decreasing trend of participation with time, starting with $n = 20/23$ (86.7%) self-reports at time point 1 E1 and continuing with $n = 15/23$ (66.21%) at time point E2, and $n = 17/23$ (73.91%) and $n = 11/23$ (47.83%) at time points 3 and 4, respectively. The corresponding figures for proxy evaluation were 21/23 (91.3%) at time point 1 E1 and continuing with $n = 18/23$ (78.26%) at time point E2, and $n = 16/23$ (69.57%) and $n = 11/23$ (47.8%) at time points 3 and 4, respectively. Both for self- and proxy-report, the largest observed decline is between time point E3 and E4 (decline 26.11% and 18.77%, respectively).

For proxy-QoL evaluation, the median ages of the independent norm group ($n = 233$; $10.64 \text{ years} \pm 3.73$) and study cohort ($n = 21$; $10.81 \text{ years} \pm 3.56$) for E1 was not significantly different with a p -value of .84. The gender ratio was also not significantly different ($p = .08$), with the corresponding male/female ratio of 135/98 (1.40) and 13/8 (1.63), respectively. Table 2 details the QoL proxy scores-comparison E1–E6 of the study population versus the norm group. The QoL scores across the eight domains range from 69.2 (Autonomy) to 82.8 (Body image) in the norm group. At E1, these corresponding scores were substantially lower, ranging from 48.3 (Physical functioning) to 71.5 (Social functioning-*family*) for the study cohort. The E1 scores difference between the study cohort versus norm group for the Autonomy, Emotional functioning, Body image, Cognition, Physical functioning, Social functioning-*peers*, Social functioning-*family*, and General well-being domains were approximately 9, 7, 18, 6, 17, 13, 10, and 21 points, respectively. Significant differences between E1 and the norm group were found for the domains Autonomy ($p = .043$), Emotional functioning ($p = .028$), Body image ($p < .01$), Physical functioning ($p < .01$), Social functioning-*peers* ($p = .014$), and General well-being ($p < .01$). For Cognition ($p = .13$) and Social functioning-*family* ($p = .059$), the scores were however not significantly different.

Noteworthy, the scores increased substantially 2–3 years after PT (i.e., from E4 onwards) depending on the domains. The E4 score differences between the study group and normative cohort remained significant only for Body image ($p = .003$), Social functioning-*peers* ($p = .014$), and Social functioning-*family* ($p = .016$) domains. For Autonomy ($p = .403$), Emotional functioning ($p = .349$), Cognition ($p = .123$), Physical functioning ($p = .299$), and General well-being ($p = .162$) domains, these scores were however not significantly different.

At E6, these scores were distinctively higher, ranging from 62.5 (Physical functioning) to 79.2 (Emotional functional and Social functioning-*family*) and were mostly not significantly different from those of the norm group. Interestingly, the study cohort 4-year post PT proxy scores in three of eight (37.5%) domains were higher to those of the norm group (Table 2).

For self-QoL evaluation, the median ages of the independent norm group ($n = 794$; $12.17 \text{ years} \pm 3.17$) and study cohort ($n = 20$; $11.2 \text{ years} \pm 3.48$) for E1 were not significantly different with a p -value of .10. The gender ratio was also not significantly different ($p = .11$) with the corresponding male/female ratio of 363/429 (0.85) and 13/7 (1.9), respectively.

Table 3 details the QoL self scores-comparison E1–E6 of the study population versus the norm group. The QoL scores across the eight domains range from 59.9 (Physical functioning) to 76.7 (Emotional functioning) in the norm group. At E1, these corresponding scores ranged from 50.0 (Physical functioning) to 78.6 (Emotional functioning) for the study cohort. The E1 scores difference between the study cohort versus norm group for the Autonomy, Emotional functioning, Body image, Cognition, Physical functioning, Social functioning-*peers*, Social functioning-*family*, and General well-being domains were approximately 3, 2, 8, 5, 9, 2, 8, and 10 points, respectively. Significant differences between E1 and the norm group were only found for Body image (significantly better, $p = .044$) and for Physical functioning

TABLE 2 Comparison of PEDQOL (eight domains) scores (proxy) for the study group ($n = 21$) and norm group ($n = 233$) at the E1 (baseline) to E6 (4 years) time points

PEDQOL proxy	Autonomy n ; mean \pm SD	Emotional functioning n ; mean \pm SD	Body image n ; mean \pm SD	Cognition n ; mean \pm SD	Physical functioning n ; mean \pm SD	SocFunct-peers n ; mean \pm SD	SocFunct-family n ; mean \pm SD	Subjective well-being n ; mean \pm SD
PEDQOL norm	190; 69.21 \pm 13.94	232; 75.13 \pm 13.94	230; 82.83 \pm 16.80	230; 76.57 \pm 17.30	231; (65.19 \pm 8.91)	232; 79.78 \pm 13.83	232; 81.96 \pm 17.42	231; 81.02 \pm 17.84
EWING E1	16; 60.10 \pm 21.31	21; 68.12 \pm 13.08	19; 64.21 \pm 25.41	20; 70.92 \pm 15.82	20; 48.33 \pm 13.94	20; 66.00 \pm 23.12	20; 71.53 \pm 22.82	20; (60.00 \pm 25.59)
EWING E2	14; 64.12 \pm 19.25	18; 66.36 \pm 13.27	18; 61.85 \pm 20.36	18; 69.47 \pm 15.00	18; 45.37 \pm 12.53	18; 67.01 \pm 18.27	18; 72.22 \pm 19.50	16; (51.04 \pm 23.94)
EWING E3	14; 69.60 \pm 16.08	16; 73.26 \pm 14.86	16; 74.79 \pm 20.14	16; 67.57 \pm 15.79	16; 57.81 \pm 11.96	16; 69.17 \pm 22.43	16; 70.31 \pm 13.75	15; (71.11 \pm 20.38)
EWING E4	11; 72.32 \pm 17.46	11; 66.41 \pm 15.98	11; 71.51 \pm 15.22	11; 70.30 \pm 22.38	11; 57.58 \pm 11.46	11; 63.79 \pm 22.53	11; 72.47 \pm 21.53	10; (75.00 \pm 22.57)
EWING E5	7; 71.43 \pm 27.49	7; 73.81 \pm 22.27	7; 79.05 \pm 22.58	7; 82.86 \pm 15.80	7; 65.48 \pm 12.20	7; 80.95 \pm 22.58	7; 82.14 \pm 22.27	7; (73.81 \pm 25.20)
EWING E6	6; 72.22 \pm 18.92	6; 79.17 \pm 11.49	6; 68.89 \pm 19.17	6; 78.89 \pm 21.26	6; 62.50 \pm 8.74	6; 70.00 \pm 19.24	6; 79.17 \pm 18.82	6; (75.00 \pm 13.94)

Abbreviations: E1, evaluation before proton therapy (PT); E2, evaluation 2 months after PT; E3, evaluation 1 year after PT; E4, evaluation 2 years after PT; E5, evaluation 3 years after PT; E6, evaluation 4 years after PT; PEDQOL, quality-of-life questionnaire for children 4–18 years; SocFunct, social functioning.

TABLE 3 Comparison of PEDQOL (eight domains) scores (self) for the study group (n = 20) and norm group (n = 794) at the E1 (baseline) to E6 (4 years) time points

PEDQOL self	Autonomy		Emotional functioning		Body image		Cognition		Physical functioning		SocFunct-peers		SocFunct-family		Subjective well-being	
	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD	n; mean ± SD
PEDQOL norm	793; 63.99 ± 17.34	794; 76.70 ± 16.06	785; 67.77 ± 19.53	793; 68.79 ± 17.66	794; (59.86 ± 10.71)	791; 74.34 ± 17.88	791; 74.94 ± 19.08	789; 74.67 ± 13.74								
EWING E1	16; 66.04 ± 15.47	20; 78.61 ± 12.68	20; 75.67 ± 25.55	20; 73.77 ± 19.24	19; 50.00 ± 17.56	20; 76.33 ± 16.82	20; 66.38 ± 22.05	19; 64.91 ± 31.37								
EWING E2	15; 60.74 ± 18.60	15; 75.00 ± 10.91	15; 65.55 ± 26.47	15; 63.85 ± 16.66	15; 52.22 ± 15.25	15; 67.00 ± 20.00	15; 70.37 ± 21.22	15; 58.88 ± 28.77								
EWING E3	16; 71.18 ± 18.28	17; 80.39 ± 11.76	17; 77.25 ± 23.69	17; 67.45 ± 19.13	17; 62.74 ± 12.88	17; 76.96 ± 13.31	17; 74.01 ± 14.09	17; 76.47 ± 23.61								
EWING E4	11; 69.29 ± 16.19	11; 76.51 ± 13.34	11; 70.90 ± 18.20	11; 73.33 ± 21.49	11; 62.12 ± 13.62	11; 76.96 ± 13.78	11; 75.75 ± 19.16	11; 74.24 ± 23.99								
EWING E5	8; 70.14 ± 25.71	8; 73.96 ± 20.62	8; 76.67 ± 21.97	8; 82.50 ± 14.67	8; 64.58 ± 11.57	8; 80.00 ± 21.08	8; 81.25 ± 20.77	8; 70.83 ± 24.80								
EWING E6	7; 69.84 ± 19.47	7; 77.38 ± 11.50	7; 72.86 ± 22.15	7; 80.95 ± 12.43	7; 60.32 ± 10.60	7; 74.29 ± 16.97	7; 72.62 ± 24.87	7; 66.67 ± 23.57								

Abbreviations: E1, evaluation before proton therapy (PT); E2, evaluation 2 months after PT; E3, evaluation 1 year after PT; E4, evaluation 2 years after PT; E5, evaluation 3 years after PT; E6, evaluation 4 years after PT; PEDQOL, quality-of-life questionnaire for children 4–18 years; SocFunct, social functioning.

(significantly worse, $p = .004$; Figure 1). A trend toward significance was observed for Social functioning-family ($p = .08$; Figure 1). For all other domains, scores between the study cohort and the healthy controls were not significantly different (Figure 1) at the E1 time point. At E4, no significant differences were observed anymore for all domains between the study cohort and the healthy controls (Figure 1).

Due to the differences in compliance of QoL response before and 2 years after PT (i.e., E1 and E4), the following longitudinal comparison with patients with at least one time rating was performed using only descriptive statistics.

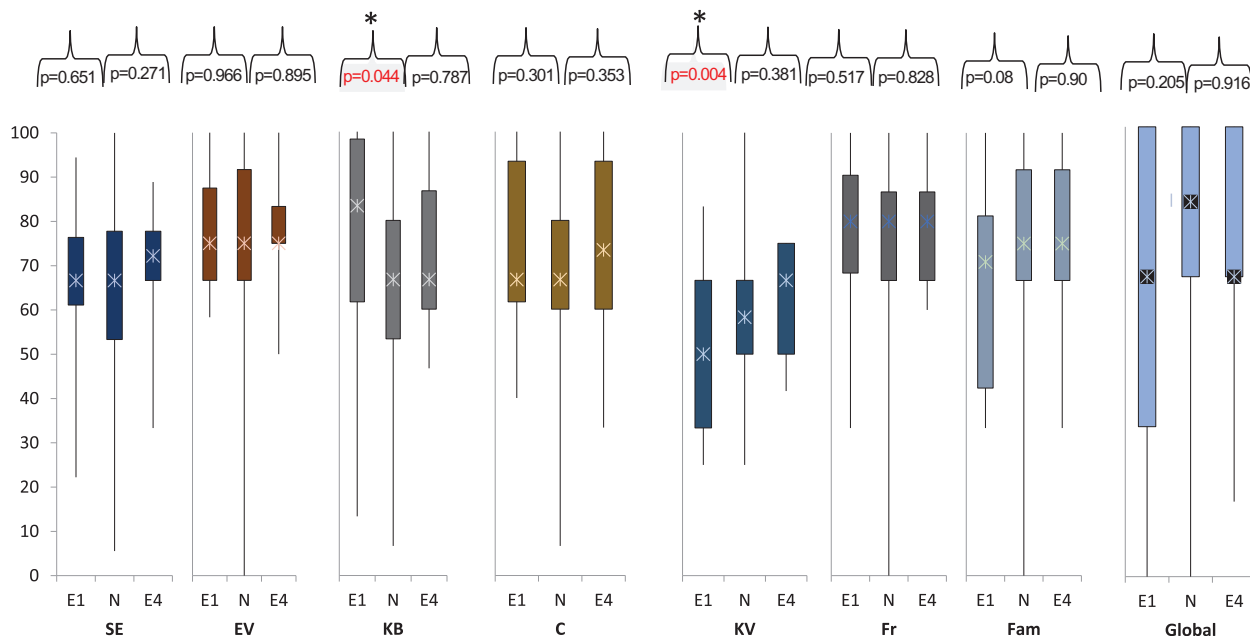
For proxy-QoL longitudinal evaluation, the median ages of the E1 ($n = 21$; 10.81 years \pm 3.56) and E4 ($n = 10$; 13.23 years \pm 2.45) cohorts were significantly different, with a p -value of $<.001$. The gender ratio was also significantly different ($p < .001$), with the corresponding male/female ratio of 13/8 (1.40) and 4/7 (0.57), respectively.

Table 4 details the longitudinal comparison of PEDQOL scores (proxy) for the E1 ($n = 21$) and E4 ($n = 11$) groups. For proxy evaluation, scores for five domains (Autonomy, Body image, Physical functioning, Social functioning-family, and Subjective well-being) were increased and three other domain (Emotional functioning, Cognition, Social functioning-peers) scores were decreased.

For self-evaluation, scores for four (Autonomy, Physical functioning, Social functioning-family, and Subjective well-being), two (Cognition and Social functioning-peers), and another two (Emotional functioning and Body image) domains increased, remained stable and decreased, respectively (Table 4).

4 | DISCUSSION

The aims of this study were to assess the QoL of EWS children and adolescents, when compared to a normative group, treated with PT and to explore the longitudinal evaluation of QoL after this treatment modality. We have observed that given time, QoL increased substantially after PT for EWS patients treated with chemo-radiation therapy. Noteworthy, children evaluated their QoL substantially higher than did their parents/legal guardian. They even rated Body image significantly better compared to the norm group at baseline (E1). Children rated only Physical functioning as significantly lower, when compared to the normative group at E1, with a trend toward significance for also lower QoL scores for the Social functioning-family (Figure 1), whereas parents/legal guardians rated QoL consistently lower at all time points and for all domains (Table 2). This finding is in contrast to data from Brazil. Rodrigues et al. reported on the health-related QoL of 45 adolescents (median age, 14 years) during cancer treatment, using the Health Utilities Index (HUI) for scoring.¹³ A high correlation among HUI was observed for patients and families after the onset of treatment and 4–6 months later. Interestingly, physicians in this study underestimated the health-related QoL of their patients. It is conceivable that agreement between self and proxy assessment is highest with proxy assessors who have a close daily contact (i.e., parents/caregivers) and probably decreases with restriction in day-to-day contacts (i.e., health-care providers). Using the aforementioned HUI utility scoring system



*Significant (Mann-Witney-U Test), Median

FIGURE 1 Self-evaluation quality-of-life scores study cohort versus healthy controls before (E1) and 2 years (E4) after proton therapy

(HUI3), Fu et al. report an improved intra-class correlations (ICC) for patients/parents (.43) than patients/physicians (.34).¹⁴ Similarly, Horsman et al. report also better agreement between children and parents, with ICC of .67 for the former correlation and .37 for patient/physician agreement.¹⁵ Finally, using the HUI Mark 2 Glaser et al. reported ICC of .57, .40, and .15 for patients/parents, patients/physiotherapists, and patients/physicians, respectively.¹⁶ The reasons for these discrepant observations in our study could be either the cultural difference of high- versus middle to low-income countries, the various cancer types in this cohort of teenagers, the type of predominant symptom (i.e., pain) and/or the evaluation tool used in the South America's study. Conversely, the observed lack of patient-proxy scores was also detected in an adult Canadian cancer population admitted in an acute palliative care unit.¹⁷ Using the McGill QoL Questionnaire, statistically significant mean scoring differences were observed between the patients and both the family caregivers and the attending physicians (i.e., proxies), with a maximum difference detected early (i.e., 3 days after admission) as opposed to later (6 days) in the hospitalization process. As observed in our study, proxies usually underestimated the cancer patient QoL compared to the patient's self-report. The observed differences were moderate to high, especially for the physical symptoms and psychological subscales. Interestingly, an improved correlation was however observed with cancer patients who reported cognitive difficulties and more symptom burden, which was rarely the case for our patients (data not shown for the latter). It is evidently problematic to compare this latter series to our study cohort, but our data suggest that the parent/legal guardian opinion concerning the EWS children/adolescent QoL and well-being should be interpreted with caution during and after treatment.

Noteworthy, we did not capture in our study which parent/legal guardian performed the proxy evaluation. Rensen et al. have shown recently no significant differences between paternal and maternal proxy scores for a cohort of 120 cancer patients who were on average slightly older (11.0 ± 5.7 years) than our children (8.1 ± 4.9 years).¹⁸ This is in line with other non-oncologic studies showing that paternal/maternal proxy QoL reporting was interchangeable for adolescent burn survivors,¹⁹ or those attending an outpatient psychotherapy treatment unit.²⁰ Interestingly, this caregiver's potential issue could be problematic for the E1 evaluation, as the Dutch group observed that some maternal/paternal disagreement (up to 25% of cases) in the scores could be observed for children benefitting from active treatment, which was the case in our study at this time landmark.

Not surprisingly, the QoL-impaired domains reported by the parents/legal guardians 2 years after treatment were Body image and Social functioning. These domains are also problematic in a normal population and it is conceivable that our mostly pre-adolescent patients (median and mean age, 10.2 and 8.1 years) will not be immune to the normal transition occurring during teenagehood. Interestingly, our patients did not self-rate these domains as problematic and they believe that they mostly enjoyed an identical QoL when compared to the control population (Figure 1).

Our prospective study has several limitations. First, in the cross-sectional analysis, the observed low correlation between EWS patients' and parents/legal guardians' scores may be due to small sample size, variability of scores, or unreliability of the QoL measures. For this comparison, we did not capture the current status of the proxies and divorced parents may actually score QoL lower but this should be confirmed in future research. As mentioned, we did not register

TABLE 4 Longitudinal comparison of PEDQOL scores (proxy and self) for E1 (baseline; n = 21) and E4 (2 years; n = 11) groups

	Autonomy n; mean ± SD	Emotional functioning n; mean ± SD	Body image n; mean ± SD	Cognition n; mean ± SD	Physical functioning n; mean ± SD	SocFunct-peers n; mean ± SD	SocFunct-family n; mean ± SD	Subjective well-being n; mean ± SD
PEDQOL proxy								
EWING E1	16; 60.10 ± 21.31	21; 68.13 ± 13.08	19; 64.21 ± 25.41	20; 70.92 ± 15.83	20; 48.33 ± 13.94	20; 66.00 ± 23.12	20; 71.53 ± 22.82	20; 60.00 ± 25.59
EWING E4	11; 72.32 ± 17.75	11; 66.41 ± 15.98	11; 71.51 ± 15.23	11; 70.30 ± 22.38	11; 57.58 ± 11.46	11; 63.79 ± 22.54	11; 72.47 ± 21.53	10; 75.00 ± 22.57
PEDQOL self								
EWING E1	16; 66.04 ± 15.47	20; 78.61 ± 12.68	20; 75.67 ± 25.55	20; 73.78 ± 19.25	19; 50.00 ± 17.57	20; 76.33 ± 16.83	20; 66.39 ± 22.06	19; 64.91 ± 31.38
EWING E4	11; 69.29 ± 16.20	11; 76.52 ± 13.34	11; 70.91 ± 18.20	11; 73.33 ± 21.50	11; 62.12 ± 13.62	11; 76.97 ± 13.78	11; 75.76 ± 19.16	11; 74.24 ± 23.99

Abbreviations: E1, evaluation before proton therapy (PT); E4, evaluation 2 years after PT; PEDQOL, quality-of-life questionnaire for children 4–18 years; SocFunct, social functioning.

the information on which parent/legal representative was the primary caregiver, although mothers are usually the primary caregivers in our high-income societies. For the longitudinal analysis, only descriptive analyses could be provided as the various compliances of patients and proxies alike and the different patients at certain time point made the statistical analyses not possible. Finally, our QoL instrument was a child/caregiver report-only measure of QoL; no formal interviews with children or parents were performed.²¹

5 | CONCLUSIONS

As shown by the cross-sectional analysis, children/adolescents with EWS usually recovered well to normal QoL levels within 2 years after the end of PT. No significant QoL differences were observed at 2 years after treatment in all domains. They tended however to rate their QoL substantially higher than their parents or legal guardian. Two years after PT, differences of QoL mean scores were observed between the study and healthy control cohorts in 38% and 0% of the domains for proxy- and self-evaluations, respectively. In the longitudinal analysis at 2 years, children rated their Emotional functioning and Body image scores somewhat poorly.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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