Open access Review

Unravelling the heterogeneity of soft tissue and bone sarcoma patients' health-related quality of life: a systematic literature review with focus on tumour location

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ABSTRACT

Patients with sarcoma experience many physical and psychological symptoms, adversely affecting their health-related quality of life (HRQoL). HRQoL assessment is challenging due to the diversity of the disease. This review aims to unravel the heterogeneity of HRQoL of patients with sarcoma with regard to tumour location and to summarise the used measures in research. English-language literature from four databases published between January 2000 and April 2019 was reviewed. Studies that described adult sarcoma HRQoL outcomes were included and classified according to primary sarcoma location. Eighty-seven articles met the inclusion criteria covering sarcoma of the extremities (n=35), pelvis and axial skeleton (n=9), pelvis and extremities (n=5), head and neck (n=4), retroperitoneum (n=2) and multiple sarcoma locations (n=33), respectively. Urogenital and thoracic sarcoma were lacking. Fifty-four different questionnaires were used, most often cancer-generic or generic HRQoL questionnaires. Patients with sarcoma reported lower HRQoL than the general population. Distinctive patterns of HRQoL outcomes according to tumour location regarding symptoms, physical functioning, disability and psychosocial well-being were identified. In metastatic sarcoma, mostly constitutional symptoms were present. To comprehensively assess HRQoL, a sarcoma-specific measurement strategy should be developed and used covering the heterogeneity of sarcoma including location-specific issues to improve personalised HRQoL assessment in future research and clinical practice.

INTRODUCTION

Sarcomas are a heterogeneous group of malignant neoplasms arising from mesenchymal cells. There are >70 histological subtypes with widely different patterns of stage at diagnosis, prognosis and treatments.[1] Sarcomas can affect patients of any age and occur at almost any anatomical site. They are broadly classified into soft tissue sarcomas (STS; 84% of all sarcomas) and bone sarcomas (BS). The overall incidence of sarcoma is about 7 in 100 000 persons per year, with 30 000 new cases per year in Europe.[2] The 5-year relative survival in Europe (period 2000–2007) is 60% and 50% for STS and BS, respectively.[3] In 2008, 280 000 people were estimated to be alive in Europe following a sarcoma diagnosis.[4]

The treatment of sarcomas is dependent on patient characteristics such as age and gender and the site, stage, grade and histology of the tumour. For patients with localised STS the treatment consists of surgery, which might be combined with (neo)adjuvant radiotherapy or neoadjuvant chemotherapy. In patients with localised BS, surgery is standard treatment, and is combined with chemotherapy in case of osteosarcoma and chemotherapy and radiotherapy in case of Ewing sarcoma. Surgical approach to localised BS and STS can broadly differ, ranging from complex orthopaedic reconstructions for extremity BS to extended multivisceral resection for retroperitoneal STS. In patients with metastatic STS or BS, systemic treatment is the mainstay of therapy and—on indication—radiotherapy, surgery or other local treatment of metastases.

Although survival rates for sarcoma have improved in the past two decades, overall survival especially in the metastatic setting is still poor, for example, in STS median overall survival is 12–20 months.[3 5 6] Most research in sarcoma is thus focused on further improvement of survival rates, but treatment for sarcoma may come at a cost of short-term and long-term side effects.[7 8] Therefore, it is important to assess treatment effectiveness both in terms of objective outcomes (eg, recurrence, response and survival) and in terms of subjective patient-reported outcomes (PROs) including health-related quality of life (HRQoL). This is a multidimensional concept that includes the patient's perception of the impact of the disease and its treatment on physical/biological, psychological and social functioning,[9] according to the biopsychosocial model.[10] Incorporating PROs into clinical practice improves patient-provider communication, symptom control and treatment satisfaction[11 12] and routine PRO monitoring in the metastatic setting and immediate response to adverse events leads to less hospital admissions and a survival benefit.[12]

High-quality HRQoL data of patients with sarcoma are sparse.[8 13] Two systematic reviews have recently been published on the impact of sarcoma on HRQoL in the patient population as a whole, reporting lower scores in physical and psychological HRQoL domains than the general population.[14 15] This can be attributed to decreased physical and cognitive functioning, disease interference in family life, social and leisure activities and an intense experience of disease-related and treatment-related symptoms such as fatigue and pain.[7 16] However, given the heterogeneity of the disease, the results of these systematic reviews are difficult to apply to individual patients as they report on generic HRQoL issues and therefore miss important sarcoma-specific problems related to subtype, location, age or treatment.

A sarcoma-specific HRQoL measure is currently lacking, as existing HRQoL measures for patients with sarcoma are focused on physical functioning only (eg, Toronto Extremity Salvage Score (TESS) as measure of physical disability[17]) or patient experiences (eg, Sarcoma Assessment Measure (SAM)[18]). However, assessment of HRQoL in this heterogeneous population is challenging.

Unravelling the heterogeneity of HRQoL of adult patients with sarcoma is the next step in improving our knowledge of the impact of sarcoma on patients' daily life and developing a strategy for HRQoL measurement making HRQoL more applicable in future research and clinical practice. The objectives of this systematic literature review were to gain insight into the (1) generic and tumour location-specific HRQoL issues in adult patients with sarcoma; (2) HRQoL measures currently used in sarcoma research.

METHODS

Search strategy

A systematic search of the literature through the search engines Medline, Embase, PsycINFO and Web of Science was performed on 8 April 2019, according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[19] The search strategy combined MeSH terms and keywords for sarcoma and quality of life. Keywords for qualitative research were added to ensure that all qualitative research done in this field was found. The full search string is presented in online supplemental appendix 1.

Selection criteria

Full paper studies reported in English and published in 2000 or later were included if: (1) the objective was to describe HRQoL of patients with sarcoma; (2) patients had an age at sarcoma diagnosis of ≥15 years, as previous research has shown that patient-reported outcome measures (PROMs) that were developed for adults are applicable to adolescents and young adults (AYAs).[20]

Studies were excluded: (1) if they presented data of a study sample that included patients with gastrointestinal stromal tumours, desmoid-type fibromatosis, giant cell tumours, tenosynovial giant cell tumour formerly known as pigmented villonodular synovitis, Kaposi sarcoma, carcinosarcoma or benign bone or soft tissue lesions that comprised >20% of the total population; (2) if the study sample consisted of multiple cancer types including sarcoma but the HRQoL outcomes for patients with sarcoma could not be extracted; (3) if they presented data of fewer than 10 patients with sarcoma and (4) if they presented physician-reported outcome data (eg, Musculoskeletal Tumour Society Score). The described selection criteria were applied to the hits. The abstracts, titles and full papers were reviewed by two investigators (DdH and MR).

Data extraction and synthesis for location-specific HRQoL

Study aim and design, study population, used HRQoL measures and HRQoL outcomes were extracted from included articles. We stratified the selected articles according to tumour location as described in the original papers in the following categories: retroperitoneal and abdominal, head and neck (including scalp and skull base), axial skeleton (spine and pelvic bones), extremities (upper and lower), pelvic and extremity sarcoma (described as a separate category, because five studies reported HRQoL for these patients as one group), thoracic (including thoracic wall, pleurae, lung, heart, breast) and urogenital (including uterine and paratesticular). If one article reported HRQoL for different specific locations, the results are included for each category separately. Articles that presented HRQoL for multiple locations of sarcoma together were analysed in a separate category as sarcoma-generic issues. Due to the heterogeneity of inclusion criteria and methods, it was not possible to conduct a meta-analysis, so results were reported descriptively.

RESULTS

Sample

A total of 3947 studies were identified in the search. After title and abstract screening, 355 met our criteria for full-text review. From the full-text papers, 87 articles could be included in this review. The flow chart of the selection procedure is shown in figure 1.

Study characteristics

In total, 87 articles were included, which were published between 2000 and 2019. Studies had a qualitative (n=5), quantitative (retrospective n=47; prospective n=27) or interventional (n=8) design. The study characteristics and main findings are summarised in table 1 and online supplemental appendix 2. Fifty-four different PROMs

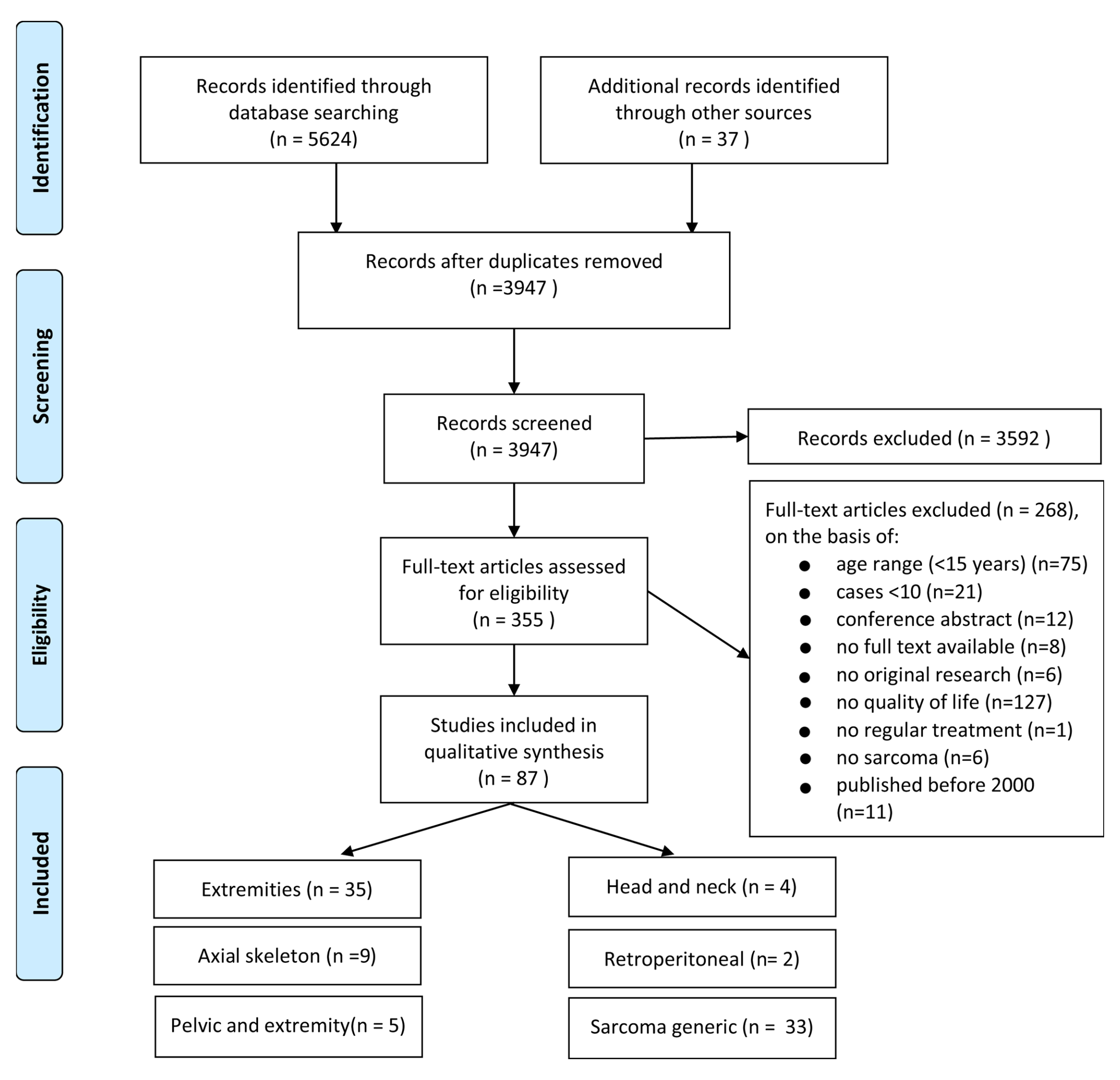

Figure 1 Selection procedure.

were used, of which 7 were solely focused on functional outcomes and 47 on HRQoL or some of its domains. The characteristics of 17 measures used in more than one study are described in table 2. The sarcoma-specific TESS was the most frequently used questionnaire (n=28), followed by the cancer-generic HRQoL questionnaire European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) (n=19), and generic HRQoL measures Short Form Health Survey (SF-36) (n=18) and EuroQol-5 dimensions questionnaire (EQ-5D) (n=14) (table 2).

Location-specific HRQoL

Extremity sarcoma (n=35)

Studies (2 interventional, 10 prospective, 23 retrospective studies of which one with qualitative design) included patients with extremity BS (N=8) or STS (N=20) or both (N=7).[21–55] Mean HRQoL or TESS scores did not differ between BS and STS except in one study, however, no statistical tests were applied for comparison of these subgroups.[51] Four studies also included patients who had undergone amputation: one with BS patients only, one with STS patients only and two with both subtypes.[41 42 45 49] Only three studies compared outcomes between patients with upper and lower extremity sarcoma.[26 36 51]

Overall HRQoL or health status, as measured by EQ-5D (-VAS), EORTC QLQ-C30 or SF-36, was comparable to that of the normative populations in 10 studies.[23–25 28 36–40 43] Additionally, one retrospective cohort study reported that 74% of patients who had undergone limb salvage surgery were satisfied with their current health status.[44] In one prospective study, at 1 year after surgery 32%, 24% and 20% of patients experienced a clinically important improvement, deterioration or no change in HRQoL as measured by EQ-5D, respectively.[25]

Ten studies found lower physical functioning, physical role functioning or physical component scores as measured by the SF-36, SF-8 or EORTC QLQ-C30 in patients with extremity sarcoma compared with a normative population.[22 26 27 30 33 35 38 39 41 43] Six studies further support this finding using other PROMs and report lower

Table 1 Included studies according to tumour location

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Extremity sarcoma					
Gerrand, 2004, Canada[54]	Examine the influence of anatomical location on functional scores	Retrospective Single centre	N=207, 48.8%, age 15–89 years, localised lower-extremity STS, LSS	TESS	Treatment of deep tumours did lead to significant changes in TESS postoperatively, but not in superficial tumours. TESS was lower postoperatively in deep tumours compared with superficial tumours.
Cassidy, 2016, USA[50]	Evaluate outcomes after conservative resection and radiotherapy	Retrospective Single centre	N=11, gender missing, median age 49 years, localised STS involving hand/wrist or foot/ankle, LSS and adjuvant RT	TESS	This treatment plan achieves robust functional preservation.
Fuchs, 2001, USA[29]	Assess function of lower extremity after LSS and complete resection of the sciatic nerve	Retrospective Single centre	N=10, gender missing, age at Dx* 28–84 years, localised STS of the thigh, LSS±RT	TESS	Tumours involving the sciatic nerve can be treated with LSS which provides acceptable functional outcome.
Heaver, 2016, UK[51]	Investigate what patient factors affect physical function outcomes	Retrospective Single centre	N=386, 70%*, age 20–85 years, primary extremity BS or STS, LSS	TESS	No direct comparison between the reported groups was made, but patients with BS had lower scores than patients with STS. Scores for upper extremity sarcoma were higher than for lower extremity sarcoma.
Jones, 2010, Canada[31]	Identify the functional implications for patients following femoral nerve resection	Prospective Single centre	(1) N=10, 0%, age at Dx 47–78 years. Localised STS, surgery including femoral nerve resection ±RT; (2) N=9, 56%, mean age 52±16 years; localised STS, surgery including sciatic nerve resection ±RT; (3) N=33, 0%, mean age 55±17 years; localised STS, anterior resection without nerve resection; (4) N=79, 58%, mean age 55±15 years, large anterior thigh STS resection without nerve resection	TESS	Femoral nerve resection appears more morbid than anticipated. Patients are prone to falls and its associated risks.
MacArthur, 2018, Canada[32]	Assess ambulation and function after microsurgical reconstruction for extensive STS tissue defects	Retrospective Single centre	N=17, gender missing, age 24–81 years, extensive lower extremity STS, microsurgical reconstruction after tumour resection±RT±CT	TESS	Microsurgical reconstruction of lower extremity sarcoma defects enables preservation of independent ambulation. Three activities had the lowest TESS scores: kneeling, participating in sporting activities and getting up from kneeling.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Saebye, 2017, Denmark[36]	Identify tumour-related and patient-related factors associated with reduced functional outcome and QoL	Retrospective Multicentre	N=128, 57.8%, median age 61 years (IQR 47–70); localised STS, LSS	TESS EORTC QLQ-C30	Anatomical location in the lower limb, compared with location in the upper limb, was associated with reduced outcome. Results for the EORTC QLQ-C30 were not reported separately.
Schreiber, 2006, Canada[37]	Evaluate functional disability and HRQOL at 1-year postsurgery	Prospective Multicentre	N=79 (TESS), 95 (RNL), 73 (EQ-5D-VAS), gender missing, age 18–86 years, localised STS, LSS±RT	TESS RNL EQ-5D-VAS	Patients on average reported little participation restrictions and high levels of functioning and HRQoL.
Tang, 2015, Australia[40]	Identify the prevalence, trajectory and determinants of distress and characterise sources of stress in patients with extremity sarcoma	Prospective Single centre	N=76, 59.2%, age at Dx 16–86 years; localised STS or BS, surgery±neoadjuvant CT or RT	TESS EORTC QLQ-C30 DASS21† SSS†	Distress was reported by about a third of the cohort. Proportion of patients reporting moderate/severe stress and depression increased with time, proportion reporting moderate/severe anxiety scores reduced with time. Pain scores improved from 6 months after surgery to 12 months after surgery. TESS scores decreased significantly from baseline to 6 months postoperatively, back to baseline at 12 months. No differences in QoL, mental health and physical function between baseline and 12 months after surgery.
Townley, 2013, Canada[47]	Report experience with free flap microsurgical reconstruction of irradiated STS defects	Retrospective single centre	N=21, gender and age missing, localised STS, neoadjuvant RT and resection+free flap reconstruction (N=15), Control group (N=6): localised STS or BS resection±postoperative RT	TESS	No difference in functional outcomes between the two patient groups.
Tunn, 2008, Germany[53]	Obtain a standardised evaluation and comparison of functional long-term outcome	Retrospective single centre	N=55, gender missing, age 26–73 years, Localised BS, LSS+reconstruction with tumour endoprosthesis	TESS RNL	Physical disability and activity limitations are perceived to only a small degree by patients. The proportion of occupational disability and unfitness for work was 14% in age group 26–40 years vs 63.6% in age group 41–73 years.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Davidge, 2009, Canada[23]	Examine the relationship between pretreatment outcome expectations and postoperative function and HRQoL	Prospective Single centre	N=157, 62%, age at Dx 16–87 years, localised STS, LSS±RT	TESS RNL EQ-5D-VAS LOT Questionnaire on outcome expectations	The perceptions of the ability to reintegrate into life roles and situations (RNL) and global health state (EQ5D-VAS) were higher postoperatively, whereas activity limitations (TESS) were similar. Patient's outcomes expectations were high.
Davidge, 2010, Canada[24]	Evaluate the impact of flap reconstruction compared with primary closure on postoperative function and health status	Prospective Multicentre	N=247, 57%, mean age 58.2±16.7 years (flap reconstruction group) and 54.0±16.9 (primary closure group), localised STS, LSS±RT	TESS RNL EQ-5D-VAS	At baseline, flap reconstruction had more activity limitations and participation restrictions than primary closure. Postoperatively soft tissue reconstruction had more activity limitations than primary closure. Most patients maintained a higher level of HRQoL.
Davidson, 2016, Canada[25]	Estimate change in HRQoL between time of diagnosis and 1 year following surgery	Prospective Single centre	N=220, 59%, mean age at Dx 54.4±16.6 years, primary or recurrent localised STS, surgery±RT±CT	TESS EQ-5D-5L	The overall sample was relatively stable with regard to HRQL and activity limitations over this time frame. The domain which demonstrated the most qualitative change in the distribution of levels was anxiety/depression.
Biau, 2007, France[21]	Assess the results of the reconstruction in regard to function, disability and HRQoL	Retrospective Single centre	N=18, 72%, age at Dx 18–76 years, localised lower extremity BS, resection+reconstruction with allograft-prosthesis composite	TESS Self-reported Harris Hip† Score SF-36	Function and disability scores were good, although some patients yielded poor functional results.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Davis, 2002, Canada[26]	Evaluate physical function and general health status comparing preoperative and postoperative radiotherapy	Interventional Multicentre	N=185, 45%, age 18–93 years, localised STS, combined (preoperative/postoperative) RT and LSS	TESS SF-36	1 year after surgery, mean scores on all measures returned to pretreatment levels for both groups. Two-year mean scores for SF, RE and MH were higher than the prerandomisation scores for both treatment arms. The PF, RP, RE, BP and GH subscale for both treatment groups were lower than normative data at all time points. The vitality, social and mental health subscale scores at 2 years for both treatment groups approximated the reported normative values. TESS change scores were predicted (negative impact) by lower-extremity as opposed to upper-extremity tumour location.
Davis, 2000, Canada[27]	Evaluate tumour and treatment variables predictive of post-treatment functional outcomes	Retrospective Single centre	N=172, 51%, mean age 51±15.2 years, localised lower extremity STS, LSS	TESS SF-36	On average, patients had a relatively limited disability. PF, RP, GH and PCS are below the normative data. Patients with large, high-grade tumours who required major motor nerve resection had greater physical disability or difficulty with routine daily activities.
Heyberger, 2017, France[30]	Investigate the difference between primary and revision megaprosthesis of the distal femur in function and activity-related outcomes	Retrospective Single centre	N=71, 56%, age at Dx 19–43 years, localised BS, reconstruction with cemented fixed hinge custom-made megaprosthesis after resection of a primary malignant bone tumour of the distal femur or after revision of a previous megaprosthesis	TESS SF-36	Patients in the revision group performed significantly better on disability scores and on HRQoL scores than patients who are operated for a primary distal femoral replacement.
Malo, 2001, Canada[33]	Understand impact of distal femoral endoprosthetic replacement on patients’ function	Retrospective Multicentre	N=56, 50%, mean age 36±18 years, localised lower extremity BS, resection and distal femoral endoprosthetic replacement±CT	TESS SF-36	Most frequently reported as difficult were: kneeling, performing sports activities, rising up from kneeling, gardening, performing heavy household duties, walking upstairs and downstairs and walking up and down hills. SF-36 subscales PF and RP were lower than normative data.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
O'Sullivan, 2002, Canada[34]	Determine whether timing of external-beam RT affected the number of wound healing complications	Interventional Multicentre	N=182, 52%, age >15 years, localised STS, randomised to preoperative or postoperative RT	TESS SF-36	Patients given postoperative radiotherapy had significantly better function, but also more pain at 6 weeks after surgery than did those in the preoperative group.
Rivard, 2015, Canada[35]	Document functional and QoL outcome measures	Prospective Single centre	N=45, 67.3%, age* 24–83 years, primary or recurrent trunk (n=2) or extremity STS (n=43), preoperative CT+RT and surgery	TESS SF-36	Baseline scores were lower (data not shown) than the normative SF-36 scores. By 12 months, there was significant improvement in TESS, PCS and MCS scores, as well as RP, BP, VT, SF and RE.
Tanaka, 2016, Japan[38]	Predict the knee extension strength and postoperative function in quadriceps resection	Retrospective Single centre	N=18, 77.8%, age at Dx 34–85 years, localised STS of the thigh, quadriceps resection±CT±RT	TESS EQ-5D-5L SF-8	For SF-8, median values for the physical scales of PF, RP, BP and PCS in the eight subscales and two summary scores were below the national standard values. Median values for the mental scales of SF, RE, MH and MCS were at or above the national standard values. Median TESS and EQ-5D scores were relatively high.
Tanaka, 2017, Japan[39]	Evaluate the postoperative function after knee flexor muscle resection	Retrospective Single centre	N=17, 47.1%, age 36–86 years, localised lower extremity STS, knee flexor muscle resection	TESS EQ-5D-5L SF-8	Median values of PF, RP, BP and PCS of the SF-8 were below the Japanese national standard. Median values of the mental scales, SF, RE, MH and MCS were above the national standard. Median TESS and EQ-5D scores were relatively high.
Bekkering, 2010, The Netherlands[22]	Compare HRQoL between young adults following surgery to healthy controls	Retrospective Multicentre	N=48, 48%, age 16–25 years, BS around the knee, LSS or ablative surgery	TAAQOL in patients >15 years SF-36	Scores on gross motor, cognitive functioning, pain and daily activities were lower compared with healthy peers. Lower scores were found in the patients with sarcoma for the domains PF, RP, GH and PCS compared with their healthy peers. Mean MCS was higher in patients with sarcoma.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Bekkering, 2012, The Netherlands[55]	Evaluate patients' QoL, functional ability and physical activity postoperatively	Prospective Multicentre	N=34, 61%, age ≥15 years, all stages lower-extremity BS, LSS or amputation	TAAQOL SF-36	Between 3 and 12 months after surgery, gross motor functioning, daily activities, and PCS scores of the TAAQOL and the PF, SF, RP and PCS scores of the SF-36 improved significantly. Changes between 12 and 24 months were not significant, except for the PF and PCS scales.
Fischer, 2015, Germany[28]	Measure the outcome of hamstring transfer for quadriceps reconstruction after STS resection	Retrospective Single centre	N=17, 39.5%*, age* 30–84 years, localised STS of the anterior thigh compartment, resection and hamstring transfer±CT±RT	SF-36	Overall QoL assessment and postoperative patients satisfaction was good.
Thijssens, 2006, The Netherlands[41]	Gain insight into the QoL and aspects possibly affecting QoL, compared with general population	Retrospective Single centre	N=39, 41%, age at Dx 14–72 years, locally advanced STS (some also metastatic), isolated limb perfusion with TNF-α and melphalan followed by resection±adjuvant RT. Some patients would still undergo amputation in follow-up	SF-36 IES	Patients reported lower PF and RF. Patients who underwent amputation reported worse PF and SF, and had more role limitations due to physical and emotional problems than patients whose limb could be saved. Eleven patients (28%) had a total stress response symptom score of 0. Eight patients (20.5%) had a score ≥26, which suggested that psychological counselling was needed. None of the patients with amputations had a clinically significant PTSD.
Peiper, 2011, Austria[43]	Report outcome and QoL of patients undergoing compartmental resection	Prospective Single centre	N=28, 39%, age* 18–82 years, localised STS (two patients with distant metastasis), surgery±CT±RT	EORTC QLQ-C30	Decreased scores in all dimensions compared with a normal population were found, with the greatest decrease in scores for overall physical function, physical role function and social function. Symptom scores all were markedly higher as well. The personally sensed overall health status hardly differed from the norm population.
Bressoud, 2007, Switzerland[42]	Assess the functional, psychological and familial status of long-term survivors	Retrospective Single centre	N=10, 50%, age 15–34 years, localised extremity (and one pelvic) BS, LSS or amputation±CT	MSTS: pain and emotional acceptance† GHQ-28† Inventory scale for traumatic neurosis	Symptoms of depression and post-traumatic stress disorder or poor emotional acceptance are observed in around one-third of patients. A majority of patients showed poor emotional acceptance. .

Continued

Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Refaat, 2002, USA[44]	Evaluate QoL after treatment for a primary bone or soft tissue sarcoma of the lower extremity and compare LSS and amputation	Retrospective Single centre	N=342, 47%, age at Dx 22–97 years, high-grade lower extremity BS or STS, LSS	Own design† (functional status, physical, occupational and psychosocial adjustment to disease and its treatment)	82% of 279 patients had to use a leg brace; >50% needed a cane or crutch; 89% indicated they had a limp; 281 were able to drive automobiles without difficulty; 58% of men and 42% of engaged in sports; 85% of the males and 70% of the women in the limb-sparing group were employed, respectively; 33% (31/94) of the male patients reported loss of potency; 75% of the patients maintained an active sex life; 19% of 140 patients had either sired or borne a child; 17% was periodically depressed. Periodical anxiety occurred in 22%; 24% of the patients stated they had periodic disturbances of sleep; 23% required pain medication periodically; 74% expressed satisfaction with their current status.
Skaliczki, 2005, Hungary[52]	Report the outcome of endoprosthetic reconstruction	Prospective Single centre	N=22, 45%, mean age at Dx 25 years, BS of the knee region, LSS with endoprosthetic replacement	OKQ†	The results in cases of distal femoral tumours were significantly better than in those of proximal tibial tumours.
Wilke, 2019, USA[45]	Use PROMIS to compare outcomes of patients with sarcoma with the US population	Retrospective Single centre	N=138, 56%, age 18–94 years, localised STS and BS, LSS or amputation±RT±CT	PROMIS 43	Physical function (ie, worse function) and depression scores were reduced when compared with US general population (ie, less depression); 47% of the patients scored the lowest (best) score for depressive symptoms.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Wilke, 2019, USA[49]	Use PROMIS to compare outcomes between limb salvage and amputee patients	Retrospective Single centre	N=138, 56%, mean age 58 years, localised STS and BS, LSS (n=114) or amputation (n=24)±RT±CT	PROMIS 43	Physical function scores were low after surgery. The LSS cohort demonstrated higher physical function scores than the amputation cohort. Patients initially reported low scores in the ability-to-participate domain. This increased to normal levels in the amputation cohort and higher levels in the LSS cohort compared with that in the general population in the late follow-up cohort. When compared with the US population, patients who underwent LSS reported less difficulty with depression, fatigue and sleep disturbance.
Wilke, 2019, USA[46]	Compare PROMIS outcomes between a planned resection versus initial unplanned excision	Retrospective Single centre	N=85, 61%, mean age 60±18 years, localised STS who underwent an unplanned or planned excision±adjuvant RT±CT	PROMIS 43	Significantly lower physical function score in the planned resection cohort when compared with the US general population was found, but not in the unplanned excision group. Depression and fatigue levels in both the planned and unplanned resection cohorts were significantly lower (ie, less depression/fatigue) than in the US general population.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Parsons, 2008, Canada[48]	(1) Characterise experiences of illness; (2) characterise the experiences of resuming vocational pursuits in the context of OS; (3) understand and explain the relationship between these experiences	Retrospective Single centre	N=14, 57%, age 16–35 years, osteosarcoma (disease stage not specified), LSS and CT	Qualitative (interview)	Respondents recounted three kinds of work in which they engaged: illness work, identity work and vocational work. Illness was depicted by respondents as a crisis in their lives, characterised by intensive ‘work’. The all-consuming nature of illness work was the primary reason offered by respondents for stopping vocational pursuits for considerable periods. The crisis of illness also precipitated important ‘identity work’. Respondents told of ‘becoming other’ to who they had been prior to illness. As a result of these transformative experiences, respondents noted that they returned to the vocational sphere different from when they left it. As such, they recounted a changed relationship to vocation.
Sarcoma of the axial skeleton					
Kiiski, 2018, Finland[56]	Evaluate the results of sacrectomy reconstruction and its impact on patients’ QoL	Prospective Single centre	N=10, 57%, age at Dx 22–81 years. BS (disease stage not specified), sacrectomy±reconstruction (immediately or delayed)	EQ-5D-5L	No differences were found between the preoperative and postoperative EQ-5D index or any of its dimensions, but there was a trend towards reduced pain and discomfort postoperatively.
Song, 2017, USA[57]	Characterise symptom burden and life challenges that chordoma patients and their caregivers experience	Retrospective Through chordoma foundation	N=101 with sacral or coccyx localisation/ N=92 for chordoma of the mobile spine (of 327 in total), 56%*, age range* 18–74 years, chordoma, surgery, RT, systemic therapy or multiple treatments	Own online survey†	Most common symptoms in sacral or coccyx chordoma: difficulty sitting (55%), difficulty walking (53%) and sexual dysfunction (49%). In chordoma of the mobile spine, the most common symptoms were chronic pain (54%), difficulty walking (49%) and limited mobility (41%).

Continued

Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Phukan, 2016, USA[58]	Compare QoL based on level of sacral resection (S1–S5) in terms of physical and mental health, pain, mobility and incontinence and sexual function	Prospective Multicentre	N=33, 59.7%, age 22–72 years, BS of the sacrum (disease stage not specified), surgery	PROMIS: multiple domain surveys ICS voiding and incontinence scores† MODS†	Patients with more caudal resections had higher physical health, less intense pain, less interference resulting from pain, higher mobility and were more functionally able to achieve orgasm. No difference was found for Mental Health Subscore, Sex Interest, Sex Satisfaction, modified obstruction and defecation score and International Continence Society Voiding and Incontinence. All scores were not worse than the general population, except for patients who had resections at S4 and below: they had a mean pain and mobility scores that were lower than that of the general population.
Fisher, 2005, Canada[59]	Validate appendicular surgical oncology principles	Prospective Single centre	N=14, 46%*, age at Dx 16–70 years, localised BS or STS of the spine, surgery	SF-36	Decreased mean PCS compared with normative population. Similar mean MCS compared with normative population.
Schwab, 2017, USA[60]	Compare measures of the QoL after resection with the national averages in the USA	Retrospective Single centre	N=48, 65%, age 45–65 years, Chordoma of the mobile spine, surgery or RT	EQ-5D-3L PROMIS anxiety, depression and pain interference surveys	Patients had worse QoL scores than the average in the population of the USA, and they had more anxiety and difficulty coping with pain. Patients with cervical chordoma had better QoL scores than those with thoracic or lumbar chordoma.
Aljassir, 2005, Canada[61]	Evaluate survival, function and complications of a saddle prosthetic reconstruction	Retrospective Single centre	N=27, 67%, 24–76 years, pelvic sarcoma (BS+STS) 26% had metastatic disease, saddle prosthesis reconstruction after pelvic resection±CT	TESS	The functional results seem to confer an advantage when compared with the considerable disability incurred after hemipelvectomy.
Griesser, 2012, USA[62]	Compare QoL after internal hemipelvectomy with and without prosthetic reconstruction and external hemipelvectomy	Retrospective Single centre	N=15, 73%, age 18–69 years, pelvic (4 advanced, 11 localised) BS, internal hemipelvectomy with and without (flail hip) prosthetic reconstruction or external hemipelvectomy±CT±RT	TESS SF-36	Functional outcome is reduced in patients. There was no statistical difference between external and internal hemipelvectomy in terms of TESS and PCS. MCS is similar to the general population.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Wafa, 2014, UK[63]	Evaluate the functional and oncological outcome of extracorporeally irradiated autografts for reconstruction	Retrospective Single centre	N=10, 80%, age 16–62 years, all stages of pelvic BS, en bloc resection with re-implantation of the extracorporeally irradiated segment of bone±preoperative or postoperative adjuvant CT	TESS	Extracorporeal irradiation and re-implantation of bone has an acceptable morbidity and a functional outcome that compares favourably with other available reconstructive techniques.
Beck, 2008, USA[64]	Compare functional outcomes and HRQoL of patients following hemipelvectomy	Retrospective Single centre	N=97, 68%, age at surgery 33–66 years, localised or metastatic (n=13) pelvic sarcoma (BS+STS), internal or external hemipelvectomy	LASA†	Overall QoL and subcategories on LASA were similar between internal and external hemipelvectomy except pain severity (more pain after external hemipelvectomy).
Sarcoma of the pelvis and extremities					
Benedetti, 2016, Italy[65]	Analyse the rehabilitation needs of patients with primary malignant musculoskeletal tumours	Prospective Single centre	N=22, 77%, age 15–52 years, pelvic or extremity BS or STS, disease stage not specified, LSS or amputation±CT	VAS (pain) For VAS≥3: McGill Pain Questionnaire Short Form† EORTC QLQ-C30 PDI†	QoL increased with time, as did the functional scores. Symptom scores decreased correspondingly. The PDI did not undergo substantial changes over time. Pain was the worst postoperatively and required treatment with painkillers.
van der Geest, 2002, The Netherlands[66]	Analyse functional outcome and QoL	Retrospective Single centre	N=45, gender missing, age at Dx 18–79 years, localised extremity or pelvic chondrosarcoma, surgery	CIS SCL-90 EORTC QLQ-C30 RAND-36-PF LOT	Patients are more severely fatigued and have a lower motivation and less optimism than healthy controls. They also score higher on somatisation, obsessive-compulsive behaviour and sleep disturbances. The mean score of the physical functioning subscale from the RAND-36 was lower for patients compared with scores of controls.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Fauske, 2015, Norway[67]	Explore how former bone patients with sarcoma experience physical and psychosocial late effects after treatment	Retrospective Single centre	N=10, 70%, age 18–60 years, localised osteosarcoma in hip/pelvic region, surgery±CT±RT	Qualitative (interview)	Important consequences of treatment are limping, impaired physical activity, daily use of crutch/stick, problems with balance, pain affecting daily life, fatigue influencing daily life, daily practical challenges, being on disability benefit, daily use of wheelchair, taking care of colostomy or urostomy takes a lot of effort and energy when going away from home and loss of important hobby. They experience impracticalities of daily life, lost opportunities and an altered future. Social life is affected when they are unable to participate in activities in the same way as before. Identity has been affected, being defined as being disabled.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Fauske, 2016, Norway[68]	Identify how visible body changes following surgical treatment affect the life and identity of primary bone sarcoma survivors	Retrospective Single centre	N=18, 61%, age 18–60 years, BS (disease stage not specified) of the hip/pelvic region or lower extremities, surgery±CT±RT	Qualitative (interview)	Half of the participants expressed concerns about their visible differences, particularly those with functional impairment. They felt that it is important to hide the bodily signs of changes to appear as normal as possible. These changes influence their self-realisation, especially their social life. Most important problems were: limping, crutches/cane, wheelchair, amputation, erectile dysfunction, hernia, scars, thinner leg, shorter leg, discolouration, avoid undressing at the beach. They were hiding bodily deviations, did not want to be different, felt less attractive, wanted to be seen for who you really are, wanting to appear attractive and healthy, They face daily practical challenges and have a lack of energy. Participants experiences changes and losses in leisure time and social life, infertility concerns, and positive changes: having a changed sense of life and self, having more compassion for others.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Kain, 2017, USA[69]	Determine the sources and categories of information patients sought. Investigate how participants coped with physical and psychological issues that accompany treatment.	Retrospective Single centre	N=20, 55%, age 22–79 years, localised BS+STS, surgery±CT±RT	Qualitative (focus group)	Social support: ▶ family and friends provided most of the support but can also be a source of distress and anxiety; ▶ discussion with others with similar challenges was helpful; ▶ social media was a good source of emotional/psychological support. Restoration to 'normal' ▶ frustration that physical therapy was not focused on reaching a pretreatment level of activity; ▶ expectations for recovery differed by individual, with some expecting attaining a high level of function; ▶ managing psychological recovery can be more challenging than the physical limitations.
Head and neck sarcoma					
Diaz, 2014, Canada[70]	Measure functional outcome and QoL and identify determinants	Retrospective Single centre	N=83, gender missing, age <20–70 years, Skull base chordoma, surgery±RT±CT	SF-36 V.2.0 PHQ-9†	Patients with skull base chordomas have a lower QoL than the general US population. Presence of neurological symptoms is negatively associated with PCS and MCS.
Song, 2017, USA[57]	Characterise symptom burden and life challenges that chordoma patients and their caregivers experience	Retrospective Chordoma foundation	N=131 with skull base localisation (of 327 in total), 56%*, age* 18–74 years, chordoma, surgery, RT, systemic therapy or multiple treatments	Own online survey†	The three most common symptoms were double vision (50%), depression or severe anxiety (32%) and chronic sinus problems (31%).
Utyuzh, 2018, Russia[72]	Develop and assess efficacy of comprehensive treatment and rehabilitation	Interventional Single centre	N=21, 61.9%, osteosarcoma of the mandible (TisN0M0 or T1N0M0), preoperative CT, osteoplasty and further corrective surgery and postoperative CT; interventional group (N=10): additional mesodiencephalic modulation after surgery	SF-36	At 2 weeks postsurgery, overall QoL in the experimental was higher than in the control group. At 2 months after denture installation, QoL scores in all scales were higher in both study groups compared with T1, however scores were higher in the experimental group compared with the control group.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Srivastava, 2013, Italy[71]	Document changes in QoL of patients with chordoma treated with proton beam therapy	Prospective Single centre	N=12, 47%*, age* 21–73 years, chordoma of the skullbase, proton beam therapy (±prior surgery)	EORTC QLQ-C30	During treatment, HRQoL is not adversely affected. With stratification in the form of clinically important difference (>10 points change) for each category individually, both clinically important improvement and deterioration were detected in all domains of HRQoL.
Retroperitoneal sarcoma					
Callegaro, 2015, Italy[73]	Study long-term morbidity after extended surgery	Retrospective Single centre	N=95, 46%, age 44–64 years, primary retroperitoneal STS, disease stage not specified; surgery±CT±RT	Semi-structured interview BPI-SF LEFS†	Incisional hernia, bowel obstruction, constipation, diarrhoea, change in urinary habit and changes in sexual function occurred after multivisceral surgery. Chronic pain and lower limb motor impairment are rare.
Wong, 2017, Canada[74]	Examine how treatment-related toxicities affect QoL	Prospective Multicentre	N=48 (11 QoL at baseline and follow-up; 37 at follow-up only), 54.2%, age at Dx 38–82 years, primary or recurrent retroperitoneal STS, preoperative RT and surgery	EORTC QLQ-C30	Treatment toxicities (especially diarrhoea) seem to contribute to QoL recovery during the first 36 months. Global QoL of patients improved over the course of time to higher scores than before treatment.
Sarcoma generic					
Coens, 2015/van der Graaf, 2012 (PALETTE), Belgium[81 82]	Compare efficacy, safety and HRQoL outcomes of pazopanib with placebo	Interventional Multicentre	N=369 (246 pazopanib; 123 placebo), 41%, age 19–84 years, advanced STS and progressive disease after first-line CT, treated with pazopanib or placebo	EORTC QLQ-C30 EQ-5D-5L	Significant differences were found for diarrhoea, loss of appetite, nausea or vomiting and fatigue, with 10 point or more worse symptom scores for pazopanib. No differences were observed in scores for global health/QoL or on any of the functioning scales.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Gough, 2017, UK[88]	Describe symptom prevalence and severity in patients undergoing different treatment options for advanced STS	Prospective Single centre	N=113, 33%, mean age 59±14.5 years, advanced STS treated with first-line palliative CT (FLC), active surveillance (AS), prepalliative (AS pre-FLC) and postpalliative CT (AS-post-FLC) or palliative care alone (PC)	MSAS-SF†	Most symptoms were reported in the PC group, followed by FLC, AS post-FLC and AS pre-FLC. Most common physical symptoms reported by ≥40% of patients were pain, lack of energy, difficulty sleeping, feeling bloated, shortness of breath, difficulty concentrating, lack of appetite, drowsiness and constipation. Over 70% (n=79) reported psychological symptoms. Lack of energy, pain, shortness of breath, difficulty concentrating, drowsiness, feeling bloated, taste change and swelling of arms/legs all had >70% prevalence in those undergoing no further treatment. Patients with STS have a baseline symptom number and MSAS scores comparable with a mixed metastatic cancer population, except MSAS-PSYCH scores were higher.
Hudgens, 2017, USA[89]	Explore the relationship between disease progression and HRQoL	Interventional Multicentre	N=442, 33%, age 24–83 years, advanced STS, randomised in the eribulin (n=228) or dacarbazine (n=219) arm	EORTC QLQ-C30	At baseline, there were no differences between two treatment arms for any of the global health score and functioning domains. Patients had a >10-point change in dacarbazine and overall scores (total population) in role functioning from baseline to progression. Dacarbazine patients had a >10-point increase in fatigue and appetite loss, in the total population (overall) there was a >10-point increase in fatigue.
Mo, 2018, China[87]	Evaluate CT-guided iodine-125 (^{125}I) brachytherapy for patients with metastatic STS after first-line CT failure	Retrospective Single centre	N=93, 51%, age 20–65 years, metastatic STS that progressed after first-line CT, ^{125}I brachytherapy+second-line gemcitabine (N=45, group A) or second-line gemcitabine only (N=48, group B)	EORTC QLQ-C30	After treatment, the improvement in QoL scores were significantly higher in group A than group B.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Reichardt, 2012, Germany (SABINE study)[86]	Describe utility weights and assess HRQoL among patients with metastatic STS or BS	Retrospective Multicentre	N=116, 41.4%, age at metastatic disease Dx 16–83 years metastatic STS (mSTS) (n=96) or BS (mBS) (n=20) patients who had attained a favourable response to CT	EQ-5D-5L EORTC QLQ-C30 3-item cancer-related symptoms†	The mean EQ-5D utility score was 0.69 for the pooled patient sample with little variation across health states. Patients with progressive disease had lower utility than patients with stable disease that are off CT. For patients with progressive disease, there was large decrease in QoL compared with patients off CT with stable disease. Role and social functioning had the lowest scores. Pain and respiratory symptoms were common. Results for symptoms were consistent across the mSTS and mBS subsamples.
Schöffski, 2016, Belgium[83]	Compare overall survival in advanced or metastatic STS treated with eribulin or dacarbazine (QoL as exploratory end point)	Interventional Multicentre	N=437, 33%*, age 24–83 years, advanced or metastatic leiomyosarcoma or liposarcoma with progressive disease after at least two standard systemic regimens for advanced STS, eribulin or dacarbazine	EORTC QLQ-C30 EQ-5D-5L	Most patients had maintained or improved QoL and there were no significant differences between the eribulin and dacarbazine group.
Seddon, 2017, UK (GeDDiS trial)[85]	Compare efficacy, toxicity and QoL of gemcitabine and docetaxel versus doxorubicin	Interventional Multicentre	N=132, 40%*, age* 45–64 years, high-grade advanced STS, either gemcitabine and docetaxel, or doxorubicin as first line palliative treatment	EORTC QLQ-C30 EQ-5D-5L EORTC-FA13†	QoL measures did not differ between the treatment groups at 12 weeks postrandomisation, although numerically GHS was lower for gemcitabine/docetaxel.
Tap, 2017, USA[84]	Assess benefit of adding evofosfamide to doxorubicin for advanced STS	Interventional Multicentre	N=640, 46%, age 49–67 years, unresectable or metastatic STS, of intermediate or high-grade, evofosfamide+doxorubin or doxorubicin as first-line palliative treatment	EQ-5D-5L	No differences in EQ-5D-5L outcome measures were reported on the basis of individual items scores, VAS or health utility index, despite higher rates of toxicity in the combination group than in the doxorubicin alone group.
Granda-Cameron, 2011, USA[96]	Examine symptom distress and QoL	Prospective Single centre	N=11, 36.4%, age at Dx 20–61 years, all stages of STS and BS, newly diagnosed patients receiving CT	ESAS† FACT-G	Total mean FACT-G scores decreased from cycle 1 to cycle 6. Functional well-being had the lowest mean functioning score at each chemotherapy cycle except at cycle 8. Patients with BS had increased fatigue and drowsiness over time, as well as decreased physical well-being. Patients with STS experienced diminished overall QoL scores over time.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Admiraal, 2013, The Netherlands[102]	Examine differences in distress levels between different cancer types	Retrospective Multicentre	N=49, 37.4%*, age* 21–89 years, STS and BS (disease stage not specified), all treatments	DT/PL† HADS	Comparable mean scores for distress were found for sarcoma, compared with patients with lung, breast, digestive, gynaecological, urological and head/neck cancer.
Buchner, 2004, Germany[91]	Report outcome, functional results and QoL of elderly patients (aged >70 years) after surgery	Prospective Single centre	N=39, 47%*, age at Dx* 70–91 years, stage I–III BS+STS, surgery (sparing or amputation)±CT±RT	Life Satisfaction Index A† EORTC QLQ-C30-GHS	QoL of elderly patients with sarcoma was only slightly inferior to results reported in a population of older people without tumour disease and almost equalled those reported for younger patients with sarcoma.
Chan, 2015, Singapore[7]	Investigate the symptom burden and relationship between symptom burden and HRQoL	Retrospective Single centre	N=42, 58.2%* mean age* 57.3±15.2 years, BS+STS (disease stage not specified), surgery, CT or RT	RSCL† BAI† FACT-G	Patients with sarcoma (non-GIST) reported more activity impairment, higher physiological symptom burden, psychological symptoms, higher anxiety scores and a lower HRQoL score compared with patients with GIST.
Farooqui, 2013, Malaysia[93]	Assess the profile HRQoL of Malaysian patients with oncology	Retrospective Single centre	N=11, 34%*, mean age 54 years*, all stages of BS, treatment not specified	EORTC QLQ-C30	Patients with bone cancer had the lowest mean global health score compared with other cancer sites.
Henderson, 2009, USA[76]	Determine efficacy and safety of chordoma treatment with CyberKnife stereotactic radiosurgery	Prospective Single centre	N=18, 50%, age 24–85 years, chordoma, CyberKnife stereotactic radiosurgery (CK/SRS)	SF-12	Scores for the MCS of QoL remained stable, regardless of whether the patients had undergone surgery and CK/SRS or irradiation alone. Overall, the mean PCS and MCS scores of patients improved and sustained a durable improvement throughout the period of observation.
Horick, 2017, USA[104]	Investigate self-reported QoL outcomes of a rare cancer diagnosis and treatment	Prospective Multicentre	N=50, 59%*, age* 18–86 years, sarcoma subtype, stage and treatment not specified	SF-12 BSI-18† 3-item loneliness scale†	Mean psychological distress score varied significantly by cancer type, with patients with sarcoma reporting the least distress (less than the population mean of 50) compared with other cancer types.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Kuo, 2011, UK[97]	Investigate prevalence of pain in patients with sarcoma, adequacy of pain control	Retrospective Single centre	N=149, 44%, age 19–98 years, all stages BS and STS, all treatments	BPI S-LANSS† PMI†	Prevalence of any pain in the previous 7 days in the study population was 53%; 61% of patients who reported pain had background pain for over 3 months in duration. Breakthrough pain was problematic in 57%; 39% had unresolved breakthrough pain for >3 months; 63% who reported pain were not adequately treated; 36 patients had pain of nociceptive origin, 7 neuropathic and 36 mixed nociceptive and neuropathic. Of those with a neuropathic component, 11 were taking adjuvant analgesics such as antidepressants or anticonvulsants. Seven patients felt that their pain was due to direct pressure from the tumour, one due to metastatic disease. Fifty patients had pain due to anticancer treatment, and 21 had pain from non-cancer causes.
Lazenby and Khatib, 2012, Jordan[103]	Determine whether spiritual well-being is correlated with HRQoL	Retrospective Single centre	N=11, 33.3%*, age* 19–77 years, Muslim patients with cancer including those with BS+STS (disease stage not specified), treatment not specified	FACT-G FACIT-Sp†	FACIT-Sp scores are comparable to scores for patients with other types of cancer. Social well-being was positively correlated with the FACIT-Sp for patients with sarcoma.
Leuteritz, 2018, Germany[95]	Describe overall life satisfaction in AYA patients with cancer	Prospective Multicentre	N=21, 25%*, age at Dx* 18–39 years, sarcoma subtype and treatment not specified	FLZ-M module A† PACIS† ISSS-8†	Compared with other cancer types, patients with sarcoma had the worst FLZ-M scores at both measurement points.
Naik, 2017, Canada[94]	Collect HU scores from patients with cancer with multiple disease sites	Retrospective Single centre	N=48, 47%*, age 18–100 years*, sarcoma subtype, stage and treatment not specified	EQ-5D	Mean utility scores were significantly higher in patients with sarcoma compared with patients with acute lymphoblastic leukaemia (reference category).
Ostacoli, 2012, Italy[92]	Compare HRQoL and anxiety and depression between patients undergoing chemotherapy for STS and patients with common types of cancer	Retrospective Multicentre	N=56 (STS)+N=56 (other cancer), 50%, mean age 53±14 localised, locally advanced or metastatic STS of the trunk, limbs, H&N, retroperitoneum, CT	FACT-G HADS	No statistical differences between the two groups with regard to QoL and anxiety. Significantly higher depression mean scores and moderate or severe depression are more frequent in the sarcoma group.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Paredes, 2011, Portugal[79]	Examine prevalence and levels of anxiety and depression in different phases of disease and analyse determinants of emotional adjustment of patients with sarcoma	Retrospective Multicentre	N=142, 56%, mean age 48±17 years, localised sarcoma, subtype not specified (disease stage not specified), surgery±CT±RT	HADS	<10% exhibited moderate or severe anxiety; 8.3% had moderate or severe depression with highest prevalence of cases with clinical depression during the treatment phase. Patients presenting with recurrence had higher levels of anxiety and depression symptoms in the diagnostic phase. During follow-up, patients who had been diagnosed for a longer time and patients who had terminated treatments for a longer time showed lower anxiety and depression levels.
Paredes, 2012, Portugal[80]	Examine change on emotional distress of patients with sarcoma from the diagnostic to treatment phases, the distinct trajectories of adjustment	Prospective Multicentre	N=36, 52.8%, mean age at Dx 40±16 years, localised BS or STS, neoadjuvant or adjuvant CT or RT or both	HADS Brief Cope†	Both in the diagnostic and treatment phases, patients' mean anxiety and depression scores were below the 'caseness' threshold and there were no significant differences between the two phases. Anxiety from diagnosis to treatment phase: 25% maintained clinically significant anxiety; 13.9% increase to clinically significant anxiety and 8.3% decreased to non-significant anxiety. Depression from diagnosis to treatment phase: 11.1% maintained clinically significant depression, 13.9% increased to clinically significant depression and 8.3% decreased to non-significant depression.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Paredes, 2011, Portugal[75]	Analyse change or stability in QoL of patients with sarcoma, and to identify the distinct trajectories of change from diagnostic to treatment phase	Prospective Multicentre	N=36, 52.8%, mean age at Dx 40±16 years, localised BS or STS, neoadjuvant or adjuvant CT or RT or both	EORTC QLQ-C30	Mean scores of patients with sarcoma in the functioning scales of QoL and mean global health/QoL score in the diagnostic and treatment phase were lower compared with the general population. Patients experienced more symptoms than the general population and more financial difficulties at both timepoints, except for pain that was higher at baseline only. During treatment, patients with sarcoma reported worse physical functioning and more fatigue, nausea and vomiting and appetite loss than at the time of diagnosis but a better overall QoL and less pain. A trajectory of change from a condition of ‘low QoL’ in the diagnostic phase to a condition of ‘high QoL’ in the treatment phase was found for 11.1% of patients, while 22.2% showed an inverse trajectory (from ‘high QoL’ cluster at baseline to ‘low QoL’ cluster at treatment).
Parsons, 2012, USA[105]	Examine the impact of cancer on work and education in a sample of AYA patients with cancer	Prospective Multicentre	N=18, 64%*, age at Dx* 15–39 years, osteosarcoma, Ewing sarcoma or rhabdomyosarcoma, disease stage and treatment not specified	Own survey† PedsQL-Modified Work/School functioning scale†	44.4% believed that cancer had a negative impact on plans for work or education among full-time workers and students prior to diagnosis. Patients with sarcoma who were full-time workers/students before diagnosis were more likely to be working/in-school at follow-up than patients with acute lymphocytic leukaemia and non-Hodgkins’s lymphoma.
Riad, 2012, Canada[99]	Compare clinical and functional outcomes of radiation-induced STS with sporadic STS	Retrospective Multicentre	N=18, 40.9%*, age* 27–85 years, radiation induced STS (RI-STS) of the extremities or chest wall/trunk (disease stage not specified), surgery±neoadjuvant CT±RT	TESS	Functional outcome was not significantly different in patients with RI-STS compared with sporadic STS. Six of 13 patients who received irradiation for their RI-STS developed late complications of fibrosis and/or lymphoedema.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Rustøen, 2003, Norway[98]	Examine how disease-specific variables affected pain in patients with cancer	Retrospective Single centre	N=28, 37%*, age* 18–80 years, sarcoma subtype, stage and treatment not specified	EORTC QLQ-C30 HADS	Similar pain levels were reported by patients with head and neck, lung, cervical and gastrointestinal cancer. Patients with sarcoma had significantly higher pain levels than patients with skin cancer.
Sachsenmaier, 2015, Germany[77]	Define a risk profile for new patients with sarcoma with the aim of offering early specialised treatment options, eg, psycho-oncological support	Retrospective Single centre	N=66 to 54.6%, localised BS or STS, surgery	Own design questionnaire†	Twenty patients (30%) could continue working without limitations. In 22% the attitude to their jobs after diagnosis changed; 27.3% suffered financial strain. Patients mentioned undesirable effects of therapy as the main stress factor (44.44%). Employed patients declared chemotherapy-related hair loss as significant impairment or main handicap compared with the unemployed group; 53% patients expressed great confidence in the future and 37.5% considered themselves to be completely emotional stable. Patients with poor emotional condition had wanted more support by the psycho-oncological service during treatment. Physical condition was considered very stable and excellent (n=26) or moderate (n=26).
Servaes, 2003, The Netherlands[78]	Investigate fatigue complaints in disease-free patients treated for bone or soft tissue tumours	Prospective Single centre	N=56, 54%*, age* 18–65 years, localised BS or STS, surgery±adjuvant CT±RT	CIS SCL-90 EORTC QLQ-C30 RAND-36-PF LOT CAS†	Grades 1, 2 chondrosarcoma : 26% severe fatigue Classical osteosarcoma: 22% severe fatigue Ewing's sarcoma: 29% severe fatigue Synovial sarcoma: 17% severe fatigue Results from other measures were not reported separately.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion
Shchelkova and Usmanova, 2015, Russia[115]	Investigate the basic aspects of QoL and relation to disease	Retrospective Single centre	N=59, 57%*, age* 18–67 years, BS (osteosarcoma or chondrosarcoma), stage and treatment not specified	SF-36 EORTC QLQ-C30 EORTC QLQ-BM22†	Patients with OS and chondrosarcoma have higher physical (SF-36) and social functioning (EORTC QLQ-C30) scores compared with patients with giant cell tumours (GCT). They experience less financial difficulties. Patients with GCT characterised their pain as more widespread. Patients with OS have significantly higher mental health scores and global health status than patients with GCT. Patients with chondrosarcoma had more difficulties with respect to the psychosocial aspects of pain compared with patients with GCT.
Smith, 2013, USA[100]	Describe the HRQoL and associated characteristics of AYA patients with cancer	Prospective Multicentre	N=25, 63.3%*, age* 15–39 years, Ewing's sarcoma, osteosarcoma or rhabdomyosarcoma, stage, and treatment not specified	SF-12 PedsQL	Patients with sarcoma reported significantly worse PCS scores on both SF-12 and PedsQL compared with patients with germ cell cancer (reference).
Stish, 2015, USA[101]	Assess patient-reported functional and QoL outcomes	Retrospective Single centre	N=36, 62%*, age 18–54 years, Ewing's sarcoma (localised, metastatic or recurrent) survivors, surgery and/or RT	TESS PEDSQL	A majority of survivors of Ewing's sarcoma report excellent functional and QoL outcomes.
Skalicky, 2017, USA[90]	Develop a disease-specific symptom inventory for soft tissue sarcoma	Retrospective Multicentre Through patient advocacy groups or rare patient research panels	N=10 patients (interview), 0%, age 32–67 years; N=27 (websurvey), 4%, age 32–67 years, N=3 HCPs, advanced STS subtypes: leiomyosarcoma, synovial sarcoma, liposarcoma, undifferentiated sarcoma, treatment not specified	Literature review Questionnaire review Qualitative (interview)	The draft 12-item STS-specific symptom inventory (most frequently reported in %) includes abdominal pain (50%), pressure in abdomen (40%), poor appetite or early satiety (20%), bloating, gastrointestinal pain, muscle pain, bone pain, heavy menstrual flow, shortness of breath (20%), chest pain (30%), cough (40%) and painful menstruation.

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Table 1 Continued

Author, year, country	Aim	Study design and setting	Patient characteristics (number of patients with sarcoma, gender male %, age range, sarcoma type, disease stage, treatment)	HRQoL measure	Main results/conclusion

*Range or distribution for entire study population as it was not reported for eligible patients specifically.

†Questionnaires that were used once.

Age range, age range at time study; Age range at Dx, age range at diagnosis; AYA, adolescent and young adult; BAI, Beck Anxiety Inventory; BP, Bodily pain (scale SF-36); BPI-SF, Brief Pain Inventory-Short Form; BS, Bone sarcoma; BSI-18, Brief Symptom Inventory; CAS, Cancer acceptance scale; CID, clinically important difference; CIS, Checklist Individual Strength; con, control group; CT, chemotherapy; DASS21, The Depression Anxiety and Stress Scale 21; DT/PL, Distress Thermometer/Problem List; EORTC-FA-13, European Organization for Research and Treatment of Cancer Fatigue module; EORTC QLQ-BM22, European Organization for Research and Treatment of Cancer Bone Metastases Module; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D, EuroQol-5 dimensions questionnaire; ESAS, Edmonton Symptom Assessment Scale; exp, experimental group; FACIT-Sp, Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; FACT-G, Functional Assessment of Cancer Therapy-General; FLZ-M, Questions on Life Satisfaction Module; GH, General Health (subscale SF-36); GHQ-28, General Health Questionnaire 28; GHS, global health scale; HADS, Hospital Anxiety and Distress Scale; HRQoL, health-related quality of life; ICS, International Continence Society; IES, Impact of Event Scale; IQR, interquartile range; ISSS-8, Illness-Specific Social Support Scale Short Version-8; LASA, Linear Analog Self Assessment; LEFS, Lower Extremity Functional Scale; LOT, Life Orientation Test; LOT, Life Orientation Test; LSS, Limb Salvage Surgery; MCS, Mental Component Summary score(subscale SF-36); MDASI, MD Anderson Symptom Inventory; MDASI-GIST, MD Anderson Symptom Inventory Gastrointestinal Stromal Tumor Module; MODS, Modified Obstruction and Defecation Score; MSAS-SF, Memoral Symptom Assesment Scale-Short Form; MSTS, Musculoskeletal Tumor Society scoring system; NA, not applicable; NRS, numeric rating scale; NS, not significant; OKQ, Oxford Knee Questionnaire; OS, osteosarcoma; PACIS, Perceived Adjustment to Chronic Illness Scale; PCS, Physical Component Summary score(subscale SF-36); PDI, Psychological Distress Inventory; PEDSQL, Paediatric Quality of Life Inventory; PF, Physical Functioning (subscale SF-36); PHQ-9, Patient Health Questionnaire-9; PMI, Pain Management Index; post-RT, postoperative radiotherapy; pre-RT, preoperative radiotherapy; PRO-CTCAE, Patient Reported Outcomes-Common Terminology Criteria for Adverse Events; PROMIS, Patient Reported Outcome Measurement Information System; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; QoL, quality of life; QoL, quality of life; RE, Role Emotional (functioning subscale SF-36); RF, role functioning; RNL, Reintegration to Normal Living Index; RP, Role Physical (functioning subscale SF-36); RSCL, Rotterdam Symptom Checklist; RT, radiotherapy; SCL-90, Symptom Checklist-90; SD, Standard Deviation; SF-8, Short Form Health Survey; SF-12, Short Form Health Survey; SF-36, Short Form Health Survey; SF, Social Functioning (subscale SF-36); S-LANSS, Leeds-Assessment of Neuropathic Symptoms and Signs; SSS, Shame and Stigma Scale; STS, Soft Tissue Sarcoma; TAAQOL, TNO-AZL(Netherlands Organisation for Applied Scientific Research-Leiden University Medical Centre) Questionnaire for Adult's Quality of Life; TESS, Toronto Extremity Salvage; TS, total sacrectomy; VAS, Visual Analogue Scale; VT, Vitality (subscale SF-36).

Table 2 Characteristics of the frequently used questionnaires†

	Questionnaire, year, reference	Full name	HRQoL domains that are measured	Number of items, score range, score interpretation	Availability in different languages	Number of studies in this review that have used questionnaire
1	TESS, 1996[17]	Toronto Extremity Salvage Score	Physical function (one version for upper extremities and one for lower extremities)	30 items for either upper or lower extremities, total score 0%–100% Higher scores represent better function	8	28
2	EORTC QLQ-C30, 1993[116]	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30	Cancer-generic HRQoL in five functional domains (physical, role, emotional, cognitive and social functioning) Three symptom scales A global health status/QoL scale Six single items	30 items, 0–100 points per domain or item Higher scores for a functional scale or global health status/QoL represent higher level of functioning and QoL Higher scores for a symptom scale or item represents a high level of symptomatology or problems	>100	19
3a	RAND-36/SF-36, 1992[117]	Short Form Health Survey	Functional health and well-being in eight domains: Physical functioning Role limitations due to physical health Role limitations due to emotional problems Vitality Emotional well-being Social functioning Bodily pain General health perceptions Physical component score (composed of four scales, that is, physical function, role limitations caused by physical problems, bodily pain and general health) Mental component score (composed of four scales, that is, vitality, social functioning, role limitations caused by emotional problems and mental health)	36 items, 0–100 points per domain Higher scores represent better functioning, emotional well-being and general health, higher vitality, fewer role limitations and less pain	>170	18
3b	SF-8, 2001[118]	Short Form Health Survey	Similar eight domains as SF-36	8 items, 1 item per domain, 0–100 points per domain Higher scores represent better functioning, emotional well-being and general health, higher vitality, fewer role limitations and less pain	Unknown	2

Continued

Table 2 Continued

	Questionnaire, year, reference	Full name	HRQoL domains that are measured	Number of items, score range, score interpretation	Availability in different languages	Number of studies in this review that have used questionnaire
3c	SF-12, 2002[119]	Short Form Health Survey	Similar eight domains as SF-36	12 items, 1 or 2 questions per domain, 0–100 points per domain Higher scores represent better functioning, emotional well-being and general health, higher vitality, fewer role limitations and less pain	Unknown	3
4	EQ-5D-3L or EQ-5D-5L, 1990[120]	N/A	Measurement of General Health Status in two parts: descriptive and the EuroQol Visual Analogue Scale (EQ-VAS) Descriptive system contains five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety depression The EQ-VAS records the patient's self-rated health on a vertical VAS	5 items, 3 or 5 levels per item, range 1–3 or 1–5 per item, can be converted to EQ-5D index with range 0–1 EQ-VAS has 1 item, range 0–100 Higher scores in the descriptive system indicate more problems in that dimension. Higher EQ-VAS scores represent better health	>150	14
5	HADS, 1983[121]	Hospital Anxiety and Depression Scale	State of depression and anxiety	14 items, 2 subscales (anxiety and depression) or total score for distress, range 0–21 for each subscale Higher scores indicate more symptoms of depression or anxiety 0–7: no depression/anxiety 8–10: possible depression/anxiety 11–21: probable depression/anxiety	118	5
6	FACT-G, 1993[122]	Functional Assessment of Cancer Therapy-General	Well-being in physical, social, emotional and functional dimensions and relationship with doctor	28 items, 5 subscales, range 0–112 for total score, subscale scores range 0–28 for physical, functional and social, 0–20 for emotional and 0–8 for relationship with doctor, respectively. Lower scores indicate diminished well-being	58	4
7a	PROMIS, 2010[123]	Patient-Reported Outcomes Measurement Information System	Physical, mental and social health in general population and individuals living with chronic conditions, approximately 70 domains measuring pain, fatigue, depression, anxiety, sleep disturbance, physical function, social function and sexual function, among other areas	System with over 300 measures, which can be combined Number of items differs per measure, sum scores are converted to normalised T-scores with standardised mean in general population of 50±SD 10	27	2

Continued

Table 2 Continued

	Questionnaire, year, reference	Full name	HRQoL domains that are measured	Number of items, score range, score interpretation	Availability in different languages	Number of studies in this review that have used questionnaire
7b	PROMIS 43 Profile, 2010[123]	Patient-Reported Outcomes Measurement Information System	A predefined collection of 6-item short forms assessing seven domains: anxiety, depression, fatigue, pain interference, physical function, sleep disturbance and ability to participate in social roles and activities as well as a single pain intensity item	43 items in 7 domains+single pain intensity item, raw scores are converted to T-scores per domain, US reference population is normalised to 50±10	27	3
8	RNL index, 1988[124]	Reintegration to Normal Living Index	Degree to which individuals achieve reintegration into normal social activities after illness or severe trauma	11 items with VAS response line, summed score (max 110) is converted to 0–100 point scale Higher scores represent fewer participation restrictions	3 (English, French, Chinese)	4
9	LOT, 1985[125]	Life Orientation Test	Level of optimism in a person	(8 items+4 filler items (to disguise the underlying purpose of the test), range 0–32 points Higher scores represent more optimism	Unknown	3
10	Pain measurement with VAS, 1923[126]	Visual Analogue Scale	Pain severity	1 item, range 0–10 OR 100 points, measured as the distance from one end of the scale to the subject's mark on a straight line of which the end anchors are labelled as the extreme boundaries of pain. Higher score indicates more pain	N/A	2
11	TAAQOL, 2001[127]	TNO-AZL Questionnaire for Adult's Quality of Life	HRQoL and emotional impact of self-reported functional problems in 12 scales: Gross motor functioning Fine motor functioning Cognition problems Sleep problems Pain problems Social contacts problems Daily activities problems Sex problems Vitality Happiness Depressive mood Anger	45 items in 12 scales, for all scales the sum-scores are linearly transformed to range 0–100. Higher score indicates higher HRQoL	2 (Dutch, English)	2
12	BPI-SF, 1994[128]	Brief Pain Inventory-short form	Evaluate pain and its impact on daily function	11 items (4 pain items, 7 interference items), range 0–10 per item Higher scores indicate more pain or interference	52	2

Continued

Table 2 Continued

	Questionnaire, year, reference	Full name	HRQoL domains that are measured	Number of items, score range, score interpretation	Availability in different languages	Number of studies in this review that have used questionnaire
13	CIS, 1994[129 130]	Checklist Individual Strength	Measure fatigue and its aspects: Fatigue severity Concentration Motivation Physical activity	20 items (8 for severity, 5 for concentration, 4 for motivation and 3 for physical activity), range 20–140 Higher scores indicate high levels of fatigue, concentration problems, low motivation and low level of physical activity. Score of 35 or higher on fatigue severity indicates severe fatigue	Unknown	2
14	PedsQL V.4.0, 2001[131 132]	Paediatric Quality of Life Inventory	Assess HRQoL in four domains: Physical Emotional Social School/work functioning	23 items, range 0–100 Higher scores indicate better HRQoL	>125	2

*Questionnaires that were used once are listed in table 1 and online supplemental appendix 2.
BPI-SF, Brief Pain Inventory-Short Form; CIS, Checklist Individual Strength; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; EQ-5D, EuroQol- 5 dimensions questionnaire; FACT-G, Functional Assessment of Cancer Therapy-General; HADS, Hospital Anxiety and Distress Scale; HRQoL, health-related quality of life; LOT, Life Orientation Test; PEDSQL, Pediatric Quality of Life Inventory; PROMIS, Patient Reported Outcome Measurement Information System; QoL, quality of life; RNL, Reintegration to Normal Living Index; SF, Social Functioning (subscale SF-36); SF-8, Short Form Health Survey; SF-12, Short Form Health Survey; SF-36, Short Form Health Survey; TAAQOL, TNO-AZL(Netherlands Organization for Applied Scientific Research-Leiden University Medical Center) Questionnaire for Adult's Quality of Life; TESS, Toronto Extremity Salvage; VAS, Visual Analogue Scale.

gross motor function and more problems with daily activities than controls.[22 45 46 49 52 55] Function scores at 12 and 24 months did significantly improve in one study,[55] but not in two other studies.[26 35] Patients who underwent amputation for extremity STS showed significantly worse physical functioning than those who underwent limb-sparing surgery.[41 49] Patients' perceptions of limitations in the ability to reintegrate into life roles and situations, as measured by the Reintegration to Normal Living (RNL) index, were favourable and showed improvement after sarcoma treatment.[23 24 37 53] In one retrospective study among patients with BS and STS, 89% of patients indicated that they had a limp after limb-sparing surgery.[44] Three articles reported that 50%–80% of patients needed a walking aid and 82% used a leg brace.[29 31 44]

Twenty-three studies (2 interventional, 7 prospective and 14 retrospective) used the TESS to measure physical disability in patients with extremity sarcoma before and after multimodality treatment including limb-sparing surgery.[21 23–27 29–40 47 50 51 53 54] On average, physical abilities were relatively well preserved. Two prospective studies showed that, after a deterioration in TESS in the first months after surgery, at 12 months post-treatment scores were similar to preoperative scores.[23 25] Patients with STS located in the groin, femoral triangle or thigh had the lowest TESS, especially when the femoral or sciatic nerve had to be resected.[29 31] Furthermore, TESS outcomes were negatively affected by the presence of a lower-extremity tumour compared with upper-extremity tumour.[26 36 51] Three studies specified the activities that were most frequently reported as difficult in patients with lower extremity sarcoma, that is, performing sports, rising up from kneeling, performing heavy household duties, walking stairs and walking on an incline.[29 32 33] Factors most often listed as limiting everyday activities were stiffness, weakness or decreased mobility and sensory loss.[29] Five studies showed that patients with extremity sarcoma experience more pain than a normative population,[26 34 38 39 43] although two other studies found no significant difference.[27 33] One prospective trial showed that pain got worse during the first 6 months after surgery, but improved significantly at 12 months after surgery.[40] Periodical use of pain medication was reported for 25%–30% of patients in two studies, 30% of patients required regular non-narcotic drugs.[29 44]

Two studies report sleeping problems in patients with extremity sarcomas.[43 44]

One study described the consequences for sexual functioning after limb-sparing surgery: 33% of men had loss of potency and 75% of patients maintained an active sex life.[44]

Most of the studies investigating social functioning, as measured by SF-36 or EORTC QLQ-C30, found no differences or even higher functioning among patients with sarcoma compared with a normative population.[27 33 35 38–40] Contrarily, three studies reported lower social functioning, but in two of these the social function subscale improved significantly over time.[26 43 55] One study comparing amputation for extremity STS with limb-sparing surgery showed significantly lower social functioning in the amputation group.[41] A qualitative paper focusing on BS described the experiences related to vocation.[48] The illness was characterised as intensive 'work' and often led to the need to stop vocational pursuits for a period of time. Patients considered themselves as a changed person on return to work, and also had to deal with the physical changes impacting their ability to resume their vocation. Mental health scores (SF-36) were comparable to the normative population in six studies, with one showing improved scores over the 2 years after limb-salvage surgery.[21 26 27 30 33 35] Three studies even reported less depression among patients with extremity sarcoma than the normative population.[45 46 49] Three studies reported prevalence of depression in 17%–30% of patients, and anxiety was found in 22% of patients in two studies.[40 42 44] Patients reported disruption of life as the main source of distress. Furthermore, 20% and 30% of patients had scores suggesting post-traumatic stress disorder and the need for psychological counselling in two retrospective studies.[41 42] One study found significantly more emotional problems in patients who underwent amputation for STS when compared with the normative population, while another reported similar depression scores among amputees using Patient Reported Outcome Measurement Information System.[41 49]

In summary, patients with extremity BS or STS have impaired physical function; however, disability can improve with time. Problems with sleeping and sexual functioning occur due to sarcoma. Social functioning and mental health can be affected as well, but the majority of patients have similar overall HRQoL compared with the general population.

Sarcoma of the axial skeleton (n=9)

Three studies focused on sacral BS (two prospective and one retrospective). One prospective study showed no significant differences between the preoperative and postoperative general health status, as measured by EQ-5D score, or any of its five dimensions.[56] Patients with sacral chordoma reported difficulty sitting, difficulty walking and sexual dysfunction as most common symptoms.[57] The other prospective study showed that patients who underwent sacral resection had similar scores on all investigated quality of life (QoL) domains compared with the general population norms. Patients with a higher level of sacral resection had lower physical function scores, more intense pain and more interference from pain than patients with lower sacral cuts. The ability to have a satisfying orgasm increased significantly with a more caudal resection. No differences were observed in global mental health, anxiety, depression, sexual interest, problems with voiding of urine, urinary incontinence or constipation.[58]

Three studies described HRQoL after tumour resection in patients with BS or chordoma of the spine. A prospective study showed a decreased mean Physical Component Score (PCS) and similar Mental Component Score (MCS) of the SF-36 compared with a normative population.[59] The first retrospective study reported a lower median general health score, and higher anxiety and pain scores measured by EQ-5D among patients with chordoma compared with the national average in the US norm population. Among regions of the spine, EQ-5D scores were significantly different with best scores for the cervical and worst scores for the lumbar region, respectively. Patients who had a neurological deficit had a worse EQ-5D score compared with those who did not.[60] Problems with mobility, self-care and usual activities occurred in 80%, 44% and 91% of patients, respectively. The second retrospective study among patients with chordoma found that chronic pain, difficulty walking and limited mobility are the most common symptoms.[57]

Four retrospective studies investigated functional outcome among patients with pelvic sarcoma. Three showed important disability, measured by the TESS.[61–63] One study (with median time since surgery of 5.8 years) reported higher pain levels in patients who had undergone external hemipelvectomy compared with internal hemipelvectomy, but no differences in physical or emotional well-being.[64] Another study (with mean time since treatment of 43 months) found lower physical function scores using the SF-36 in patients with pelvic sarcoma compared with a healthy control population and no statistical differences were found between external and internal hemipelvectomy.[62] MCS scores were not different.

In summary, physical functioning is diminished in patients with sarcoma of the axial skeleton. Mental well-being and overall HRQoL are similar to or worse in comparison with the general population. Patients experience a variety of symptoms and pain caused by the tumour itself or its treatment depending on the level of the tumour.

The prospective study showed improvement of HRQoL and functioning scales measured by the EORTC QLQ-C30 from 15 days to 12 months postoperatively.[65] The symptom scores decreased over time, while psychological discomfort remained the same.

In one retrospective study (mean time since surgery was 6 years), patients with chondrosarcoma who were successfully treated with surgery reported significantly more fatigue, lower motivation and less optimism than healthy controls.[66] Scores on the 'Symptom Checklist-90' were higher for somatisation, obsessive-compulsive behaviour and sleep disturbances compared with a healthy population. Finally, physical functioning scores of the SF-36 were significantly lower in ex-chondrosarcoma patients.

Two qualitative papers (total 28 patients) described the experiences of patients with BS with regard to the physical and psychosocial late effects of treatment, and the impact of visible body changes.[67 68] Amputation, limping, use of a crutch, stick or wheelchair, scars, discolouration of skin, a thinner leg, a shorter leg, were all visible consequences of their illness. These led to impaired physical activity, problems with balance and loss of important hobbies which has consequences for their social life as well. With regard to body image, ex-patients felt less attractive, avoided undressing in front of others and felt different from others. They wished to be seen for who they really are and not as being disabled or unhealthy. Their illness has taken away opportunities in life, but they also experienced positive changes such as a changed sense of life and self and having more compassion for others.

Finally, one qualitative study investigated how patients with pelvic or extremity sarcoma (both STS and BS) coped with physical and psychological consequences of treatment.[69] Functional limitations were often more significant than anticipated, and patients felt frustrated that physical therapy was not focused on reaching a pretreatment level of functioning as they expected to attain a high level of function again. Some patients indicated that managing the psychological recovery could be more challenging than the physical limitations as they had a desire for life to return to normal. Family and friends provided support, but could also be a source of distress and anxiety. Discussions with fellow-patients and on social media were a good source of support.

In summary, in patients with sarcoma of the pelvis and extremities HRQoL, pain and physical functioning can improve, but compared with the general population they experience physical limitations, psychosocial problems (eg, related to body image) and fatigue.

Two retrospective studies investigated patients with skull base chordoma. Cranial nerve deficit (most commonly diplopia), headache, chronic sinus problems, sensory deficit, gait disturbance and anxiety were most common symptoms. Moderate-to-severe depression was observed in 29% of the patients.[57 70] Patients reported significantly lower physical and mental health scores of the SF-36 than the US normative population.[70] Motor deficit, sensory deficit and bowel/bladder dysfunction at presentation were significantly associated with worse PCS. A similar association was found for current symptoms of headache, cranial nerve deficit, motor deficit, sensory deficit, gait disturbance and bowel/bladder dysfunction. For the MCS, headache and neck pain at presentation were adversely associated.[70]

A prospective study among patients with skull base chordoma showed no significant or clinically meaningful changes in HRQoL and its domains after proton beam therapy, except for a clinically important improvement in financial difficulties.[71]

One interventional study investigated HRQoL after multimodality treatment (ie, chemotherapy, tumour removal and corrective surgery, postoperative rehabilitation) for osteosarcoma of the mandible.[72] QoL, measured by SF-36, improved at 2 months after denture installation. Lowest scores were seen on scales for bodily pain and emotional role functioning.

In summary, chordoma in the head and neck region and its treatment can lead to worse physical and mental HRQoL scores. Proton beam therapy causes no significant changes in HRQoL. Scores for pain and emotional role functioning are lowest in patients undergoing treatment for osteosarcoma of the mandible.

Retroperitoneal sarcoma (n=2)

The retrospective study (median time since surgery was 49 months) described significant long-term morbidity after multivisceral resection for retroperitoneal sarcoma (RPS) such as sensory disorders of the thigh, groin or genital region and impaired motor function.[73] Pain occurred mostly in the legs; and abdomen and back. Patients with moderate-to-severe pain reported interference of daily activities with regard to general activity, mood, walking and working ability. Patients mentioned bowel obstruction, change in bowel habit and urinary habit after surgery. Sexual function was also impacted, with loss of libido, sexual impotence, retrograde ejaculation and dyspareunia.

In a prospective study in 11 patients on preoperative radiotherapy and surgery, a significant increase in diarrhoea and a decrease on the social functioning scale from baseline to 1 month postradiotherapy was found.[74] From 6 months postradiotherapy onwards, both scores recovered to baseline levels. Global QoL, physical and role functioning scores significantly improved from time of diagnosis to 36 months postradiotherapy in patients without relapse.

In summary, extensive surgery with or without radiotherapy for RPS leads to long-term morbidity with neurological, functional, sexual and gastrointestinal problems. On the other hand, long-term relapse-free survivors report a higher global QoL after preoperative radiotherapy compared with time of diagnosis.

Sarcoma-generic HRQoL (n=33)

Thirty-three studies described more heterogeneous groups of patients with sarcoma with regard to tumour location, without a description of location-specific HRQoL issues. Findings will be discussed according to disease stage and domains of the biopsychosocial model since important differences in HRQoL were found. Six studies included patients with localised disease only, nine studies with metastatic disease only and seventeen studies with all stages (or did not specify stage).

Localised sarcoma

With regard to overall HRQoL, prior to start of any treatment scores of a heterogeneous group of patients with localised sarcoma were worse than the general population's mean scores.[75]

Within the biological domain, most symptom and functioning scores were already worse than the general population's mean scores before treatment.[75 76] During treatment, fatigue, nausea and vomiting, appetite loss, drowsiness, shortness of breath and poor general wellbeing increased and physical functioning deteriorated, but pain scores improved.[75 76] When treatment was completed, almost 50% of patients considered their physical condition as stable and excellent[77]; 17%–29% of patients reported severe fatigue.[78]

With regard to psychological well-being, 20%–30% of a heterogeneous group of patients with sarcoma experienced moderate or severe anxiety after diagnosis, with higher rates among patients who had recurrent disease.[79 80] The majority of patients did not change from non-clinical to clinical levels of anxiety or vice versa during treatment.[80] Approximately 20% of patients experienced moderate or severe depression in the diagnostic or treatment phase.[79 80] Undesirable effects of therapy were considered as the main stress factor.[77] After curative treatment, only one-third of patients regarded themselves to be completely emotionally stable and just over 50% had great confidence in the future.[77]

Lower social functioning scores and more financial problems than the normative population were reported by patients with sarcoma at diagnosis.[75] In a cross-sectional study, 30% of patients with BS and STS could continue working without limitations after surgical treatment and financial strain was reported by 27%.[77]

Metastatic sarcoma

Five clinical trials investigating palliative systemic treatment in patients with metastatic STS reported the effects on HRQoL. Patients maintained similar overall HRQoL levels or global health status during different treatment schedules compared with baseline, even if symptom scores increased.[81–85] Patients with stable disease after chemotherapy had clinically relevant higher utility and HRQoL scores than patients with progressive disease.[86] Addition of iodine-125 brachytherapy to second-line chemotherapy, to increase local control of disease, improved QoL scores.[87]

One prospective and one retrospective study measured symptom prevalence, and severity in patients with advanced BS or STS.[86 88] Most prevalent symptoms were pain, lack of energy, difficulty sleeping, feeling bloated, shortness of breath, difficulty concentrating, lack of appetite, drowsiness and constipation.[88] Mobility problems and problems with usual activities were also frequently reported. Seventy per cent of the population experienced ‘worrying’, ‘feeling nervous’ or ‘sadness’ at least occasionally. Symptom burden was the lowest before start of chemotherapy and increased during chemotherapy. During active surveillance after palliative chemotherapy, symptom burden decreased.[88] Patients with disease progression after eribulin and dacarbazine as at least third-line treatment did have a clinically important increase in fatigue, as measured by EORTC QLQ-C30, at progression compared with before start of treatment.[89] One qualitative study developed a specific symptom inventory for patients with advanced or metastatic STS through patient and healthcare professional interviews.[90] Tumours were mostly located in the pelvic region (37%), abdomen (33%) and chest (18%) and participants were not receiving chemotherapy at time of study. The most frequently reported tumour symptoms were abdominal pain (50%), pressure in the abdomen (40%), cough (40%), chest pain (30%), poor appetite or early satiety (20%) and shortness of breath (20%). Early satiety, bloating, gastrointestinal pain, muscle pain, bone pain, painful menstruation and heavy menstrual flow were the other items.[90] Patients undergoing best supportive care only had a large symptom burden with lack of energy, pain, shortness of breath, difficulty concentrating, drowsiness, feeling bloated, taste change and swelling of arms/legs, all having a prevalence of >70%. Over 25% of patients reported at least quite a bit of symptom distress.[88]

Patients with metastatic STS with disease progression after at least third-line chemotherapy did have a clinically important decrease in role functioning.[89]

All stages (or stage not specified)

Equal HRQoL scores were found among patients with sarcoma aged 70 years or older compared with patients aged between 18 and 70 years.[91] When compared with other cancer types, higher, lower and similar HRQoL scores were found depending on the comparison groups.[92–95]

Most prevalent symptoms during chemotherapy in either curative or palliative setting were fatigue, lack of appetite and drowsiness.[96] Pain was prevalent in over half of patients with sarcoma. The majority of these patients experienced long-term pain and indicated that pain was not adequately treated.[97] No differences in pain levels were found compared with most other cancer types.[92 98]

Physical functioning was decreased in a heterogeneous group of patients with sarcoma and disability, measured with TESS, was present.[99 100] However, in a survivor population it was found that TESS levels can increase to acceptable levels again.[101]

Psychological well-being decreased, during chemotherapy in both curative and palliative setting.[96] Similar levels of anxiety, distress and spiritual well-being were found in comparison with patients with other frequent types of cancer, and higher depression rates.[92 102 103] Compared with other rare cancers psychological distress levels were lower.[104] Nearly 50% of patients who were full-time workers or students at time of diagnosis believed that sarcoma had a negative impact on their plans for work or education.[105]

In summary, the heterogeneous sarcoma population reports decreased HRQoL. During the treatment period the symptom burden and psychosocial problems increase, however, overall HRQoL does not always change accordingly. Pain is frequent and can improve during sarcoma treatment, however, in many patients pain still is not managed adequately. After completion of treatment patients with localised sarcoma can experience a health status, functioning and symptoms similar to the general population. In metastatic sarcoma, tumour location is less important in relation to HRQoL and burden of disease and limited role functioning has greater impact.

DISCUSSION

In the available literature, patients with all subtypes and locations of sarcoma report important impairments of HRQoL as a consequence of their illness and its treatment. However, different patterns of HRQoL issues can be recognised in the heterogeneous sarcoma population. Primary sarcoma of extremities and axial skeleton are the most investigated tumour locations and there is an emphasis on reduced physical functioning and disability in these groups, while the psychosocial impact of these limitations is significant as well. No studies investigated HRQoL in urogenital or thoracic sarcoma, whereas a few papers reported outcomes for sarcoma of the head and neck or retroperitoneum. In the first group, neurological symptoms and its impact on physical and mental well-being stand out. Treatment for RPS leads to important morbidity with functional and gastrointestinal problems. In patients with metastatic sarcoma, tumour location has less impact on HRQoL.

The overall HRQoL scores in patients with localised sarcomas are lower in patients with chordoma or axial sarcoma compared with the general population. Interestingly, despite experiencing a lot of long-term toxicities, patients with RPS reported higher HRQoL scores after treatment than before, indicating that removal of the large tumours improves their well-being. Long-term effects of extremity sarcomas do not impact overall QoL significantly.

More specific symptoms that affect HRQoL can be identified per location. Patients with localised RPS undergo extensive resection, which might include resection of bowel, psoas muscle and femoral nerve resection. As a consequence, patients report changed bowel habits, limitations in movement of the leg and sensory dysfunction. Both patients with RPS and patients with sarcoma of the axial skeleton report sexual dysfunction.

Physical functioning is mostly measured using generic PROMs, showing lower physical function scores in sarcoma of the head and neck, axial skeleton and extremities. Disability scores (either sarcoma-specific or generic) are lowest in patients with sarcoma of the axial skeleton or lower extremities. Patients who underwent amputation for extremity STS showed significantly worse physical functioning than those who underwent limb-sparing surgery, which was similar to results of a previous systematic literature review in patients with extremity sarcoma.[8] After surgery disability worsens, often more than the patients anticipated, but it can improve to presurgical levels with time. In contrast, physical functioning scores did not recover in a similar fashion. Skull base chordoma also causes neurological problems, such as cranial nerve impairment (eg, diplopia), and gait disturbance.

The psychosocial impact of sarcoma and its treatment was only described in qualitative studies for patients with extremity sarcoma. They reported problems with body image, social activities and challenges related to return to work. Patients with skull base chordoma reported lower mental health scores and more depression. However, mental health scores were similar or even better in patients with extremity and axial sarcoma compared with the general population. This is in contrast with significantly higher rates of depression and anxiety disorders found in German patients with STS and to a lesser extent in patients with cancer in general compared with cancer-free controls.[106 107] Furthermore, the described rate of suicide and self-induced injuries is significantly higher in patients with sarcoma than the general US population. Notably, patients with cancer of the vertebral column and pelvis have the highest incidence of suicide compared with other locations.[108]

In patients with metastatic sarcoma, a generally high symptom burden is reported. This increases during systemic treatment, while overall HRQoL scores remain stable. However, at time of disease progression HRQoL does decrease. Living with advanced disease and related symptoms also hampers the patients' ability to fulfil their previous role in society and/or their families. In case of metastatic sarcoma, primary tumour location has less impact on HRQoL, but it is important to realise that this category can consist of patients in whom their primary tumour was resected and patients who still have their primary tumour or irresectable locally recurrent tumour in situ. HRQoL outcomes in these groups need to be investigated further. It should be noted that most palliative systemic treatment clinical trials lack HRQoL end points.

The results of the studies included in this review show important differences in HRQoL between sarcoma locations which we would have liked to describe in detail. However, there are important issues that impair drawing conclusions for each subgroup. First, sample sizes were small (<100) in many studies, hampering the generalisability of findings for certain subgroups. Second, there is a notable difference in numbers of studies that focus on HRQoL for a specific location of sarcoma. The majority report on extremity sarcoma (n=35), followed by sarcoma of the pelvis and/or axial skeleton (n=9). Only two and four studies included patients with retroperitoneal or head and neck sarcoma, respectively. No studies reporting on HRQoL issues of thoracic or urogenital sarcomas were identified, while location-specific issues might be expected. For example, female patients with STS reported that painful menstruation and heavy menstrual flow were important tumor-related symptoms that were missing from existing HRQoL measures.[90] With this location as an example, assuming that the impact of treatment for uterine sarcoma is similar to surgery for carcinoma of the uterus is questionable, as there are important differences in phenotype (eg, age, obesity) between patients with carcinoma and sarcoma. Therefore, tailored HRQoL measurement in specific subgroups of sarcoma seems necessary.

Fifty-four different PROMs were used to assess HRQoL or function, which makes it difficult to compare results between different studies. Most studies used a generic

HRQoL questionnaire (EORTC QLQ-C30, FACT-G) or the EQ5D (measuring not HRQoL but health status), which cover relevant issues but do not capture all of the unique experiences of patients with sarcoma and consequences of treatment, and thus lack content validity.[8 14 15] For example, several studies reported no difference in HRQoL, despite the presence of considerable treatment-related adverse events. This indicates that most likely important issues are not being addressed in these questionnaires.[81 82 84] Recently, the SAM was developed, but it has not yet been used in clinical studies. The 22-item questionnaire is focused on clinical utility with items for which support could potentially be provided and is based on issues reported by patients irrespective of sarcoma subtype or location.[18] Two other studies created a questionnaire for chordoma and for four subtypes of soft tissue sarcoma, but they are not yet validated or used in clinical studies.[57 90] For extremity sarcoma, a location-specific PROM, TESS, is already widely used, which consists of questions about limitations in daily activities for patients who have undergone limb-salvage surgery.[17] However, it is debated whether TESS measures the ability to cope with physical limitations rather than the impairment itself.[109] Two studies also showed that pretreatment management of expectations of postoperative functioning is extremely important.[23 69] Functional outcome should be considered a multidimensional concept of its own which involves both psychosocial factors and physical functioning.[110] Some studies point out that it is not disability but participation restrictions that impair functional well-being and HRQoL, therefore the use of a more comprehensive approach towards measurement of HRQoL in patients with extremity sarcoma seems justified.[37 95]

The results of this review show that in order to detect with more sensitivity, side effects, symptoms and psychosocial and functional problems in specific subgroups of patients with sarcoma, a new instrument is needed. Traditionally, the problem of insufficient content coverage has been solved by developing a disease-specific module. Given the heterogeneity of sarcomas, in terms of subtype, localisation, age and treatment and the rapid evolution of treatment options, development of a module might be challenging and may not be the best option to meet the needs of academia and industry to assess the impact of new treatments.[7 111] A new strategy is currently being developed that is shifting from a static approach to a static plus flexible approach.[112] This would ensure adequate assessment of both adverse events of new treatments, and their impact on common functional health problems reported by patients.[113] This so-called EORTC Item Library can be used to create item lists based on existing items from available EORTC questionnaires, and newly created items in a sublibrary if needed, which can be used in clinical research. For example, questions can be added to evaluate common side effects of a specific treatment such as hand-foot syndrome or other skin reactions in patients receiving pazopanib, a tyrosine kinase inhibitor that can be prescribed as second-line or later treatment for patients with advanced STS. This flexible approach offers the possibility to encompass the full range of age-specific, location-specific and treatment-specific issues relevant to patients with sarcoma. The use of this strategy for HRQoL assessment in patients with sarcoma is currently being investigated by the EORTC Quality of Life Group in cooperation with the EORTC Soft Tissue and Bone Sarcoma Group (ClinicalTrials.gov Identifier: NCT04071704).[114]

Due to the rarity and heterogeneity of sarcomas, this review has some limitations. The number of patients included in studies with some specific sarcoma locations is low. Furthermore, there is a lack of studies using a prospective design and due to the heterogeneity of study designs included in this review a quality assessment could not be done. Finally, results for patients with sarcoma diagnosed at age <15 years were excluded as the experience of undergoing treatment and living with its consequences at a young age is vastly different from those of adult patients. However, the population of sarcoma survivors consists foran important part of childhood sarcoma survivors, especially in certain subtypes, for example, Ewing sarcoma or rhabdomyosarcoma. The findings of this review are thus not fully representative for this group.

The strength of this systematic review is that it is the first study to stratify HRQoL outcomes to specific location-based subgroups of patients with sarcoma. This will help focus the efforts of collecting more information on HRQoL in patient groups that are underrepresented in the currently available literature (eg, uterine sarcoma). Furthermore, it gives clinicians insights useful for counselling their patients and making shared treatment decisions. Finally, it provides an outline for a new approach towards a sarcoma-specific measurement strategy for HRQoL incorporating the voice in clinical research and capturing the heterogeneity of sarcoma.

In conclusion, sarcoma and its treatment impact the patients' lives substantially. Unravelling the heterogeneity of HRQoL according to tumour location improves applicability of PROs to specific sarcoma subgroups. Furthermore, other factors such as disease stage should be taken into account as well to prioritise patients' needs. The majority of the currently available literature is focused on extremity sarcoma, and most studies only used generic PROMs and thus lack content validity. To measure HRQoL in future studies, a sarcoma-specific measurement strategy should be used and location-specific issues should be included.

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