A multidisciplinary approach to assessing the impact of local therapy in pediatric bone sarcoma patients and survivors: a cross-sectional study of adverse events and health-related quality of life

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Summary

Background Pediatric bone sarcoma patients undergo intensive treatment including life-changing local therapy, which results in a high burden of adverse events (AEs) and reduced health-related quality of life (HR-QoL). Given this multidimensional impact, optimal follow-up care requires a multidisciplinary expert team. We setup a multidisciplinary follow-up clinic with carousel consultations—including pediatric oncologists/late effects specialists, orthopedic surgeons, rehabilitation physicians, physical therapists, and psychologists—to screen for local therapy-related issues using standardized measurements. In addition to enhancing care, this clinic enables the study of a nationwide cohort.

Methods This cross-sectional study included patients diagnosed with pediatric bone sarcoma from 2003 onwards who completed local therapy and subsequent treatment, and attended the multidisciplinary follow-up clinic between 18 November 2021 and 7 March 2024. Patient satisfaction was assessed using a modified satisfaction questionnaire, and care output was documented based on healthcare professionals' actions following the consultations using a predefined action list. AEs and HR-QoL of the patients seen at the multidisciplinary clinic were evaluated using the Common Terminology Criteria for Adverse Events, Henderson classification, and PedsQL™ Generic Core Scales.

Findings Satisfaction with the provided care was reported by 99% (135/136) of patients. Healthcare professionals documented 182 actions, with counseling for identified patient needs being the most frequent. AEs were present in 96% (138/144) of patients, including moderate events in 72% (103/144) and severe events in 41% (59/144). Common AEs included musculoskeletal deformity, muscle weakness, decreased range of motion, gait disturbance, pain, and unequal limb length. HR-QoL scores were lower across all domains compared to the general population, with a high AE burden associated with poorer HR-QoL (B = −8.7, 95% CI −16.8 to −0.7, p = 0.035).

Interpretation The multidisciplinary follow-up care achieved high patient satisfaction and substantial care output, while enabling expert-led, high-quality data collection. The high prevalence of local therapy-related AEs and reduced HR-QoL are important to consider in follow-up and shared decision-making for local therapy in future patients. This multidisciplinary framework is broadly applicable to oncology patients facing treatment-related challenges, with the potential to improve outcomes and advance oncology research and practice.

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Research in context

Evidence before this study

We searched MEDLINE (via PubMed) for studies reporting on multidisciplinary follow-up care, adverse events or quality of life outcomes in patients and survivors of pediatric bone sarcoma, without language or date restrictions. The search strategy included the terms (bone sarcoma OR Ewing OR osteosarcoma) AND (pediatric OR child OR adolescent) AND (multidisciplinary OR ((local therapy OR surgery OR radiotherapy) AND (adverse event OR quality of life))), along with related synonyms. Although the importance of a multidisciplinary approach in diagnosis and treatment of bone sarcoma is widely recognized, we found no studies evaluating its implementation or outcomes in follow-up care. Several studies have examined adverse events in general pediatric oncology survivor cohorts that included bone sarcoma survivors, but these lacked specific attention to local therapy-related events. Although amputation or limb-sparing surgery were included as severe adverse events, the consequences of local therapy, e.g. gait disturbance, muscle weakness, and decreased range of motion, were not systematically reported. Nevertheless, bone sarcoma survivors have been shown to experience a high cumulative incidence and burden of adverse events after treatment. Quality of life studies report worse physical functioning in bone sarcoma patients and survivors compared to the general population, but findings vary for other domains, such as emotional or social functioning.

Added value of this study

This study evaluates the implementation of a multidisciplinary follow-up clinic for pediatric bone sarcoma patients and survivors, providing comprehensive expert-led assessment of complex local therapy outcomes, including adverse events and health-related quality of life. Assessment findings were translated into targeted actions when needed. Patients expressed high satisfaction with the care provided, and the clinic generated considerable output, including frequent patient-tailored counseling, referrals, and treatment adjustments based on multidisciplinary team discussions. Next to enhanced patient-centered follow-up care, this clinic enables systematic data collection on patient outcomes, leading to high-quality research alongside clinical practice. Our assessment of patient outcomes revealed a high prevalence of local therapy-related adverse events that can affect daily life, including musculoskeletal deformity, muscle weakness, reduced range of motion, gait disturbance, pain, and limb-length discrepancy. Additionally, patients scored worse on all domains of health-related quality of life compared to the general population, with a high burden of adverse events being significantly associated with poorer health-related quality of life outcomes.

Implications of all the available evidence

The findings of this study underscore the critical role of multidisciplinary follow-up care in supporting bone sarcoma patients and survivors. They provide healthcare professionals with valuable insights into the life-altering implications of local therapy, which are essential for optimizing follow-up care—through screening and support for adverse events and health-related quality of life concerns—and for counseling future patients during shared decision-making about local therapy options. By combining clinical expertise with systematic outcome assessments, a multidisciplinary approach not only enhances the quality of follow-up care but also generates practical, patient-centered insights that can directly inform and improve clinical practice. This framework extends beyond bone sarcoma, serving as a model for addressing the complex effects of oncological treatments across diverse cancer populations.

Introduction

Patients with osteosarcoma and Ewing sarcoma undergo intensive treatment, including chemotherapy and local therapy. For most patients, local therapy involves major surgery. Surgical options include amputation, rotationplasty, or limb-sparing surgery with endoprostheses, autografts, allografts, or a combination. In Ewing sarcoma, radiotherapy may be added based on individual risk factors or, in specific cases, used as a standalone treatment.

As a consequence of their treatment, bone sarcoma patients experience a high burden of adverse events (AEs) and report worse health-related quality of life (HR-QoL) than the general population, particularly in the physical domain.[1–3] Addressing these challenges requires a multidisciplinary approach, yet maintaining such care during follow-up remains challenging. Therefore, we established a multidisciplinary follow-up clinic for patients treated for pediatric bone sarcoma at the Princess Máxima Center, the national center responsible for the diagnosis, treatment, and follow-up of all children with cancer in the Netherlands. This clinic aims to provide integrated care and focuses on local therapy-related effects. Patients are seen by a pediatric oncologist or late effect specialist, orthopedic surgeon, rehabilitation physician, physical therapist,

and psychologist. The rehabilitation physician and physical therapist jointly see the patients. Next to patients' specific requests for help, professionals screen patients using standardized measurements to systematically assess outcomes after local therapy, including AEs, functional outcomes, psychosocial outcomes and HR-QoL. During pre- and postclinic team meetings, the healthcare professionals discuss findings and synchronize plans.[4] This systematic, multidisciplinary approach enhances follow-up care while enabling the collection of high-quality data by bone sarcoma experts, providing valuable insights into a nationwide cohort. Such expertise is essential to assess outcomes accurately, given the complexity of local therapy.

Current pediatric oncology studies tend to focus on systemic therapy-related AEs, with limited attention to those arising from local therapy.[3,5] Furthermore, while short-term surgical complications—such as infections, aseptic loosening, and fractures—are reported, their long-term implications remain poorly defined.[6,7] Consequently, the overall impact of local therapy on AEs for patients and survivors of pediatric bone sarcoma is largely unclear. Similarly, more research is needed on these patients' HR-QoL, as existing studies show considerable variability in findings, particularly regarding social and emotional outcomes, and frequently rely on small or outdated cohorts, limiting the reliability of conclusions.[8,9]

This nationwide study aims to evaluate the integrated multidisciplinary care for patients and survivors of pediatric bone sarcoma with specific focus on local therapy-related outcomes. We assessed satisfaction with the multidisciplinary follow-up clinic and evaluated the output of care. The clinic also allowed us to: 1) assess the prevalence, severity, and types of AEs after local therapy, 2) compare the patients' HR-QoL to the general population, and 3) explore the relationship between AEs and HR-QoL. Findings will help refine follow-up care and shared decision-making for future patients, with the ultimate goal of improving the HR-QoL of bone sarcoma patients. Subsequent papers will detail the functional and psychosocial outcomes of this cohort.

Methods

This report is part of a larger cross-sectional study evaluating outcomes after local therapy for pediatric bone sarcoma. We describe the methodology relevant to the outcomes reported here; overarching study details have been published previously.[4]

Study design and participants

This cross-sectional nationwide study assessed the outcomes of bone sarcoma patients attending a multidisciplinary follow-up clinic focused on local therapy-related outcomes.

Patients were eligible if they: 1) had a pediatric osteosarcoma, Ewing sarcoma, or Ewing-like sarcoma of the extremity or pelvis; 2) were diagnosed in or after 2003; 3) underwent local therapy; 4) were more than two years post-diagnosis; and 5) completed treatment and had no evidence of disease.

Ethics

The Medical Research Ethics Committee of the University Medical Center Utrecht confirmed that the Medical Research Involving Human Subjects Act does not apply to this study (reference 21/733). Our hospital's center-wide informed consent policy assured that outcomes from the multidisciplinary clinic can be utilized for the study. All participants in this study provided informed consent under this policy.

Sample size

Before nationwide centralization of care, pediatric oncology patients were treated at six University Medical Centers (UMCs) in the Netherlands. Since June 2018, all patients under the age of 18 with cancer receive their diagnostic work-up, treatment, follow-up and late effects care at the national Princess Máxima Center for pediatric oncology. Many patients previously treated at a UMC have been transferred to the Máxima for follow-up or late effects care. Based on this transition, along with data from the Dutch Childhood Oncology Group national childhood cancer registry and Long-Term Effects After Childhood Cancer registry, around 180 patients were expected to be invited to the clinic. Accounting for a non-participation rate of 20%, 145 patients were anticipated to be included.

Multidisciplinary clinic: standardized assessments

During the multidisciplinary clinic, patients were screened for local therapy-related effects using a standardized assessment set, including history-taking, physical examinations, patient-reported outcome measures (PROMs) and AE reporting. Patients completed the PROMs online in the week before the clinic, and results were discussed during the consultations. AEs were documented by the healthcare professionals afterward.

AEs were reported using the Common Terminology Criteria for Adverse Events (CTCAEv5.0). Five grading levels are distinguished: mild (1), moderate (2), severe or disabling (3), life-threatening (4) and AE-related death (5).[10] For each patient, items relevant to the tumor location and type of local therapy were selected (Appendix p 3–51). The Henderson classification was used to report additional AEs specific to limb-sparing surgery. This classification categorizes six failure modes and includes two versions: one for endoprosthetic and one for biological reconstructions.[11] To ensure consistency in AE reporting, items were discussed among the team and coding rules established

(Appendix p 6–51). After each clinic, AE forms were reviewed for completeness and adherence to coding rules by the coordinating investigator (LT). Inconsistencies were discussed with the relevant healthcare professional and corrected where applicable. Only AEs present at the follow-up clinic were reported. If a past AE continued to impact the patient's current condition, it was also included. For example, a past prosthesis infection treated with antibiotics would not be scored, but an infection requiring prosthesis removal or secondary amputation was included.

The Pediatric Quality of Life Inventory Generic Core Scales (PedsQL™ GCS) was used to evaluate HR-QoL in four domains (physical, emotional, social and school/work functioning) through 23 items completed on a 5-point Likert scale.[12] Scores range from zero to 100 with higher scores indicating better HR-QoL. A total score and psychosocial summary score (emotional, social and school/work functioning) can be calculated. The PedsQL™ GCS has demonstrated sufficient measurement properties, with reference data available from a large Dutch population.[13–17] In this study, the internal consistency was acceptable for most domains in this study (Cronbach's α: 0.64–0.92) except for social functioning of patients aged 13–17, where Cronbach's α was moderate (0.51).

Patient satisfaction was assessed using a modified version of the satisfaction questionnaire developed by Blaauwbroek and colleagues (Appendix p 52), which were distributed to patients after their final consultation and completed without supervision from healthcare professionals or investigators.[18] Care output was evaluated during the postclinic meeting using a predefined list, documenting the implemented actions for each patient (Appendix p 53). Only actions addressing patient needs identified at the clinic were recorded; protocolized interventions or standard procedures were not included.

Statistics

Categorical variables were presented as frequencies (n) and percentages (%), and continuous variables as means and standard deviations if normally distributed, or medians and interquartile ranges if not. Missing data were minimal and not imputed. As missingness was mainly due to logistical reasons rather than patient refusal, the risk of bias was considered low.

Patient satisfaction and output of care were assessed using descriptive statistics. For reporting purposes, actions that defined similar output of care were grouped (Appendix p 54).

Henderson classification items were adapted to align with CTCAE items and grading, creating a unified system for reporting AEs. Additionally, similar AEs were grouped (Appendix p 55). The number of AEs per patient, prevalence of each grade, highest toxicity grade, most common AEs, and burden score were evaluated by descriptive statistics. This burden score, adapted from Geenen and colleagues, combines prevalence and severity of AEs into a low, medium, high or severe burden (Appendix p 56).[3] Descriptive statistics were also used to explore the relationship between AEs and patient and treatment factors, such as age at diagnosis (categorized considering the growth spurt), time since local therapy, tumor location and treatment.

Patients' HR-QoL was compared to the Dutch general population using a multiple linear regression model adjusted for attained age and sex. We calculated and interpreted effect sizes according to Cohen: small (0.2), medium (0.5) and large (0.8).[19] The Benjamini-Hochberg procedure was applied to correct for multiple testing, with a false discovery rate of 5%.

A multiple linear regression model adjusted for attained age and sex was used to assess the relationship between AE burden and HR-QoL. Only patients with available HR-QoL data were included. The assumptions for the model were checked and met.

All statistical analyses were conducted using R version 4.4.0.[20]

Role of funding source

No specific funding was received for this study. Therefore, funders had no role in its design, conduct or reporting.

Results

Between 18 November 2021 and 7 March 2024, 363 patients treated for a pediatric bone sarcoma in the pelvis or extremity in the Netherlands were identified of which 213 were registered at the Princess Maxima Center. Fifty-three could not participate due to clinic visits outside the study period (n = 39), personal circumstances (n = 5), living abroad (n = 5), follow-up care in another hospital (n = 3), or linguistic barrier (n = 1). Consequently, 160 patients were invited to the multidisciplinary clinic, and 149 attended. We excluded three patients without informed consent and two patients because of two primary bone tumors complicating group-level comparisons, leaving 144 patients in this report (Appendix p 57). AE data were available for all patients, output of care for 143 patients, satisfaction for 136 patients and HR-QoL for 135 patients.

The distributions of sex, diagnosis, tumor location, and age at diagnosis were representative of nationwide distributions (Table 1).[21] There were no significant differences between the study population and non-participants (Appendix p 58). Patients were, on average, 20.2 years old when visiting the clinic (range: 5.7–34.7) and underwent local therapy median 6.1 years ago (range: 1.6–20.3). Lower extremity tumors were mostly located around the knee (89%, 91/102), pelvis tumors in the iliac bone (57%, 12/21), and upper extremity tumors in the proximal humerus (52%, 11/21) (Appendix p 59).

	Total	Upper extremity	Pelvis	Lower extremity
	N_{pt} = 144	N_{pt} = 21	N_{pt} = 21	N_{pt} = 102
Attained age, years				
Mean (SD)	20.2 (5.7)	20.3 (7.2)	22.0 (6.1)	19.7 (5.3)
Median (Q1, Q3)	19.4 (16.8, 23.6)	19.8 (15.2, 24.7)	21.3 (18.8, 25.4)	19.0 (16.6, 22.2)
Range	5.7–34.7	6.3–32.7	5.7–31.6	8.3–34.7
Age at diagnosis, years				
Median (Q1, Q3)	13.0 (9.0, 14.2)	10.0 (9.0, 13.0)	13.0 (11.0, 16.0)	13.0 (9.0, 14.0)
Range	1.0–17.0	1.0–17.0	2.0–17.0	2.0–17.0
Time since local therapy, years[a]				
Median (Q1, Q3)	6.1 (3.0, 11.3)	8.8 (2.7, 14.8)	7.6 (3.8, 13.6)	5.3 (3.0, 10.0)
Range	1.6–20.3	1.6–18.6	1.7–18.5	1.6–20.3
Sex, N (%)				
Female	63 (44%)	9 (43%)	9 (43%)	45 (44%)
Male	81 (56%)	12 (57%)	12 (57%)	57 (56%)
Diagnosis, N (%)				
Osteosarcoma	76 (53%)	6 (29%)	3 (14%)	67 (66%)
Ewing sarcoma	64 (44%)	14 (67%)	18 (86%)	32 (31%)
Ewing-like sarcoma	4 (3%)	1 (5%)	0 (0%)	3 (3%)
Disease status at diagnosis, N (%)				
Localized	122 (85%)	17 (81%)	16 (76%)	89 (87%)
Metastasized	22 (15%)	4 (19%)	5 (24%)	13 (13%)
Type of local therapy, N (%)				
Surgery	107 (74%)	12 (57%)	7 (33%)	88 (86%)
Radiotherapy	14 (10%)	2 (10%)	10 (48%)	2 (2%)
Surgery and radiotherapy	23 (16%)	7 (33%)	4 (19%)	12 (12%)
Type of surgical local therapy, N (%)				
Amputation	17 (13%)	0 (0%)	0 (0%)	17 (17%)
Rotationplasty	20 (15%)	NA	NA	20 (20%)
Endoprosthesis ± graft	47 (36%)	6 (32%)	2 (18%)	39 (39%)
Graft	22 (17%)	3 (16%)	4 (36%)	15 (15%)
Arthrodesis ± graft	3 (2%)	2 (11%)	1 (9%)	0 (0%)
High hip	3 (2%)	NA	3 (27%)	NA
Tumor resection without reconstruction	11 (8%)	4 (21%)	0 (0%)	7 (7%)
Other	7 (5%)	4 (21%)	1 (9%)	2 (2%)

NA = not applicable; N_{pt} = number of patients; Q1 = first quartile; Q3 = third quartile; SD = standard deviation. For normally distributed variables, mean (SD) is provided in addition to median (IQR). [a]Time since surgery OR time since start definitive radiotherapy (whatever applicable).

Table 1: **Population characteristics.**

Satisfaction with the multidisciplinary clinic was reported by 99% (135/136) of patients (Appendix p 60). There were 182 actions to address identified needs among 143 patients: 71 by rehabilitation physicians/physical therapists, 55 by psychologists, 31 by orthopedic surgeons, ten by pediatric oncologists/late effects specialists, and 15 initiated by the team. For 97 patients, at least one action was recorded by a healthcare professional other than the pediatric oncologist/late effects specialist. No actions were required for 43 patients. Counseling was frequently provided: 24 times by an orthopedic surgeon, 40 times by a psychologist, and 55 times by a rehabilitation specialist/physical therapist. Much-discussed topics included sports opportunities, external prosthesis adjustments, load-bearing capacity of the reconstruction, resilience versus burden, acceptance and coping challenges, and normalization of fears and thoughts. Twenty-four patients were referred for additional care. Four patients were planned for surgery due to problems identified at the clinic. The postclinic team meeting resulted in a new action or adjustment of plans 19 times (Appendix p 61).

On average, 5.3 AEs (SD = 2.5) per patient were reported, most (57%) being grade 1 (Fig. 1). No AEs were reported for six of 144 patients (4%). Among others, 132 (92%) had at least one grade 1, 103 (72%) one grade 2, and 59 (41%) one grade 3 event. Grade 2 and 3 were the highest grades reported for both 59 (41%) patients. Most patients (93/144, 65%) experienced a medium burden of AEs, while 4% (6/144), 14% (20/144) and 17% (25/144) experienced no, low and high burdens, respectively.

Musculoskeletal deformity was the most common AE, followed by muscle weakness, decreased joint

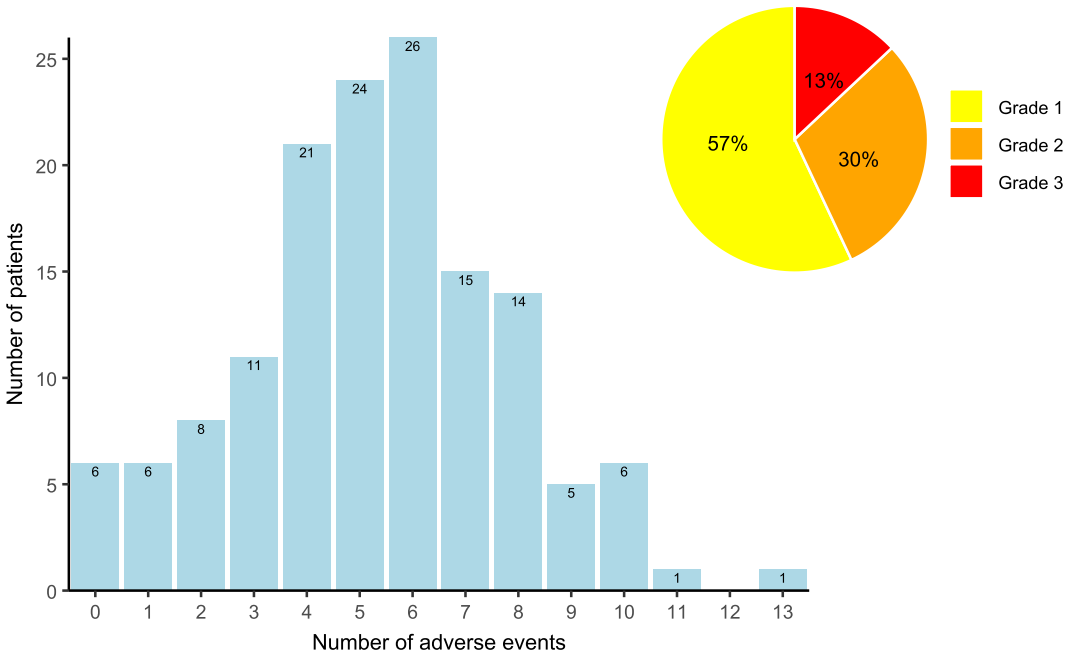

Fig. 1: Distribution of the number and severity of adverse events in the study population.

range of motion, gait disturbance, pain and unequal limb length (Fig. 2, Appendix p 62–63). Musculoskeletal deformity (n = 117) was mostly mild or moderate, predominantly affecting patients with an extremity tumor (111/117). Muscle weakness was generally mild, corresponding to a Medical Research Council (MRC) scale muscle strength grade 4, though severe weakness was more common in patients with upper extremity tumors (7 of 21 patients versus 9 of 102 patients with lower extremity and none of the patients with pelvic tumors). Decreased range of motion was severe or disabling in 67% (14/21) of patients with upper extremity tumors, compared to 10% (2/21) and 12% (12/102) of patients with pelvic and lower extremity tumors respectively. Half of pelvic tumor patients showed gait disturbance, mostly mild (8/11). Of patients with lower

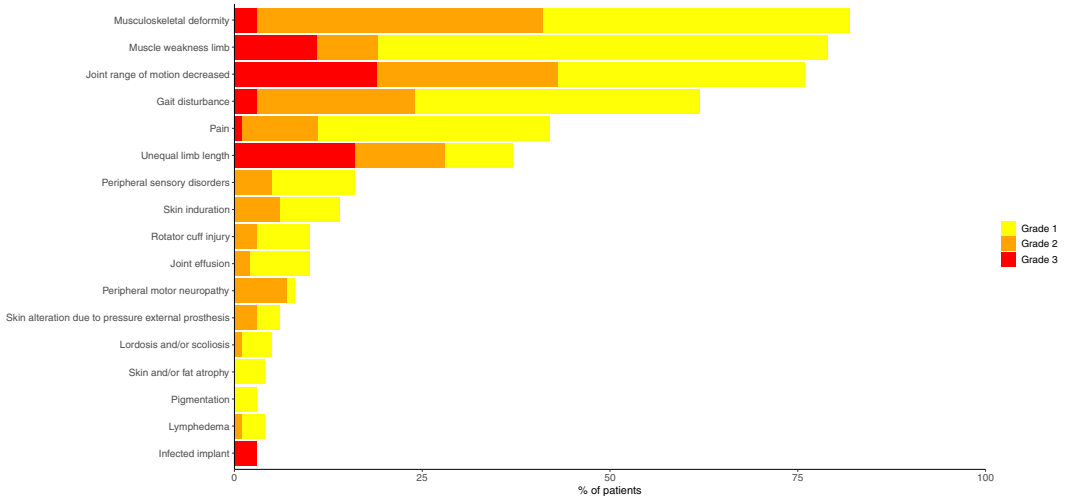

Fig. 2: Most common (occurring in ≥5 patients) adverse events including severity distribution. In case of multiple events of the same type in the same patient, one event of the type with the highest grade was shown. Details on adverse event items and grading are specified in Appendix p 3–51.

extremity tumors, 46% (47/102) had mild, 26% (27/102) moderate and 4% (4/102) severe gait disturbance. Pain was reported in 60 of 144 patients (42%), classified as neuropathic in eight, phantom pain in seven amputation patients, and nociceptive or unknown in the rest. Pain prevalence and severity were similar across tumor locations.

Of 23 patients with grade 3 unequal limb length, 12 (52%) underwent surgeries in the past, including ten epiphysiodeses, one leg shortening, and one leg extension plus epiphysiodesis. Complications from surgical local therapy led to change of reconstruction type in 14 patients, including four secondary amputations.

A high AE burden was observed in 28% (15/53) of patients diagnosed before age 12, compared to 11% (10/91) of patients diagnosed at ages 12–17 (Table 2). Severe AEs in the younger patients included unequal limb length and various surgical complications (Appendix p 64).

Despite the small sample size, 67% (14/21) of upper extremity tumor patients had at least one grade 3 event, including 43% (9/21) with a high burden of events, compared to 29% (6/21) and 10% (2/21) of pelvic and 38% (39/102) and 14% (14/102) of lower extremity tumor patients. Severe AEs in upper extremity tumor patients were often due to decreased range of motion or muscle weakness (Appendix p 66).

Patients after definitive radiotherapy and patients with pelvic tumors had low AE prevalence and burden, though sample sizes were small and overlapping: 10 of 21 pelvic tumor patients received definitive radiotherapy, and 10 of 14 definitive radiotherapy patients had pelvic tumors.

In total, 135 patients completed the PedsQL™ GCS. Patients scored significantly worse on all HR-QoL outcomes compared to the general population (Table 3). The largest effect sizes were observed for total and physical functioning scores (0.92–2.05), the smallest for social functioning (0.32–0.39).

When adjusted for attained age and sex, patients with no or low burden of AEs (N = 25; total score 76.3 ± 13.2) scored, on average, 6.1 points higher on HR-QoL compared to those with a medium burden (N = 86; total score 70.3 ± 14.7; B = –6.1, 95% CI –12.5 to 0.2; p = 0.060), and 8.7 points higher than those with a high burden (N = 24; total score 67.7 ± 17.3; B = –8.8, 95% CI –16.8 to –0.7; p = 0.035). The effect sizes were in the medium range: 0.42 for no/low burden versus medium burden, and 0.56 for no/low burden versus high burden.

Discussion

In this cross-sectional study, we assessed the outcomes of care, AEs and HR-QoL in the context of an integrated, multidisciplinary follow-up clinic for patients and survivors of pediatric bone sarcoma. Patient satisfaction was excellent, and the output of care was notable. Local therapy-related AEs were highly prevalent and burdensome, with high AE burden being significantly associated with lower HR-QoL.

Establishing a multidisciplinary follow-up clinic poses challenges, including limited consultation space, cross-specialty scheduling, digital infrastructure adjustments to support planning, and support staff training. These may be greater in systems with fragmented expertise. Nevertheless, our study shows such clinics deliver high patient satisfaction and substantial care benefits for pediatric bone sarcoma patients. In

	No. of AEs any grade		≥5 AEs any grade	≥1 grade 3 AE	High burden of AEs
	N_{pt}	Mean (SD)	N_{pt} (%)	N_{pt} (%)	N_{pt} (%)
Age at diagnosis					
<12 years	53	5.2 (2.5)	34 (64)	27 (51)	15 (28)
12–17 years	91	5.3 (2.6)	58 (64)	32 (35)	10 (11)
Time since local therapy					
0–<2 years	14	4.4 (2.8)	6 (43)	4 (29)	3 (21)
2–<5 years	48	5.7 (2.8)	33 (69)	19 (40)	8 (17)
5–<10 years	38	4.8 (2.3)	24 (63)	18 (47)	6 (16)
≥10 years	44	5.6 (2.2)	29 (66)	18 (41)	8 (18)
Tumor location					
Upper extremity	21	6.0 (2.6)	15 (71)	14 (67)	9 (43)
Pelvis	21	4.0 (3.0)	11 (52)	6 (29)	2 (10)
Lower extremity	102	5.4 (2.3)	66 (65)	39 (38)	14 (14)
Treatment					
Surgery	107	5.4 (2.1)	70 (65)	45 (42)	17 (16)
Radiotherapy	14	2.1 (2.5)	3 (21)	2 (14)	1 (7)
Surgery and radiotherapy	23	6.6 (2.7)	19 (83)	12 (52)	7 (30)

AE = adverse event; N_{pt} = number of patients; SD = standard deviation. Types of adverse events per subgroup are shown in Appendix p 64–67.

Table 2: **Adverse events versus patient and treatment factors.**

	Study population			Norm population			Study versus norm population			
	N_{pt}	Mean (SD)	Range	N_{pt}	Mean (SD)	Range	Estimate[a]	95% CI	p-value[b]	ES[c]
Total population	135			1615						
Total score		70.9 (15.1)	19.6–98.9		84.5 (12.8)	22.8–100.0	−13.6	−15.8; −11.3	<0.0001	1.06
Physical functioning		68.3 (18.8)	9.4–100.0		89.8 (14.1)	0.0–100.0	−20.8	−23.3; −18.3	<0.0001	1.52
Emotional functioning		68.0 (19.6)	15.0–100.0		78.5 (18.2)	0.0–100.0	−10.5	−13.7; −7.3	<0.0001	0.58
Social functioning		80.4 (15.4)	20.0–100.0		85.5 (16.1)	10.0–100.0	−5.8	−8.7; −3.0	<0.0001	0.32
School/work functioning		68.7 (21.3)	5.0–100.0		81.2 (16.4)	20.0–100.0	−12.7	−15.6; −9.7	<0.0001	0.76
Psychosocial summary score		72.3 (15.1)	15.0–100.0		81.7 (14.3)	25.0–100.0	−9.7	−12.2; −7.1	<0.0001	0.66
Ages 8–17 years	42			966						
Total score		69.0 (13.1)	42.4–98.9		84.9 (12.6)	29.3–100.0	−15.8	−19.7; −11.9	<0.0001	1.26
Physical functioning		66.2 (17.8)	31.2–100.0		91.6 (12.4)	12.5–100.0	−24.9	−28.8; −21.0	<0.0001	2.05
Emotional functioning		68.3 (17.3)	25.0–100.0		79.3 (18.4)	0.0–100.0	−11.6	−17.3; −6.0	<0.0001	0.60
Social functioning		78.0 (12.9)	40.0–100.0		84.4 (16.9)	10.0–100.0	−7.1	−12.3; −1.8	0.0082	0.38
School functioning		65.1 (17.5)	25.0–95.0		80.4 (16.8)	20.0–100.0	−14.2	−19.4; −9.0	<0.0001	0.91
Psychosocial summary score		70.5 (11.7)	48.3–98.3		81.4 (14.7)	30.0–100.0	−11.0	−15.5; −6.4	<0.0001	0.74
Ages 18+	93			649						
Total score		71.8 (15.9)	19.6–98.9		83.9 (13.1)	22.8–100.0	−12.6	−15.5; −9.7	<0.0001	0.92
Physical functioning		69.3 (19.3)	9.4–100.0		87.1 (16.0)	0.0–100.0	−18.9	−22.5; −15.4	<0.0001	1.11
Emotional functioning		67.8 (20.6)	15.0–100.0		77.2 (18.0)	10.0–100.0	−10.1	−14.0; −6.1	<0.0001	0.52
Social functioning		81.5 (16.4)	20.0–100.0		87.2 (14.5)	20.0–100.0	−5.6	−8.8; −2.4	0.00072	0.39
School/work functioning		70.3 (22.7)	5.0–100.0		82.3 (15.7)	20.0–100.0	−11.9	−15.6; −8.2	<0.0001	0.76
Psychosocial summary score		73.2 (16.4)	15.0–100.0		82.2 (13.7)	25.0–100.0	−9.2	−12.2; −6.1	<0.0001	0.66

CI = confidence interval; ES = effect size; N_{pt} = number of patients; SD = standard deviation. PedsQL™ scores range from zero to 100 with higher scores representing better HR-QoL. [a]The estimate concerns the regression coefficient B that represents the difference between the study population and the norm population, adjusted for attained age and sex. [b]According to linear regression analysis adjusted for attained age and sex. p-values are corrected for multiple testing by the Benjamini-Hochberg procedure (false discovery rate 5%). [c]Calculation of effect sizes: (mean study group—mean norm group)/standard deviation norm group.[19]

Table 3: **Health-related quality of life outcomes.**

this context, satisfaction captures the patients' perspective and may partly reflect the increased attention and time received from healthcare providers, whereas output of care reflects the clinic's tangible impact on clinical practice. These measures are therefore complementary, and considering both perspectives is essential for a balanced evaluation of the clinic.

A significant proportion of care output involved counseling, which aligns with previous research indicating a high need for concrete information and/or counseling among pediatric cancer survivors.[22] The lasting impact of bone sarcoma treatment on daily life leads to diverse challenges that require expertise to comprehensively understand and effectively address. This makes it difficult to fully rely on standardized resources, such as brochures or websites, or primary care professionals. A multidisciplinary clinic is particularly suited to manage these complexities. Additional integration of all expertise through pre- and postclinic meetings further optimized tailored care and likely contributed substantially to the high care output observed.

Beyond these direct benefits for patients, the structured multidisciplinary approach also enabled expert-led systematic and detailed assessment of AEs and HR-QoL, yielding a more accurate reflection of patients' situations and thereby strengthening the robustness and validity of the reported outcomes.

Moderate (grade 2) and severe (grade 3) AEs were common, affecting daily functioning and societal participation. Moderate AEs, generally defined as events impacting instrumental activities of daily living (ADL), were observed in 72% of patients. Nearly half of our patients experienced a grade 3 event, reflecting impact on self-care ADL. Some patients may adapt to these limitations, but this is not universal and depends on many factors, highlighting the importance of addressing AEs and their impact on patients' lives in follow-up care.

As expected from invasive local surgical treatment, decreased range of motion and muscle weakness were common. These AEs were particularly severe in patients with upper extremity tumors. These tumors are often located in the proximal humerus, typically requiring surgery of the shoulder joint and rotator cuff, making reconstructions highly vulnerable and prone to severe functional loss.

Patients diagnosed before age 12 also experienced a notably high burden of AEs, likely due to skeletal immaturity and the associated complications of expandable endoprostheses or other surgical (re-)interventions. As a result, these patients more often require surgical corrections and/or revisions. Surgeons

should carefully consider this during shared decision-making about local treatment options and inform patients on the likelihood of requiring subsequent surgeries after their primary resection and reconstruction.

The grading of musculoskeletal deformities revealed some challenges in coding consistency, particularly for limb-sparing surgeries which were occasionally coded as moderate rather than mild, as per the coding rules (Appendix p 6–51). This may explain the higher prevalence of moderate deformities than expected in our cohort and suggests that patients undergoing limb-sparing surgery might experience more deformity than anticipated.

Previous studies have also highlighted the high prevalence and burden of AEs among bone tumor survivors, but differences in study design and scope of AEs complicate direct comparisons.[3,5,23–25] Geenen and colleagues reported 64% of pediatric bone sarcoma survivors experiencing a high AE burden, compared to 17% in our study.[3] This discrepancy may be attributed to their inclusion of chemotherapy-related events and cumulative incidence, whereas we focused solely on current local therapy-related AEs. Additionally, the version of the CTCAE used in their study (v3) differs from ours (v5). This likely affected the reported severity of AEs and, consequently, burden scores, as disabling events were reclassified from grade 4 to grade 3 from CTCAEv4 onwards.

Local therapy-related AEs risk being underreported in cohort studies due to limited focus and expertise regarding the specific consequences of local treatment options. For instance, Bishop and colleagues focused on AEs in pediatric bone sarcoma patients, but their emphasis was primarily on chronic illnesses, leaving local therapy-related AEs underexplored.[23] Moreover, some studies seem to label local therapy itself as an AE rather than reporting its consequences, thereby overlooking the wide range of patient-specific effects it can have.[3,24] Lastly, many large studies included patients diagnosed before the 1990s.[3,5,23–25] Considering advancements in local therapy techniques and supportive care, the era of diagnosis may influence reported outcomes.[26]

To improve capturing the relevance of AEs, future research could incorporate patient-reported alongside clinician-reported AEs. While a patient-reported version of the CTCAE exists and offers insight into symptom impact on daily life, it differs from the clinician-reported version and lacks key musculoskeletal symptoms relevant to this population. Alternative AE instruments can also be considered, though identifying tools that reflect both symptom severity and impact remains challenging.

HR-QoL outcomes in our patients were significantly lower compared to the general population, particularly for physical functioning. This aligns with previous studies, although results for social and emotional functioning vary.[1,2,27] To better interpret these findings, it is crucial to explore the factors influencing HR-QoL. We found a notable association between a high AE burden and lower HR-QoL scores. While some studies have assessed the relationship between symptom AEs and quality of life in pediatric cancer patients, they lack treatment-specific insights.[28,29] Our findings suggest that a high AE burden resulting from invasive local therapy may impact the HR-QoL of bone sarcoma patients.

Taken together, our findings suggest value in extending multidisciplinary follow-up care to patients with bone sarcomas at other sites and to soft tissue sarcomas that required intensive local treatment with long-term functional impact. For example, patients who underwent extensive surgery and/or radiotherapy for extremity soft tissue sarcoma have already been seen at our clinic upon indication. Furthermore, we are planning to expand this strategy to other tumor types and locations, such as (bone) sarcomas of the trunk.

Our study has limitations. First, we could not compare multidisciplinary care outcomes to those prior to the implementation of the clinic. The Princess Máxima Center is a newly established hospital built to integrate all pediatric oncology expertise in the Netherlands and this clinic was setup as part of this initiative. Therefore, no baseline data are available for comparison. Second, the cross-sectional design limits assessment of changes over time, including causal relationships. Longitudinal data are needed to confirm our exploratory findings on AEs by time since local therapy and to clarify whether the relationship between HR-QoL and AE burden extends beyond association. As the clinic continues, we will collect these data and report findings in future publications. Third, we did not examine systematic therapy-related AEs, confining a comprehensive view of all treatment-related effects. Fourth, diversity in time since local therapy, tumor location, and treatment hinders firm conclusions and comparison of the various local therapy modes. Lastly, clinician-reported data risks underreporting, especially for symptoms like pain, possibly underestimating the true prevalence of some AEs.[30]

Our findings underscore the value of a multidisciplinary follow-up approach for patients and survivors of pediatric bone sarcoma after local therapy. This approach achieved high patient satisfaction and care output, while enabling comprehensive data collection on patient outcomes, such as AEs and HR-QoL. The expert-led data collection ensured reliable and high-quality data, which is essential given the complexity of local therapy-related outcomes. Additionally, by integrating all expertise during pre- and postclinic meetings, the clinic was truly interdisciplinary, facilitating coordinated and patient-centered care. The high prevalence of local therapy-related AEs experienced by bone sarcoma patients and survivors can profoundly affect

their daily lives and HR-QoL. These factors should be incorporated into shared-decision making when counseling future patients about local therapy options, particularly those at risk of complications and reoperations. During follow-up, AEs and HR-QoL should be carefully monitored, starting with screening, and progressing to personalized care and support as needed.

This study provides a clinical example of multidisciplinary follow-up care that extends beyond bone sarcoma, offering a framework that is broadly applicable to oncology patients facing permanent treatment-related challenges. Expanding such framework has the potential to enhance patient outcomes and advance the quality of oncology research and practice.

Contributors

LT, JM, LH, WB, HS, MN, and WK contributed to the conceptualization of the study. The study design and methodology were developed by LT, JM, LH, WB, HS, MG, LB, IO, LK, JB, and MS. LT and HH coordinated the study. Data were collected by LT, JM, WP, HH, CR, IO, LH, JB, MS, and HS. LT, HH and HM accessed and verified the underlying data, and analyses were conducted by LT, HT, and HM. LT had overall responsibility for the writing process and contributed to the original draft together with LH, WB, HS, and JM. All authors read and approved the final version of the manuscript. JM provided overall supervision of the study. LT, LH, WB, HS and JM were responsible for the decision to submit the manuscript.

Data sharing statement

Individual participant data (including data dictionaries) that underlie the results reported in this article cannot be publicly shared because parts of the overarching study from which these data originate are still under evaluation and analysis. However, de-identified data can be made available to investigators whose proposed use of the data has been approved by the Biobank Data Access Committee of the Princess Máxima Center. Additionally, the study protocol is available from the corresponding author upon request.

Declaration of interests

JM reports consulting fees from Bayer and Merck (<€5000 each, paid to the institution), serves on the Data Safety Monitoring Board of the Pervision trial (EudraCT 2022-002793-91), and holds unpaid leadership roles as Chair of the European Pediatric Soft Tissue Sarcoma Study Group and Vice Chair of the EuroEwing Consortium. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103622.

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