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Quality of life, functional ability and physical activity in children and adolescents after lower extremity bone tumour surgery

Bekkering, W.P.

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Chapter 2

QUALITY OF LIFE, FUNCTIONAL ABILITY AND PHYSICAL ACTIVITY AFTER DIFFERENT SURGICAL INTERVENTIONS FOR BONE CANCER OF THE LEG: A SYSTEMATIC REVIEW

W. Peter Bekkering, PT¹⁾

Theodora P. M. Vliet Vlieland, MD, PhD²⁾

Marta Fiocco, PhD³⁾

Hendrik M. Koopman, PhD⁴⁾

Jan Schoones⁵⁾

Rob G.H.H. Nelissen, MD, PhD²⁾

Antonie H.M. Taminiau, MD, PhD²⁾

Departments of Physical Therapy¹⁾, Orthopaedics²⁾, Medical Statistics and Bioinformatics³⁾, Medical Psychology⁴⁾ and Walaeus Library⁵⁾, Leiden University Medical Center, Leiden, The Netherlands.

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ABSTRACT

Purpose: To systematically review published studies comparing Quality of Life (QoL), functional ability and / or physical activity between different surgical interventions due to a malignant bone tumour of the leg.

Methods: A systematic literature search, covering the years 2000 - 2010 was performed using the PubMed, Embase, Web of science and Cochrane databases. Studies were included if they described and statistically compared QoL, functional ability and/or physical activity of at least two surgical interventions for lower-extremity bone cancer. In addition, the methodological quality of the selected studies was evaluated by using a 24-point scale. Where appropriate, a qualitative analysis or meta-analysis was performed.

Results: The search strategy resulted in a list of 246 citations. Based on titles and abstracts 50 full-text articles were selected, of which 13 articles describing 12 studies, were finally included. Overall, the methodological quality of the studies was moderate. Studies were heterogeneous with respect to their categorisation of surgical interventions, average age of patients and average duration of follow-up. Overall, results regarding differences between ablative and limb-sparing surgery varied largely. Meta-analysis was considered to be not appropriate due to clinical heterogeneity, methodological differences and flaws.

Conclusion: Twelve studies comparing the outcomes of QoL, functional ability and physical activity between limb-sparing and ablative surgery groups were identified, with an overall moderate methodological quality. Their largely varying outcomes suggest that no general conclusions on the advantage of either limb-sparing or ablative surgery in patients with malignant bone tumours of the lower extremity can be drawn.

INTRODUCTION

Malignant bone tumours like osteosarcoma and Ewing sarcoma represent a small percentage of cancers diagnosed and are typically occurring during the adolescent growth spurt, with a second smaller peak in the elderly. Almost 50% of the Ewing sarcoma and almost 40% of the osteosarcoma cases were reported in patients aged 10 to 19 years, thereby accounting for approximately 6% of all cancer diagnosed under the age of 20 years in western populations [1,2,3]. Both bone malignancies have a preference for origination in the metaphysical region of long bones; particularly the knee region and upper arm [3].

Survival rates for patients with bone cancer have steadily improved over the last decades of the past century to an overall 5-year survival of approximately 60% for those younger than 30 years, 50% for those aged 30 to 49 years, and 30% for those aged 50 years or older [2,3]. Additionally, novel extremity-salving surgical procedures became available as alternatives to an amputation. In parallel with these improving life expectancy and surgical innovations, there has been a growing need to examine post-surgical Quality of Life (QoL), functional ability and physical activity [4-6].

In the past two decades, four reviews aimed to summarize the results of studies on QoL and/or functional ability within patient populations after lower extremity bone tumour surgery [5-8]. Three of these reviews were published within the last decade [6-8] and two of them were systematic reviews [5,7].

In general, it was concluded that the long-term outcomes of those undergoing amputation and limb salvage were not substantially different in regard to quality of life and functional ability [5-8]. However, based on some studies included in these reviews [9-11], patients with tumour localizations above the knee were found to have better functional ability after limb-salvage surgery than similar patients with an amputation.

These reviews have several limitations: one of the systematic reviews was published more than 10 years ago [5] and two reviews were narrative reviews and did not include a systematic search of the literature [6,8]. Furthermore, none of the reviews performed so far included the degree of physical activity as an outcome measure or conducted an assessment of the methodological quality of the included studies.

Therefore we conducted a systematic search of recent literature with the aim of assessing the methodological quality and summarize findings with respect to comparisons of QoL, functional ability and/or physical activity between different limb-salvage and ablative surgical interventions in patients with bone tumours of the lower extremity.

MATERIAL AND METHODS

Study design

This systematic review consisted of 5 steps, including a systematic search of the literature (Step 1), selection of studies (Step 2), recording of study characteristics (Step 3), assessment of methodological quality (Step 4) and extraction of data on clinical outcomes and their comparisons between different surgical groups (Step 5). All activities were carried out by the principal investigator (WPB), whereas the scoring of the methodological quality was done

by two authors (WPB and TVV). All extracted data and the methodological assessments were recorded on a pre-developed form (Microsoft Excel).

Step 1: Data sources and search strategy

The literature search was done using the following electronic databases: PubMed, EMBASE, Web of Science and The Cochrane Library, from January 1, 2000 until January 2011.

The search strategies were developed and edited by a trained medical librarian (JS). The search strategy included several different terms and synonyms for *bone cancer* in combination with *lower extremity* and *quality of life, functional ability* or *physical activity* [Appendix 1].

Step 2: Selection of studies

Screening of titles and abstracts: First, all titles and abstracts were screened for the following criteria: Article concerned (1) a clinical study and (2) included patients who underwent a surgical intervention for malignant bone cancer. Moreover, (3) only articles in the English language were considered for inclusion in this review. For all selected titles and abstracts, the full-text articles were gathered for further screening.

Screening of full-text papers: Screening of full-text papers included the first three criteria supplemented with the following criteria: the study was (4) confined to surgery of the leg or the data from patients undergoing surgery of the leg were reported separately from those of patients having surgery of the upper extremity; (5) evaluations of QoL, functional ability and/or physical activity were made; and (6) statistical comparisons between at least one limb-salvage technique (allograft or endoprosthesis) and one ablative technique (amputation or rotationplasty) were made. Finally, (7) we selected only studies that included standardized outcome measures for the evaluation of QoL and functional ability. No measures for the evaluation of physical activity were selected in advance. The QoL and functional ability measures include:

QoL: Short Form Health Survey Questionnaire (SF-36) [12], EuroQoL [13], Quality of Life-Cancer Survivors (QoL-CS) [14], European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30) [15], Pediatric Quality of Life Inventory (PedsQL) [16], TNO-AZL Children's Quality of Life Questionnaire (TACQOL) [17] or the TNO-AZL Questionnaire for Adult's Quality of Life (TAAQOL) [18].

Functional ability: Measures of functional ability included both questionnaire type measures like the patient reported Toronto Extremity Salvage Score (TESS) [19] or the physician reported Musculoskeletal Oncology Society score (MSTS) [20] and measures that included both self-report and measured function like the Functional Mobility Assessment (FMA) [21].

Screening of reference lists. Additionally, the reference lists in the selected papers were scanned for relevant studies.

Step 3: Study characteristics

The following study characteristics were systematically extracted from the selected full-text papers: author, year of publication, country where study was conducted, surgical intervention types (limb-salvage; allograft or endoprosthetic replacement and ablative surgery; amputation or rotationplasty), study design (cross-sectional or prospective), the

number of patients in each surgical intervention group, age and duration of the follow-up (mean and SD or median and range).

Step 4: Assessment of methodological quality

The articles were independently assessed for methodological quality by two of the authors (WP and TVV) independently by means of a self-developed scale derived from the STrengthening the Reporting of OBServational Studies in Epidemiology (STROBE) checklist [22]. We selected 24 items of the STROBE checklist for the methodological assessment according to their relevance for the studies to be included in this review [see Appendix 2]. Each item was assigned a score 0 or 1, with 0 being “insufficient / not meeting the criterion” and 1 being “meeting the criterion”. In accordance with the STROBE checklist, the items were categorized in seven domains 1) title (n=1); 2) abstract (n=1); 3) introduction (n=2); 4) methods (n=9); 5) results (n=6); 6) discussion (n=4) and 7) other information (n=1). The total score ranged from 0-24. The initial agreement between the two authors at item level was evaluated by computing Cohen’s Kappa [23]. Then, in case of disagreement between the two assessors, a final score was given by consensus.

Step 5: Outcomes of the included studies

The following outcome characteristics and scores were systematically extracted from the selected full text papers; outcome domain (QoL, functional ability or physical activity), specific outcome measures applied and a summary of the results of the comparison between limb-salvage and ablative surgery per domain.

For the most commonly used outcome measures in this patient population (SF-36 and TESS) the scores of the selected outcome measure and the corresponding measurement of variability, the mean difference (MD) between the two surgical groups as well as the 95% confidence interval (95% CI), were extracted from the selected papers or when they were not reported in the publication computed by a statistician (MF). In case data were presented by subgroups, a pooled mean difference of comparisons of ablative and limb sparing techniques was computed.

Then potential associations between study characteristics (proportion of patients in limb salvage group, average age and duration of follow-up) and the reported or computed mean differences were examined, by computing Spearman rank correlation coefficients.

A meta-analysis was considered appropriate if the included studies were not clinically diverse and/or statistical heterogeneous. Clinical diversity among studies was assessed by two authors (WPB and TVV), taking into account the classification of patients (surgery types), age, duration of follow-up and outcome measures (domain scores of the SF-36). Disagreement was resolved by consensus. Statistical heterogeneity of the studies was investigated by means of I-squared (I^2) index [24]. If the I^2 index showed a value greater than 50% this was considered to indicate high heterogeneity. In this case a random effects meta-analysis model was appropriate.

RESULTS

Selection of the included studies

The database search resulted in a list of 246 potentially relevant citations, from which 50 citations were selected according to the initial selection criteria (See Figure 1). The full-text articles of these 50 citations were screened for the full set of inclusion criteria. Thirteen articles fulfilled the inclusion criteria. The other 37 articles were excluded, mainly because the study evaluated only one type of surgery, no distinction could be made between scores of bone tumour localizations of the leg and other localizations, or the usage of outcome measures that were not validated. No further references were added after searching the reference lists of the selected papers.

In total, twelve studies described in 13 articles were included for the analysis. In ten studies QoL was evaluated, in ten studies functional ability was measured, and in three studies physical activity levels were evaluated.

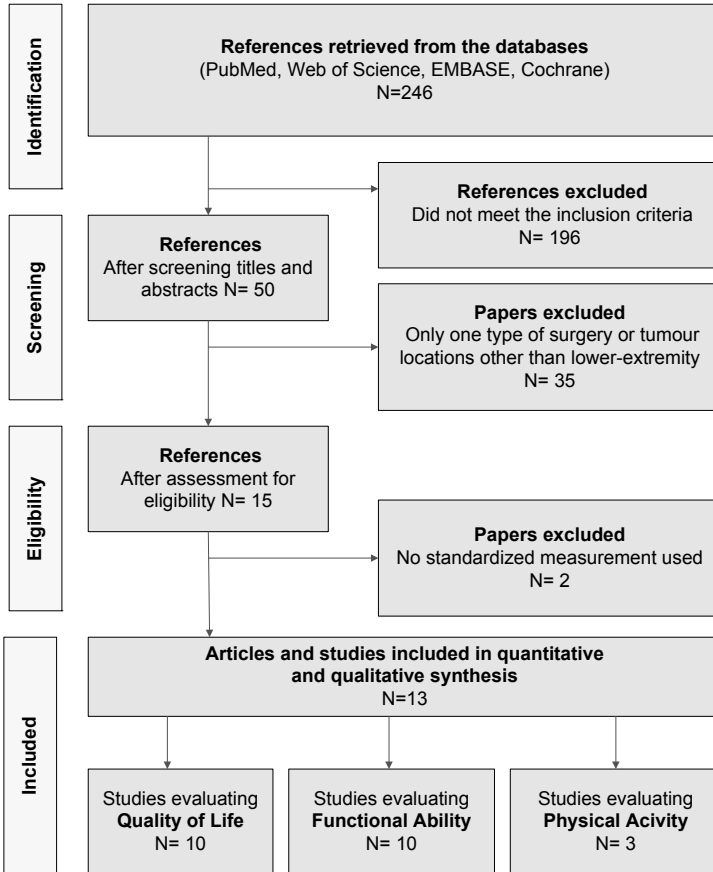


Figure 1. Study selection.

Study and patients characteristics

The study and patient characteristics are summarized in [Table I](#).

Study characteristics. All selected studies had a cross-sectional design. Ten aimed to evaluate outcome between two or more surgical interventions, two were primarily aimed to validate an outcome measure [25,26].

The minimum and maximum age of the patients included in the research populations ranged from 7 to 79 years with the average age varying from 16 to 49 years. The average duration of follow-up varied widely among studies (from 2 to 21 years).

Twelve studies compared the results of patients after limb-salvage with the results of patients after ablative surgery. In three of these studies [25,33-35] the ablative surgery group consisted of both amputation and rotationplasty patients and in five studies [10,11,26-28] of amputation patients. In three studies [30-32] patients with a rotationplasty were presented as a separate group and in one study [29] rotationplasty have been classified as a limb-salvage.

Three studies presented their data for different subgroups separately, with subgroups defined by age at diagnosis below or above the age of 12 years [28] or by tumour localisation above or below the knee [30,32].

Methodological assessment

Overall the methodological quality was moderate, with a median total score of 15 (range 9-21) ([Table II](#)). Inter-rater agreement between the initial item scores of the assessors (WPB and TVV) was seen in 94% of the scores; the agreement as computed by Cohen's Kappa was 0.88 (95% CI from 0.83-0.93), which is considered to be very good [23]. Consensus on a final score was reached in all cases.

Items for which 75% or more of the studies (9 or more) had a score of 1 included: describing the settings, locations and relevant dates; selection of the participants; explaining how the data were handled; method of assessment; and reporting outcome scores. Twenty-five % or less (3 or less) studies had a score of 1 with regard to the items clearly reporting the design of the study in title / abstract section or methods section, describing any effort to address potential sources of bias or confounders, discussing limitations in relation to potential bias and generalizability.

Outcomes after different types of surgery: descriptive analysis

The authors' conclusions on the differences between the outcomes within the limb-salvage and ablative surgery groups are summarized in [Table I](#).

Quality of life. Ten studies compared QoL between patients treated by limb-salvage and ablative surgery [10,25,27-34]. In seven studies, QoL was evaluated with the SF-36 [10,25,27,30-33]. The other three studies evaluated QoL with the EuroQoL [25], QoL-CS [28,34], EORTC QLQ-C30 [29], TACQOL and the TAAQOL [33].

Besides a significantly higher QoL score in patients after ablative surgery in one study [33] (in one of the eight subscales of the TAAQOL) no significant differences were reported within these studies.

Functional Ability. Ten studies compared functional ability between limb-salvage and ablative surgery [10,11,25,26,28,30-32,34,35]. In these studies, functional ability was

Table I. Characteristics of 12 studies included in a systematic review on Quality of Life, functional ability and physical activity after different surgical interventions for a malignant bone tumour of the leg.

Study	Year	Country	Design	N	Surgery	Age
Akahane [31]	'07	Japan	Cross-sectional	21	8 Endoprosthesis 7 Amputation 6 Rotationplasty	At diagnosis Mean 21.9 Range 7-79
Askness [10]	,08	Norway	Cross-sectional	97	18 Allograft 19 Endoprosthesis 50 Amputation	Mean 31 Range 15-57
Bekkering [33,35]	'10	The Netherlands	Cross-sectional	81	24 Allograft 14 Endoprosthesis 27 Amputation 16 Rotationplasty	Mean 16.9 SD 4.2
Dam [25]	'01	The Netherlands	Cross-sectional	20	1 Allograft 11 Endoprosthesis 6 Amputation 2 Rotationplasty	Median 49 Range 18-69
Eiser [27]	'01	United Kingdom	Cross-sectional	37	14 Limb-Salvage 23 Amputation	Mean 31 Range 12-47
Ginsberg [32]	'07	United States of America	Cross-sectional	89	65 Limb-Salvage 22 Amputation 2 Rotationplasty	Mean 20.1 SD 5.7

Follow-up (Yrs)	Domain	Measures	Results*
Mean 59.3 Range 10-172 Month	Quality of life	SF-36	No significant differences regarding SF-36 scores between subgroups amputation, endoprosthesis and rotationplasty.
	Functional ability	MSTS	Significantly better MSTS score after rotationplasty in comparison with subgroups amputation and endoprosthesis.
Mean 13 Range 6-22	Quality of life	SF-36	No significant differences regarding SF-36 scores between combined limb-salvage techniques and amputation.
	Functional ability	TESS, MSTS	Significantly better MSTS scores after combined limb-salvage techniques in comparison with amputation. No significant differences regarding TESS scores.
Mean 2.8 SD 1.6	Quality of life	SF-36, TAAQOL, TACQOL	Significantly higher TACQOL score (positive emotions) after ablative techniques in comparison with limb-salvage No significant differences regarding SF-36 and TAAQOL scores.
	Functional ability	TESS	No significant differences regarding TESS scores between limb-salvage and ablative techniques.
	Physical activity	Baecke ActiLog®	No significant differences regarding Baecke and ActiLog® scores between limb-salvage and ablative techniques.
Median 2 Range 1-13	Quality of life	SF-36, EuroQol	No significant differences regarding SF-36 and EuroQol scores between limb-salvage and ablative techniques.
	Functional ability	TESS, MSTS	No significant differences regarding TESS and MSTS scores between limb-salvage and ablative techniques.
	Physical activity	Dynaport®Baecke	No significant differences regarding Baecke and Dynaport® scores between limb-salvage and ablative techniques.
Mean 10 Range 2-33	Quality of life	SF-36	No significant differences regarding SF-36 scores between limb-salvage techniques and amputation.
	Quality of life	SF-36	No significant differences regarding SF-36 scores between limb-salvage techniques and subgroups amputation and rotationplasty.
Mean 5.6	Functional ability	TESS, FMA, MSTS	Significantly better FMA scores after limb-salvage in comparison with amputation Significantly better TESS and MSTS scores after rotationplasty in comparison with limb-salvage of the femur.

Table I. Continued.

Study	Year	Country	Design	N	Surgery	Age
Hopyan [30]	'06	Australia	Cross-sectional	45	20 Limb-Salvage 20 Amputation 5 Rotationplasty	Mean 26 SD 7 Range 10-39
Nagarajan [28]	'04	United States of America	Cross-sectional	528	192 Limb-Salvage 336 Amputation	Median 35 Range 19-49
Renard [11]	'00	The Netherlands	Cross-sectional	77	52 Limb-Salvage 25 Amputation	At diagnosis Median 30 Range 2-70
Robert [34]	'10	United States of America	Cross-sectional	57	6 Allograft 22 Endoprosthesis 25 Amputation 1 Rotationplasty	Median 33.8 Range 16-52
Saraiva [26]	'08	Portugal	Cross-sectional	48	29 Endoprosthesis 2 Arthrodesis 17 Amputation	Mean 24 Range 12-
Zahlten [29]	'04	Germany	Cross-sectional	124	34 Allo/autograft 38 Endoprosthesis 23 no surgery 7 Rotationplasty 22 Amputation	Median 35 Range 14-76

*Conclusions pertain to descriptions of outcomes of statistical comparisons of all limb-sparing techniques combined versus all ablative techniques combined; if this comparison was not available, results of comparisons of limb-sparing techniques combined versus all ablative techniques within subgroups are presented.

MSTS: Musculoskeletal Oncology Society score; **TESS:** Toronto Extremity Salvage Score; **SF-36:** Short form-36; **FMA:** Functional Mobility Assessment; **TAAQOL:** TNO-AZL Children's Quality of Life Questionnaire; **TACQOL:** TNO-AZL Questionnaire for Adult's Quality of Life Questionnaire **QoL-CS:** Quality of Life-Cancer Survivors; **EORTC QLQ-C30:** Organization for Research and Treatment of Cancer Core Cancer Quality Life Questionnaire.

Follow-up (Yrs)	Domain	Measures	Results*
Mean 13.9 SD 5.7 Range 5-26	Quality of life	SF-36	No significant difference regarding SF-36 scores between limb-salvage and subgroup above knee amputation.
	Functional ability	TESS, MSTS	Significantly better MSTS scores after limb-salvage in comparison with above knee amputation.
	Physical activity	Uptime device ^o	No significant differences regarding Uptime device scores between limb-salvage and subgroup above knee amputation.
Median 21 Range 13-31	Quality of life	QoL-CS	No significant differences regarding QoL-CS scores between limb-salvage and amputation within subgroups of patients diagnosed ≤ 12 and >12 years of age.
	Functional ability	TESS	No significant differences regarding TESS scores between limb-salvage and amputation within subgroups of patients diagnosed ≤ 12 and >12 years of age.
Median 61-80 Range 2-271 months	Functional ability	MSTS	Significantly better MSTS scores after limb-salvage in comparison with amputation.
Median 18.6 Range 12-24	Quality of life	QOL-CS	No significant differences regarding QOL-CS scores between combined limb-salvage techniques and amputation.
	Functional ability	TESS	No significant differences regarding TESS scores between combined limb-salvage techniques and amputation.
Median 10 Range 1-23	Functional ability	TESS	Significantly better TESS scores after amputation in comparison with endoprosthesis reconstruction.
Median 45 Range 14-76 Months	Quality of life	EORTC QLQ-C30	No significant differences regarding EORTC QLQ-C30 scores between limb-salvage surgery (including rotationplasty) and amputation.

evaluated according to the patient reported TESS; the physician reported MSTS score [10,25,30-32] or the FMA [30].

In one study [26], significantly better TESS scores were reported after ablative surgery in comparison with limb-salvage surgery. Significantly better TESS and MSTS scores were reported after rotationplasty in comparison with limb-salvage of the femur in one study [32]. In another study [31], significantly better MSTS scores were reported after rotationplasty in comparison with endoprosthetic replacement and amputation. However, in four studies significantly better functional ability according to the MSTS [10,11,30] or FMA [32] was reported in patients after limb-salvage surgery in comparison with amputation. Moreover,

Table II: Methodological assessment of 12 studies comparing the outcomes after different surgical techniques for malignant bone tumours of the leg.

Study	Title 0/1	Abstract 0/1	Introduction 0/2	Methods 0/9	Results 0/6	Discussion 0/4	Other 0/1	Summary 0/24
Akahane [31]	0	1	1	2	3	2	0	9
Askness [10]	0	1	1	6	5	1	1	15
Bekkering [33]	0	1	2	8	5	4	1	21
Dam [25]	0	1	1	5	4	2	1	14
Eiser [27]	0	1	2	6	4	0	1	14
Ginsberg [32]	1	0	2	7	5	3	1	19
Hopyan [30]	0	0	2	7	6	1	0	16
Nagarajan [28]	0	0	2	9	4	1	1	17
Renard [11]	0	1	1	3	2	1	0	8
Robert [34]	0	0	2	8	6	3	1	20
Saraiva [26]	0	1	1	7	5	1	1	16
Zahlten [29]	0	0	0	6	5	2	1	13

in four other studies [25,28,31,34], the differences between limb-salvage and ablative surgery did not reach statistical significance.

Physical Activity Levels. In three studies a comparison of physical activity after different surgical techniques was made [25,30,35]. In these studies, physical activity was evaluated with the Baecke questionnaire [25,35] and/or a kind of activity monitor [25,30,35]. No statistically significant differences in physical activity levels between the various surgical intervention groups were reported in these studies.

Outcomes after different types of surgery: Quantitative analysis

Data of the SF-36 could not be pooled since several different domain and summary scores were applied in the selected studies, scores such as; the physical and/or the mental component summary score, the physical functioning or a total SF-36 score.

The clinical characteristics and quantitative data of eight studies which used the TESS as measure for functional ability were ranked according to the mean differences and are presented in Table III. Data in three studies [28,30,32] were given for different subgroups separately. For each of these studies pooled mean differences (MD) and 95% confidence intervals (CI) between TESS scores within ablative and limb sparing groups were computed. The study-specific mean difference estimates (MD) are also presented in Figure 2. The horizontal bars represent the range of the corresponding 95% confidence interval (CI). The sizes of the square boxes are proportional to the total number of patients in the selected studies.

The clinical heterogeneity of these eight studies was significant, with the average age of the patients varying between 16.9 and 49.0 years and an average follow-up duration between 2 and 21 years. Furthermore, the categorization of the surgical interventions

Table III: Characteristics and quantitative data of eight studies presenting comparisons of Toronto Extremity Salvage scale (TESS) scores between limb salvage and ablative surgery groups, ranked according to the mean difference

Study	N	No. of patients per surgical technique	No. of patients with Limb-salvage or ablative surgery	TESS score Limb-salvage	TESS score Ablative surgery	Mean Difference (MD)	95% Confidence interval (CI)	Advantageous for
Hopyan [30]	# 35	17 Allograft 2 Endoprosthesis 17 Amputation 5 rotationplasty	Limb-salvage 19 Ablative surgery 22	Mean 91.3 SD 10.3	Mean 85.1 SD 11.0	MD = 6.2 P = ns	-0.38; 14.98	Limb-salvage
Dam [25]	20	1 Allograft 11 Endoprosthesis 6 Amputation 2 Rotationplasty	Limb-salvage 12 Ablative surgery 8	Median 87.3 Range 48-98	Median 81.4 Range 56-100	MD = 5.9 P = ns	-4.50; 16.30	Limb-salvage
Askness [10]	103	18 Allograft 19 Endoprosthesis 8 Resection 53 Amputation	Limb-salvage 50 Ablative surgery 53	Median 90 Range 59-100	Median 88 Range 43-100	MD = 2.0 P = ns	-2.92; 6.92	Limb-salvage
Nagarajan [28]	# 528	192 Limb-salvage 336 Amputation	Limb-salvage 192 Ablative surgery 336	Mean 85.8 SD 17.0	Mean 85.2 SD 12.8	MD = 0.6 P = ns	-2.17; 3.37	Limb-salvage
Robert [34]	57	6 Allograft 22 Endoprosthesis 22 Amputation 1 Rotationplasty	Limb-salvage 28 Ablative surgery 23	Mean 78.2 SD 17.5	Mean 78.7 SD 14.0	MD = -0.5 P = ns	-8.92; 7.92	Ablative surgery
Bekkering [35]	81	24 Allograft 14 Endoprosthesis 27 Amputation 16 Rotationplasty	Limb-salvage 38 Ablative surgery 43	Mean 84.4 SD 13.0	Mean 86.1 SD 11.1	MD = -1.7 P = ns	-7.00; 3.60	Ablative surgery
Ginsberg [32]	# 87	65 Limb-salvage 22 Amputation 4 Rotationplasty	Limb-salvage 65 Ablative surgery 26	Mean 87.0 SD 9.7	Mean 91.6 SD 8.7	MD = -4.6 P < 0.05	-8.69; -0.51	Ablative surgery
Saraiva [26]	46	29 Endoprosthesis 17 Amputation	Limb-salvage 29 Ablative surgery 17	Mean 87.9 SD 8.4	Mean 94.4 SD 8.4	MD = -6.5 P = 0.003	-11.53; -1.47	Ablative surgery

#: For this study, pooled mean difference (MD) and 95% confidence intervals (CI) were calculated.

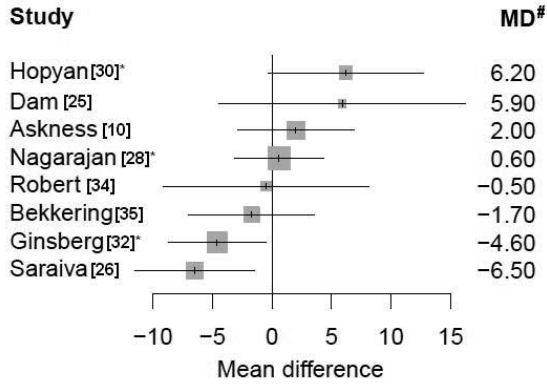


Figure 2. Forest plot of mean differences and 95% confidence intervals of Toronto Extremity Salvage Score (TESS) scores, between ablative and limb-salvage surgery.

* A negative mean difference indicates better TESS scores for patients after ablative surgery and a positive mean difference after limb-salvage surgery. * Pooled mean difference of various subgroup comparisons.

among the included studies differed. In most studies the numbers of patients who underwent limb-salvage and ablative surgery were comparable, however in one study the limb-salvage surgery group [32] and in another study the ablative surgery group [28] was relatively large. In addition, in some studies no patients with a rotationplasty or allograft reconstruction [26] were included. An overall test on heterogeneity was performed, leading to a significant result ($Q= 16.13, p =0.024$) and an I^2 index equal to 56.6%, which indicates a high heterogeneity.

Associations between the percentage of patients in the limb-salvage group, average age or duration of follow-up on the one side and the mean difference in TESS scores between limb-salvage and ablative surgery on the other side showed no significant correlations (all p -values > 0.05 Spearman’s correlation coefficients).

DISCUSSION

The purpose of this study was to systematically describe the outcomes of major surgical approaches to lower-limb bone tumours and their impact on patients by reviewing papers comparing limb-salvage and ablative surgery. Twelve studies, described in 13 papers were identified, all with a cross-sectional design.

Overall, the methodological quality of the studies was moderate. Studies were heterogeneous with respect to their categorization of surgical interventions, average age and duration of follow-up and showed various results regarding differences between ablative and limb-sparing surgery groups. Meta analysis was considered to be not appropriate due to statistical and clinical heterogeneity and methodological differences and flaws.

Considering the oncological, cosmetic and functional outcome of the various surgical options, a complicated decision in the treatment of patients with lower-extremity bone

cancer is the choice of the surgical intervention. One of the elements in the decision making process is information on the outcome. This review demonstrates that overall, differences between limb-salvage and ablative surgery with respect to QoL, functional ability or physical activity were in general small and inconsistent. The results of our review are comparable with earlier reviews concluding that clear and consistent differences between quality of life and functional ability among different surgical groups were absent as well [5-8].

There are substantial difficulties related to conducting comparative studies in this area. The choice for a specific surgical technique depends largely on the localization and size of the tumour, the relationship of the tumour with neurovascular structures, the possibility to reconstruct a functional and cosmetically acceptable limb. In addition, the presence of metastases and the response to the adjuvant chemotherapy will be considered. Moreover, preferences and skills of the treating surgeon, the age of the patient and the preferences of the patient and/or his or her parents are likely to have an impact on the decision. Therefore in all of the cross-sectional, uncontrolled studies we identified confounding by indication plays an important role [36]. In order to gain insight into the factors determining the indication for one type of surgery or the other, future studies should preferably include a clear and standardized description of the considerations underlying the surgical treatment choice.

In contrast to previous reviews, this review included an appraisal of the methodological quality of the included studies. From a wide variation of tools and scales available to evaluate the methodological quality of studies [37] we selected the STROBE guidelines. This choice was motivated by the fact that it is specifically designed for observational studies and all items are clearly described [22]. However, the STROBE guideline was not developed as grading instrument. Nevertheless, the agreement between two assessors proved to be sufficient, and the assessment highlighted several points to enhance the methodological quality of future observational studies on the outcome of surgery for bone malignancies. Besides the lack of a clear definition of the design of the study in title or abstract, our methodological assessment indicated the frequent absence of complete and clear descriptions of potential bias and confounders, and statistical analyses to adjust the data for confounders.

Regarding the analysis of the outcomes of the individual studies included in this review, we employed both a qualitative and a quantitative approach. Assessment of heterogeneity is a prerequisite for meta-analyses. Meta-analyses might miss true effects in the presence of even modest between-study heterogeneity, because they are based on the assumption of etiologic homogeneity across studies. Because of the presence of clinical and statistical heterogeneity among the studies included in our review and the considerable number of methodological flaws identified in the majority of them, a random-effect calculation of summary effects would reflect only a crude analysis. Another limitation for the generalizability of the results of the individual studies and the results of this review is the presence of ecological bias. The distribution of the surgical interventions differed strongly between the studies, with the proportions of limb-salvage surgery varying between 38 and 82%. Moreover, some studies did not include patients after rotationplasty. This observation could probably reflect variation regarding the preference of specific centres, cultural differences between countries or a time effect, since long follow-up (up to 21 years) could imply that patients were treated when limb-salving surgery was less common. Furthermore, due to the long follow-up period and incomplete description of the disease course, initial limb-salvage surgeries could probably

have led to amputations due to surgical site complications or tumour recurrences. For these reasons, a meta-analysis was considered to be not appropriate for data clear and concise conclusion.

In the large majority of studies included in this review, analyses were done on the group level, not taking into account large differences in the ages of individual patients as well as variation in duration of follow-up after surgery. With this approach specific issues that may affect children and young people following amputation or limb salvage surgery, in particular related to issues of body image, mobility and social functioning, may have been overlooked. Moreover, it implies that still little is known about the initial impact of the surgery and other forms of treatment as well as their complications on the course of QoL and functional ability over time.

With respect to the outcome measures used, this review demonstrates that a relatively large variety of QoL measures was employed. This could probably reflect the lack of suitable instruments and a failure to specify the disease specific domains in which QoL is most likely to be affected. Generic QoL measures focus on global issues and fail to provide detailed information regarding how specific aspects of disease and treatment compromise QoL. In contrast, disease-specific measures include specific disease and treatment-related issues and are therefore likely to be more sensitive to clinical change and differences within the patient population.

Although bone cancer surgery in general and amputation in particular has a mutilating effect and could result in serious limitations in daily functioning and sports, effects on body image, cosmetic contentment and sportive ability have rarely been systematically assessed. Several cancer specific QoL measures have been developed during the last decade, but to date there is only one bone tumour surgery specific measure module [38]. However, this Bt-DUX is to date not available for other than Dutch speaking countries.

For the evaluation of functional ability both questionnaire type measures (TESS, MSTs) and measures that included both self-report and measured function (FMA) were applied. The bone cancer surgery specific TESS questionnaire was used in nearly all studies. However, it was designed essentially for adults, comprises five items that are potentially inappropriate or not applicable to children and adolescents, and lacks tasks that are particularly relevant for children, adolescents and young adults, like education and leisure or sport abilities [39]. The MSTs has the fundamental problem of reflecting the clinician's perception of function rather than the patient's view and has never been tested for reliability and validity in children and adolescents [39]. Furthermore, it consists of only six items, lacking important tasks like daily living activities, kneeling, stair climbing, running or sports. The FMA combines self-report and measured functional ability and has proven to be a reliable and valid outcome measure for patients with lower-extremity sarcoma [21]. The FMA was found to discriminate between patients and healthy controls [21] and between patients with different surgical interventions [32]. However, the experience with the FMA in paediatric bone tumour research is limited [32] and the ability of this tool to identify changes over time and its independency of age still has to be determined.

Alternative options for the assessment of functional ability are for example the Activities Scale for Kids (ASK) [40], and the Pediatric Outcomes Data Collection Instrument (PODCI) [41]. However, both instruments were developed to assess paediatric physical

function whereas their applicability and validity in adolescent and adult patients has to be determined.

Moreover, our study did not include an instrument that was specifically aimed at social participation, such as the Reintegration into Normal Living (RNL) index [42]. As these aspects are very important in this patient group, the inclusion of the RNL or a similar instrument needs to be considered in future research.

The small sample size and methodological flaws in the available outcome studies indicate that larger scale, prospective, long-term follow-up studies in patients with lower-limb bone tumours, using a standardized set of outcome measures including not only activities and QoL but participation as well, are needed. In addition, a clear description of all confounders and potential sources of bias, and the application of statistical analyses adjusting for confounders are to be recommended.

REFERENCES

1. Steliarova-Foucher E, Stiller C, Kaatsch P, Berrino F, Coebergh JW, Lacour B, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet* 2004;364:2097-105
2. Stiller CA, Bielack SS, Jundt G, Steliarova-Foucher E. Bone tumours in European children and adolescents, 1978-1997. Report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 2006;42:2124-35
3. Damron TA, Ward WG, Stewart A. Osteosarcoma, chondrosarcoma, and Ewing's sarcoma: National Cancer Data Base Report. *Clin Orthop Relat Res* 2007;459:40-7
4. Eiser C. Assessment of health-related quality of life after bone cancer in young people: easier said than done. *Eur J Cancer* 2009;45:1744-7
5. Eiser C, Grimer RJ. Quality of life in survivors of a primary bone tumour: a systematic review. *Sarcoma* 1999;4:183-90
6. Nagarajan R, Neglia JP, Clohisey DR, Robison LL. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? *J Clin Oncol* 2002;20:4493-501
7. Paul SJ. Long Term Quality-of-Life Outcomes in Pediatric Bone Cancer: A Systematic Review. *J Nurs Stud Res* 2008;1:6-12
8. Ottaviani G, Robert RS, Huh WW, Jaffe N. Functional, psychosocial and professional outcomes in long-term survivors of lower-extremity osteosarcomas: amputation versus limb salvage. *Cancer Treat Res* 2009;152:421-36.
9. Rougraff BT, Simon MA, Kneisl JS, Greenberg DB, Mankin HJ. Limb salvage compared with amputation for osteosarcoma of the distal end of the femur : A long-term oncological, functional and quality of life study. *J Bone Joint Surg (Am)* 1994;76:649-56
10. Aksnes LH, Bauer HCF, Jebesen NL, Follerås AC, Haugen GS, Hall KS. Limb-sparing surgery preserves more function than amputation. *J Bone Joint Surg (Br)* 2008;90(6):786-94
11. Renard AJ, Veth RP, Schreuder HW, van Loon CJ, Kooops HS, van Horn JR. Function and complications after ablative and limb-salvage therapy in lower extremity sarcoma of bone. *J Surg Oncol* 2000;73(4):198-205
12. Ware JE , Sherbourne CD. The MOS 36 Item Short Form Health Survey (SF 36). 1. Conceptual framework and item selection. *Medical Care* 1992; 30:473-83
13. Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169-80
14. Ferrell BR, Dow KH, Grant M. Measurement of the quality of life in cancer survivors. *Qual Life Res* 1995;4:523-31
15. Aaronson NK, Ahmedzai S, Bullinger M, Crabeels D, Estape J, Filiberti A et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *JNCI* 1993;85:365-76
16. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL™ in Pediatric Cancer: Reliability and Validity of the Pediatric Quality of Life Inventory™ Generic Core Scales,

- Multidimensional Fatigue Scale, and Cancer Module. *Cancer* 2002;94:2090-106
17. Verrips GH, Vogels AGC, Verloove-Vanhorick SP, Fekkes M, Koopman HM, Kamphuis RP, et al. Health-Related Quality of Life Measure for Children—the TACQOL. *J Appl Ther* 1997;1:357-60
 18. Fekkes M, Kamphuis RP, Ottenkamp J, Verrips E, Vogels T, Kamphuis M, et al. Health-related quality of life in young adults with minor congenital heart disease. *Psychol Health* 2001;16:239-51
 19. Enneking WF, Dunham W, Gebhardt MC, et al. A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system. *Clin Orthop* 1993;286:241-6
 20. Davis AM, Wright JG, Williams JJ, Bombardier C, Griffin A, Bell RS. Development of a measure of physical function for patients with bone and soft tissue sarcoma. *Qual Life Res* 1996;5:508-16
 21. Marchese VG, Rai SN, Carlson CA, Hinds PS, Spearing EM, Zhang L, et al. Assessing functional mobility in survivors of lower-extremity sarcoma: reliability and validity of a new assessment tool. *Pediatr Blood Cancer* 2007;49:183-9
 22. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370:1453-7
 23. Cohen J, (1960). "A coefficient of agreement for nominal scales". *Educational and Psychological Measurement* 1960;20:37-46
 24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60
 25. Dam MS van, Kok GJ, Munneke M, Vogelaar FJ, Vliet Vlieland TPM, Taminiu AHM. Measuring physical activity in patients after surgery for a malignant tumour in the leg. The reliability and validity of a continuous ambulatory activity monitor. *J Bone Joint Surg (Br)* 2001;83:1015-9
 26. Saraiva D, Camargo B de, Davis AM. Cultural adaptation, translation and validation of a functional outcome questionnaire (TESS) to Portuguese with application to patients with lower extremity osteosarcoma. *Pediatr Blood Cancer* 2008;50:1093-9
 27. Eiser C, Darlington AS, Stride CB, Grimer R. Quality of life implications as a consequence of surgery: limb salvage, primary and secondary amputation. *Sarcoma* 2001;5:189-95
 28. Nagarajan R, Clohisey DR, Neglia JP, Yasui Y, Mitby PA, Sklar C, et al. Function and quality-of-life of survivors of pelvic and lower extremity osteosarcoma and Ewing's sarcoma: The Childhood Cancer Survivor Study. *Br J Cancer* 2004;91:1858-65
 29. Zahlten-Hinguranage A, Bernd L, Ewerbeck V, Sabo D. Equal quality of life after limb-sparing or ablative surgery for lower extremity sarcomas. *Br J Cancer* 2004;91:1012-4
 30. Hopyan S, Tan JW, Graham K, Torode IP. Function an upright time following limb salvage, amputation and rotationplasty for pediatric sarcoma of bone. *J Pediatr Orthop* 2006;26:405-8
 31. Akahane T, Shimizu T, Isobe K, Yoshimura Y, Fujioka F, Kato H. Evaluation of postoperative general quality of life for patients with osteosarcoma around the knee joint. *J Pediatr Orthop B* 2007;16:269-72
 32. Ginsberg JP, Rai SN, Carlson CA, Meadows AT, Hinds PS, Spearing EM, et al. A comparative analysis of functional outcomes in adolescents and young adults with lower-extremity bone sarcoma. *Pediatr Blood Cancer* 2007;49:964-9
 33. Bekkering WP, Vliet Vlieland TP, Koopman HM, Schaap GR, Schreuder HWB, Beishuizen A, et al. Quality of life in young patients after bone tumor surgery around the knee joint and comparison with healthy controls. *Pediatr Blood Cancer* 2010;54:738-45
 34. Robert RS, Ottaviani G, Huh WW, Palla S, Jaffe N. Psychosocial and functional outcomes in long-term survivors of osteosarcoma: a comparison of limb-salvage surgery and amputation. *Pediatr Blood Cancer* 2010;54:990-9
 35. Bekkering WP, Vlieland TPMV, Koopman HM, Schaap GR, Schreuder HWB, Beishuizen A, et al. Functional ability and physical activity in children and young adults after limb-salvage or ablative surgery for lower extremity bone tumors. *J Surg Oncol* 2011;103:276-82
 36. Hak E, Verheij TJ, Grobbee DE, Nichol KL, Hoes AW. Confounding by indication in non-experimental evaluation of vaccine effectiveness: the example of prevention of influenza complications. *J Epidemiol Community Health* 2002;56:951-5
 37. Sanderson S, Tatt ID, Higgins JPT. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *Int J Epidemiol* 2007;36:666-76

38. Bekkering WP, Vliet Vlieland TPM, Koopman HM, Schaap GR, Schreuder HWB, Beishuizen A, et al. The Bt-DUX: Development of a subjective measure of health-related quality of life in patients who underwent surgery for lower extremity malignant bone tumor. *Pediatr Blood Cancer* 2009;53:348-55
39. Pakulis PJ, Young NL, Davis AM. Evaluating physical function in an adolescent bone tumor population. *Pediatr Blood Cancer* 2005;45:635-43
40. Young NL, Yoshida KK, Williams JJ, Bombardier C, Wright JG. The role of children in reporting their physical disability. *Arch of Phys Med Rehab* 1995;76: 913-8
41. Daltroy LH, Liang MH, Fossel AH, Goldberg MJ. The POSNA pediatric musculoskeletal functional health questionnaire: report on reliability, validity, and sensitivity to change. *Pediatric Outcomes Instrument Development Group. Pediatric Orthopaedic Society of North America. J Pediatr Ortho.* 1998;18:561-71
42. Wood-Dauphinee SL, Opzooomer MA, Williams JJ, et al. Assessment of global function: The Reintegration to Normal Living Index. *Arch Phys Med Rehabil.* 1988;69:583-90

APPENDIX 1. SEARCH QUERIES

PubMed

((Lower Extremity Tumours OR Lower Extremity Tumour OR "Lower Extremity Tumor" OR "Lower Extremity Tumors" OR ("Bone Neoplasms"[mesh] OR "malignant bone" OR "malignant tumour" OR "malignant tumours" OR "malignant tumor" OR "malignant tumors" OR osteosarcoma OR "Ewing's sarcoma" OR osteosarcomas OR "Ewing's sarcomas" OR "Ewings sarcoma" OR "Ewings sarcomas" OR "Ewing sarcoma" OR "Ewing sarcomas") AND (leg OR legs OR "lower extremity" OR "lower extremity"[MeSH Terms] OR "lower extremities" OR "lower limb" OR "lower limbs" OR Knee OR knees OR "Leg Bones" OR "leg bones"[MeSH Terms] OR Femur OR Fibula OR Patella OR Tibia)) AND (Young Adult OR child OR Adolescent) AND ("Quality of Life" OR "Quality of Life"[mesh] OR "life quality" OR "life qualities" OR "functional ability" OR "functional abilities" OR "functional results" OR "functional result" OR ADL OR "Activities of Daily Living"[mesh] OR "Daily Living Activities" OR "Daily Living Activity" OR "Self Care"[mesh] OR "self care" OR (Limitation[tw] AND Activity[tw]) OR "physical activity" OR "Motor Activities" OR "motor activity"[Mesh] OR "motor activity" OR "Physical Activities" OR "Locomotor Activity" OR "Locomotor Activities" OR disability OR "Disabled Persons"[mesh])) AND ("2000"[PDAT] : "3000"[PDAT])

EMBASE

(Lower Extremity Tumo*.ti OR ((exp Bone tumor/ OR malignant bone.ti OR osteosarcoma*.ti OR Ewing's sarcoma*.ti OR Ewings sarcoma*.ti OR Ewing sarcoma*.ti) AND (exp Leg/ OR (leg OR legs OR lower extremity OR lower extremities OR Knee OR lower limb* OR knees OR Leg Bones OR Femur OR Fibula OR Patella OR Tibia).mp))) AND (Young Adult.mp OR child.mp OR Adolescent.mp OR exp Child/ OR exp Adolescent/) AND ((Quality of Life OR life quality OR life qualities OR functional ability OR functional abilities OR functional results OR functional result OR ADL OR "Activities of Daily Living" OR Daily Living Activities OR Daily Living Activity OR Self Care OR (Limitation AND Activity) OR "physical activity" OR Motor Activities OR "motor activity" OR "motor activity" OR "Physical Activities" OR Locomotor Activity OR Locomotor Activities OR disability).ti OR exp *"quality of life"/ OR exp *Physical activity/ OR exp *daily life activity/ OR exp *Disability/)

Web of Science

TS=(“Lower Extremity Tumo*” OR ((Bone tumo* OR malignant bone OR osteosarcoma OR osteosarcomas OR Ewings sarcoma OR Ewings sarcomas OR Ewing sarcoma OR Ewing sarcomas) AND (Leg OR legs OR “lower extremity” OR “lower extremities” OR “lower limb*” OR Knee OR knees OR Leg Bones OR Femur OR Fibula OR Patella OR Tibia))) AND TS=(Quality of Life OR life quality OR life qualities OR functional ability OR functional abilities OR “functional result*” OR ADL OR “Activities of Daily Living” OR Daily Living Activities OR Daily Living Activity OR Self Care OR (Limitation AND Activity) OR “physical activity” OR Motor Activities OR “motor activity” OR “motor activity” OR “Physical Activities” OR Locomotor Activity OR Locomotor Activities OR disability OR daily life activity) AND TS=(“Young Adult” OR child OR Adolescent OR Child OR adolescent)

Cochrane

#1(Lower Extremity Tumours OR Lower Extremity Tumour OR “Lower Extremity Tumor” OR “Lower Extremity Tumors”)

#2(Bone Neoplasms OR “malignant bone” OR “malignant tumour” OR “malignant tumours” OR “malignant tumor” OR “malignant tumors” OR osteosarcoma OR Ewing’s sarcoma OR osteosarcomas OR Ewing’s sarcomas OR Ewings sarcoma OR Ewings sarcomas OR Ewing sarcoma OR Ewing sarcomas)

#3(leg OR legs OR lower extremity OR lower extremities OR lower limb OR lower limbs OR Knee OR knees OR Leg Bones OR Femur OR Fibula OR Patella OR Tibia)

#4(#2 AND #3) #5(#1 OR #4) #6(Young Adult OR child OR Adolescen*)

#7(Quality of Life OR life quality OR life qualities OR functional ability OR functional abilities OR functional results OR functional result OR ADL OR Activities of Daily Living OR Daily Living Activities OR Daily Living Activity OR Self Care OR (Limitation AND Activity) OR physical activity OR Motor Activities OR motor activity OR motor activity OR Physical Activities OR Locomotor Activity OR Locomotor Activities OR disability)

#8(#5 AND #6 AND #7)

APPENDIX 2. METHODOLOGICAL ASSESSMENT WITH 24 ITEMS DERIVED FROM THE STROBE CHECKLIST

	No	Recommendation
Title	1	Indicate the study’s design with a commonly used term in the title or the abstract
Abstract	2	Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/ rationale	3	Explain the scientific background and rationale for the investigation being reported
Objectives	4	State specific objectives, including any pre specified hypotheses

Methods		
Study design	5	Present key elements of study design early in the paper
Setting	6	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	7	Give the eligibility criteria, and the sources and methods of selection of participants
Variables	8	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	9	For each variable of interest, give sources of data and details of methods of assessment (measurement).
Bias	10	Describe any efforts to address potential sources of bias
Study size	11	Explain how the study size was arrived at
Quantitative variables	12	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	13	Describe all statistical methods, including those used to control for confounding
Results		
Participants	14	Report numbers of individuals at each stage of study
	15	Give reasons for non-participation at each stage
Descriptive data	16	Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders
	17	Indicate number of participants with missing data for each variable of interest
Outcome data	18	Report numbers of outcome events or summary measures
Main results	19	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted.
Discussion		
Key results	20	Summarise key results with reference to study objectives
Limitations	21	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	22	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalizability	23	Discuss the generalizability (external validity) of the study results
Other information		
Funding	24	Give the source of funding and the role of the funders for the present study.