Non-oncological outcomes following limb salvage surgery in patients with knee sarcoma: a scoping review

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Author contributions: NAMD conceptualised the topic and conducted the literature search and analysis of the literature.

CO provided content from a specialist physiotherapy perspective, provided a critical review and helped refine the manuscript for publication.

MDH provided perspective from a health psychology viewpoint and provided critical review prior to submission of the manuscript.

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Limb salvage surgery is a surgical procedure for tumour resection in bone and soft-tissue cancers. Guidelines aim to preserve as much function and tissue of the limb as possible. Surgical outcome data is routeinly available as part of surgical reporting processes. What is less known are important non-oncological outcomes throughout recovery from both clinical and patient perspectives. The objective of this review was to explore non-oncological outcomes in patients diagnosed with sarcoma around the knee following limb salvage surgery.

A scoping review methodology was used and results analysed using CASP checklists.

Twelve studies were included and following appriasal and synthesis, three themes emerged as providing important measures intrinsic to successful patient recovery: 1) physical function, 2) quality of life and, 3) gait and knee goniometry. Specifically, patients develop range of motion complications that alter gait patterns and patients often limit their post-operative particpation in sport and leisure activities.

Results show the importance of exploring confounding factors, adopting a holistic view of patient recovery beyond surgical outcomes, proposing evidence-based guidance to support and inform healthcare providers with clinical decision-making. This review highlights the paucity and lack of quality of research available, emphasising how under-represented this population is in the research literature.

Keywords: enhanced recovery after surgery; limb salvage; outcome; process assessment (health care); sarcoma; surgical oncology

**Introduction**

Bone cancer, is considered a rare form of mesenchymal malignancy and is a life-threatening disease (1). The incidence of sarcoma is higher in men than women, occurring in 5.4 per million men and 4.0 per million women each year, and the predominant population is young adults, teenagers and children (2,3). This paper will focus on knee sarcoma: osteosarcoma, which forms within bone cells, is the most common type of bone malignancy, representing 56% of bone cancer cases, followed by Ewing’s sarcoma, a malignancy formed within the bone or, in rare cases, the soft tissue around the bone, representing 34% of bone cancer cases (3). Osteogenic sarcoma arises in the metaphyseal end plates of the long bones in the extremities; two-thirds of cases affect the lower extremities, with the femur being the most common location (42%), followed by the tibia (19%) (3–5). Surgical management is standard care for sarcoma with amputation and disarticulation historically recognised as the main surgical options. However, due to medical advancements in imaging techniques, chemotherapy and radiation, surgical interventions have shifted from ablative surgery (such as amputation) to limb salvage or sparing techniques (6–9). Limb salvage surgery (LSS) is one such technique and is recommend by Steinau and colleagues (10) for the treatment of sarcoma when used to locally control the disease, preserving unaffected tissue to maintain or restore limb function. From a medical viewpoint, success rates for LSS are considered high based on a 70% 5-year survival rate of non-metastatic sarcoma patients and the local control of tumours. Several factors play important roles in the decision-making phase, including the age of the patient, skeletal maturity, response to treatment, tumour size and extent, which are reportedly correlated to surgical success and outcomes (11,12). While surgical outcomes and survival rates are important oncological outcomes to report, other outcomes are also likely to be important to the patient beyond survival and into recovery.

LSS procedures can vary based on patient needs, however generally surgery occurs via a wide, local excision of the tumour and can involve autologous grafts, endoprostheses with metal implants, or a combination of both (13,14). The knee joint is the most common location for lower extremity sarcoma involving the distal femur and proximal tibia. Due to the functional movement, complexity of the knee joint anatomy and the requirement for weight bearing, the knee is considered a challenging site for successfully restoring function and minimising impairment. Surgical procedures involving the knee can be accomplished using an intra-articular technique if the tumour size is under control; however, if the tumour has spread to adjacent tissue, then extra-articular resection may be required to maintain metastasis-free tissue (13,15,16).

Functional and Quality of Life (QoL) outcomes are crucial in any surgical technique performed to patients with sarcoma (17). These non-oncological factors can be assessed by using variant subjective and objective outcome measures in order to provide evidence of success levels and associated complications of a surgical intervention and its correlation with function and quality of life afterward (18). Some papers had conducted meta-analysis and systematic review of these aspects with sarcoma patients in general (19–21). However, no review of these non-oncological outcomes has been conducted specifically to limb salvage surgery as a treatment of sarcoma around the knee in order to synthesise this evidence to help support and inform clinical decision-making. Therefore, the aim of this scoping review is to identify and synthesise knowledge on non-oncological outcomes associated with LSS in patients with sarcoma around the knee. The outcome of this scoping review will summarise and synthesise the evidence with the aim of informing clinical decision making and identifying future research priorities.

**Methods**

There is a requirement to develop comprehensive, evidence-based guidance to support and inform healthcare providers with clinical decision-making (22). While traditionally scoping reviews were defined by the absence of an assessment of quality, more recent methodological work in this area, extending the original framework of Arksey & O’Malley (23) has seen the inclusion in scoping reviews as essential for providing ‘research that in itself can be disseminated to others in a way that is useful for practice or policymaking and for future researchers.’ (24,25). As the principle of this review is to provide implications for practice, specifically rehabilitation where there is limited clinical guidance, a quality assessment is also included. In this review, the principles and approaches suggested by Booth et al (26) were applied to identify reliable studies and to synthesise those results in a rigorous way. This approach applies a detailed search question and strategy, clear inclusion and exclusion criteria, and explicit criteria for assessing the validity of the eligible studies based on the scope of the review (27).

The following is aligned to Arksey & O’Malley’s framework for scoping reviews: identifying the research question (23). The research question underpinning this review was developed with the PICO table (table 1) and defined as “*What are the non-oncological outcomes following LSS of patients with sarcoma around the knee*?”. Further, the PICO table was used to determine appropriate inclusion and exclusion criteria for the search strategy (28), and this refers to Arksey & O’Malley’s framework for scoping reviews (23): study selection; specifically, the outcomes chosen were driven by clinical decision making and represent the Author’s experiences in managing clinical outcomes for this complex patient group.

<<Please insert table 1>>

The following refers to Arksey & O’Malley’s framework for scoping reviews: identifying relevant studies (23). The European Society for Medical Oncology (29) osteosarcoma clinical recommendations and guidelines document is recognised in the field of treating sarcoma; therefore, it was identified in this literature review as the standard of care. The guidelines were reviewed and adapted to bone and soft-tissue cancer in 2018 through a partnership between the European Reference Network for Rare Adult Solid Cancers (EURACAN) and the European Reference Network for Paediatric Oncology (PaedCan) and were accepted by the American Society of Clinical Oncology (ASCO). These primary clinical guidelines influenced this literature review by shaping the search strategy to focus on studies published from 2009 onward.

An initial search of the COCHRANE database as a specialist database for high-quality systematic reviews as recommended by Aveyard (30). This step was conducted using the search terms, Boolean operators and truncations identified in table 2, which were later used for the other databases. After no matching systematic reviews were found in the COCHRANE database, a literature search was conducted in June 2019 in three databases: MEDLINE, CINAHEL and AMED. Restrictions were applied, such as date, English language articles and full-text access; the search results are recorded in the PRISMA flowchart (figure 1). A total of 131 articles were returned.

<<Please insert table 2>>

<<Please insert figure 1>>

All duplicates were removed (N=77), and inclusion and exclusion criteria in table 3 were applied on the remaining 54 articles, providing the relevant studies. The abstracts were reviewed by an Author [BLIND], whereupon 30 were excluded. Full-text versions of the remaining 24 articles were re-assessed against the inclusion/exclusion criteria. Twleve articles were finally excluded for three main reasons; 1) irrelevant intervention or insufficient outcome measures, and 2) outcome content did not match the scope of this review.

<<Please insert table 3>>

The remaining 12 articles were included in the review. The included articles were mostly observational and longitudinal studies due to the rarity of this condition. Due to the variability of the methods used in the included studies, the CASP tool was used for cohort and case–control studies (31) and the JBI Critical Appraisal Checklist was used for cross-sectional studies and case series (32). These are valid, critical appraisal tools, and are recommended by National Institute for Health and Care Excellence (33) and Sanderson et al (34).

**Results**

The results presented follow Arksey & O’Malley’s framework for scoping reviews: charting the data, and are described below and presented in the format of a narrative review, recommend by Arksey & O’Malley (23) in order to extract contextual information and add value to this under-researched area.

Papers published between 2009 and 4th September 2020 were considered for this literature review resulting in 12 papers. A summary of the relevant papers is provided in table 4 and describe both general information about the study and specific information to answer the research question. Eleven papers were retrospective and one prospective (17). The 11 retrospective articles included four cohort studies (18,19,35,36), two case-control studies (20,37), two analytical cross-sectional studies with retrospective data (21,38) and three retrospective chart reviews (39–41).

<<Please insert table 4>>

The overall study population was heterogeneous for age, stage and type of tumour, associated treatment (e.g., chemotherapy), type of endoprostheses used, surgical techniques, presence of a comparison group and the type of comparison, (ablative surgery or a healthy control group). Most studies described age variation and two papers were dedicated to paediatrics and young adults (18,21).

The study location varied; five studies were from Asia; China (18,39,41), Japan (40) and Malaysia (38) and five from Europe; Netherlands (17,21), United Kingdom (35), Germany (42) and Spain (37). The remaining papers were from the United States (19) and Australia (20,43). Most of the papers clearly addressed compliance with ethical standards of research and informed consent was obtained in all studies when needed. However, four papers (20,35,42,43) did not state whether ethical approval was obtained prior to conducting the research and accessing patient data, thus were not aligned to the World Medical Association Declaration of Helsinki (44) for medical research involving human subjects.

For transparency and ease of comparison, Table 5 summarises each paper with respect to the thematic content therein. The following thematic process follows Arksey & O’Malley’s framework for scoping reviews: Collating, summarising and reporting the results (23). were considered to be the most relevant to the research question. Themes were chosen that were considered most relevant to the research question.

<<Please insert table 5>>

*Physical Function*

Functional outcomes were measured in all of the included papers using various outcome measures and scores. The outcomes measured were physical function, walking distance, walking speed and functional mobility, utilising both disease-specific and generic outcome measures. Three papers used objective measures alongside a subjective measure, and these studies were the most focused on functional outcomes due to their use of multiple measures (17,19,21). However, it is important to stipulate that none of the functional measures take into account the patient’s perspective. Further information on the discrepancy between patient- and clinician-reported function in this population is reported in Janssen et al (45). The remaining studies relied on a subjective measure for the functional outcome. The overall Musculoskeletal Tumour Society scoring system (MSTS) mean scores in all 10 papers was 23.9, indicating good and excellent functional ability following LSS. The location of the resected tumour was associated with the MSTS score in three studies (37,39,41). For example, in distal femur groups, the MSTS mean scores were above 23, indicating excellent functional ability. However, the correlation was not statistically significant in two of the papers (37,41) and the third study did not statistically analyse this correlation (39). Two studies investigated the correlation between the type of resection, whether extra-articular (EAR) or intra-articular (IAR), and the MSTS score (35,40). One study found that the MSTS score was significantly better for IAR than for EAR (40), whereas the other study, which had a larger sample size (35), found no significant difference in the MSTS scores between the two procedures. Not all papers had descriptive data for the results of the MSTS components; however, ‘walking capacity’ and ‘use of support’ were reported in three papers and scored the lowest among the MSTS components (17,38,40). ‘Emotional capacity’ and ‘functional ability’ scored the lowest in two studies (20,41), while coversly in the same two papers, ‘pain’ was the highest scored component. All of the components appeared to be affected by age and demographics, but no statistical correlations were presented to assess significance.

Multiple objective measures were also used to assess outcomes. Performance tests were used to assess physical and functional outcomes (6-minute walk test, timed up & go, timed up & down stairs, various walking activities, and lie down & stand up). This set of tests was used in two papers (17,21). The tests conducted in van Egmond-van Dam et al (17) did not show any improvement between 2-and 7-years post-operation. Bekkering et al (21) found no correlation between the type of LSS and the results of these tests; however, they reported that the LSS group had significantly better outcomes in some of these tests in comparison with an ablative surgery group.

The Physiological Cost Index (PCI) is an objective indirect measure of oxygen cost during exercise or walking (46). It was used in two studies (19,21), but contradicting results were found. Malek et al (19) reported a significantly better gait speed and distance in the LSS group than in the amputation group. In contrast, no significant differences between the LSS and ablative groups were found in the study by Bekkering et al (21), who also used activity monitors in a cross-sectional study for 24 hrs/7days and showed no statistically significant difference between the groups. The PCI outcome measure has therefore been reported to be a valid but unreliable tool (46,47), and it has not been validated for use with sarcoma patients (19). A concluding statement of this theme is the variety of outcomes measured makes comparison difficult and this population may benefit from the development of a Core Outcome Set (48), especially given the clear definition of the cohort.

*Quality of Life*

Quality of life (QoL) encompasses a wide range of interrelated aspects that impact satisfaction and well-being (49). In soft tissue and bone cancer patients in particular, QoL aspects are considered difficult to assess due to heterogenosity of the population. McDonough et el (50) reported lower Health-Related QoL of Sarcoma patients when compared to healthy individuals in physical and psychosocial domains, despite the general lower outcme measures of this population in the different disease stages, some outcomes were found specifically higher in these patients such as fatigue, insomnia, loss of appetite and social interaction.

In this review, patient-reported outcome measures were used in 6 papers to assess the QoL of participants and its correlation with impairment and disability (17–21,37). The Toronto Extremity Salvage Score (TESS) was used in five out of the 12 reviewed papers (17–21). The range of scores in these studies varied widely, with the lowest being reported by Zhang et al (18) in a knee arthroplasty group (76.33%), and the highest was 93.2% in van Egmond-van Dam et al (17). The variation in scores suggest mild to moderate disability levels, but special consideration for confounding factors as age, gender and extent of surgery were ambiguous among the studies found. Carty et al (20) was the only study to address the TESS score in detail; the study found that the most affected components were related to kneeling movements, sport activities and walking upstairs or uphill. In four studies (17–21) no significant correlation was found between the TESS score and other variables, such as the type of procedure and comparison with an amputee group. However, Carty et al (20) found a moderate positive correlation between the TESS score and the MSTS sub-components of walking ability and emotional acceptance. QoL was assessed by other patient-reported outcome measures, such as the Baecke Questionnaire (17,21), the Short-Form 36 Questionnaire (36), the Reintegration to Normal Living Index (RNL) (19) and the Western Ontario and McMaster Universities (WOMAC) score (37). These outcome measures covered different perspectives of QoL ranging from physical and leisure activities, pain, wellbeing, social and emotional status from patient-perspectives which is essential in this aspect rather than relying solely on clinician-based outcomes. All of the self-reported outcome measures suggested a good-to-high QoL for LSS patients. The RNL score in Malek et al (19) was the only outcome measure to report a significantly better QoL level in LSS patients compared to an ablative surgery group, while the other studies found no significant difference between groups.

*Gait and Knee Goniometry*

There is a paucity of literature on gait in this field and it was investigated in only one study. Using a cross-sectional design, the authors conducted gait analysis with a small group of patients via convenience sampling at a university hospital and compared the findings with healthy data (38). The study itself had many limitations, including a small sample size and a wide variation in age (8 – 44 years) and corresponding MSTS scores. Singh et al (38) revealed significant differences between the affected and non-affected site in terms of knee goniometry and gait quality (determined as ‘pattern’ and cyclicality of gait). In addition, the affected gait pattern was positively correlated with the lowest-scoring MSTS component, which was walking ability. This finding is consistent with the three papers reporting ‘walking ability’ as having the lowest score (17,38,40). Interestingly, the study found that 90% of participants who exhibited stiff knee gait when the range of motion (ROM) was actively and passively assessed were within a normal range, although their gait was affected.

Range of motion of knee flexion and extension was measured in eight of the papers; however, its calculation was inconsistent. Zhang et al (39) reported the use of ROM to assess knee goniometry; however, it was used with patients who developed the complication of “patella alta”, which is a high position of the patella in the knee, and the rest of the participants were disregarded in this study. ROM has been used in multipurpose studies that are concerned with post-operative outcomes in terms of survival, complications and functional outcomes. Therefore, the ROM reported through the analysis of these papers ranged considerably, from 60 degrees to 140 degrees, which was the highest degree reported among the studies (20,35,38–41,50). Only four papers (18,20,35,41) addressed ROM with univariate statistical tests with either the type of procedure or location of tumour.

**Discussion**

The aim of this scoping review was to gain insights into non-oncological outcomes following LSS around the knee due to osteosarcoma. The included papers were diverse in their protocols, healthcare settings, location and population. The surgical intervention of LSS itself varied from study to study due to the anatomical site, tumour characteristics, cancer stage and the indication for chemotherapy and radiation therapy. The study design and methodology of the reviewed studies also varied widely; most of the studies were retrospective and can be considered as level III, IV or V, according to Sackett (51). Moreover, the studies consisted of small sample sizes, which may lead to systematic bias.

However, due to the low occurrence of this disease clinical trials are challenging and therefore studies are limited to longitudinal and observational methods. Some of the reviewed papers had multiple aims; therefore, these studies could not provide a coherent analysis of their findings. The results showed that non-oncological recovery outcomes were not investigated and analysed to the same extent as other outcome measures, such as survival rates or surgical complications.

*Functional Outcomes*

This review revealed the lack of studies in this field and the limited outcomes that were deemed important to measure. The Musculoskeletal Tumour Society (MSTS) scoring system is an oncology-specific subjective outcome measure that relies on the clinician to interview the patient. The MSTS score measures functional outcome with reference to six components: pain, functional ability, emotional acceptance, use of support, walking capacity and gait. Each component is assigned a score ranging from 0 (lowest) to 5 (highest), where 30 is the maximum score achievable. A score of 23 to 30 is considered an excellent functional score, 15 to 22 is good, 8 to 14 is fair, and below 8 is considered a poor functional score (41). Although the MSTS score has been translated and validated in many languages and is considered to be a reliable tool, it can over- or under-estimate functional levels because it is assessed by the clinician and not the patient (45). The mean scores from the reviewed papers showed good-to-excellent functional levels using MSTS. The study by Singh et al (38), showed four participants (20% of the sample) aged between 10 and 50 years had a fair MSTS score, especially for walking, pain and support components. The patients reported that limited functional levels are due to moderate pain experienced with walking, requiring them to use a cane in outdoor activities. The lowest scores for walking ability and support components are consistent with the findings of van Egmond-van Dam et al (17) and Ieguchi et al (40). However, the pain component contradicts the results of Carty et al (20) and Tan et al (41), where the pain score was the highest of the components. Inconsistent MSTS scores can be due to confounding factors, as reported by Davis et al (52), who found the MSTS and TESS scores to be affected by tumour size, percentage of bone resected and the involvement of nervous tissue. These factors were not analysed or reported in the reviewed papers, yet some papers surmised that other factors affected the functional levels, such as the type of LSS procedure (IAR vs EAR), as was reported by four studies (20,35,40,42). Ieguchi et al (40) was the only study that reported EAR to have reduced functional outcomes than IAR. This is consistent with the findings in related literature (53,54).

Age was widely heterogeneous in most of the reviewed papers; however, two studies were dedicated to paediatric and young adult patients (18,20) and demonstrated that some aspects of the functional levels, gait and QoL outcomes were within acceptable ranges for this subpopulation. Activity in the sport domain, as measured using the Baecke questionnaire, was lowest in (21) for this subpopulation; this is consistent with the findings of related papers (55–57), where sport activity was the most affected aspect in the lives of these children. This is an important finding, as activity in sport is reported as an important child occupation to support health and well-being, but also social interaction (58–60).

*Surgical Outcomes*

LSS was compared with ablative surgeries in four papers and the findings were contradictory; Shahid et al (35) and Malek et al (19) reported better functional and gait outcomes, where van Egmond-van Dam et al (17) and Bekkering et al (21) reported no differences. However, these four studies reported no differences for QoL aspects between the LSS and ablative surgery. The Toronto Extremity Salvage Score (TESS) is a valid and reliable outcome measure used to assess disability in sarcoma patients aged 12 to 85 years (61). TESS is a procedure-specific and self-reported questionnaire for patients following LSS. The score consists of 30 questions reporting the difficulty level of performing tasks related to dressing, grooming, mobility, work, sport and leisure. The score is calculated between 0–100, with higher scores indicating better outcomes (61).

Robert et al (62) demonstrated that the QoL did not substantially differ between the LSS and ablative surgery groups, instead they reported patients were mainly affected by the functional level and body image issues. Primary findings were supported by (63–65), reporting no differences in QoL between groups. Postma et al (63) further reported that body-image was the main issue in an amputee group, whereas the LSS group experienced more physical problems, such as pain, distress and ADL.

Nagarajan et al (64) found that low levels of education (attainment rather than literacy levels) significantly affected QoL. Aksnes et al (65), a study by the Scandinavian Sarcoma Group in Norway and Sweden, found QoL to be similar; however, physical functioning was significantly better in the LSS group.

*Other Considerations*

The findings presented here can vary based on cultural, financial and educational factors. Tan et al (41) discussed finances as an important factor in deciding the treatment protocol. Patients who were candidates for LSS with a required chemotherapy regimen, but who struggled financially, chose to undergo amputation, as they could not afford the standard treatment protocol. However, this would potentially have longer financial implications to the patient due to the life-long post-amputation rehabilitation, possible prostheses service provision and medical device supply, maintenance and repair requirements.

Jauregui et al (66)confirmed this assertion that the long-term care of amputation is slightly higher than LSS because the amputee requires life-long prosthesis maintenance, check-ups and stump care. However, this finding was positively correlated with age and the cost of the prosthesis. Therefore, the cost aspect of both procedures may vary based on demographics, the healthcare system supporting the patient, functional levels and the type of prosthesis device available.

The overall heterogeneity of the papers made the synthesis of findings difficult. This was due primarily to the resultant papers using different outcome measures and crucially, knowing what are important outcomes to measure. In such a population, one could argue that the patients themselves could help determine what is important to measure in non-oncological recovery outcomes as it directly affects their ability to engage in meaningful occupation and improve the quality of their life. The findings presented here therefore identify and synthesise knowledge on non-oncological outcomes associated with LSS in patients with sarcoma around the knee, providing a summary of the evidence to inform clinical decision making and identify future research priorities.However, it is important to note that this is scoping review only included pubished academic research. It did not include a search of the grey literature, an therefore there is a risk of ‘publication bias’ as it may not representative of all the research carried out in this field.

**Conclusion**

This scoping review investigated the non-oncological outcomes of LSS in patients with sarcoma around the knee. The findings were summarise into three themes: 1) functional outcomes, 2) QoL, and 3) gait and knee goniometry. The functional outcomes demonstrated good-to-excellent levels for LSS patients and the type of surgical procedure may affect the level of functionality. QoL did not substantially differ between the LSS and ablative surgery groups. However, studies did report that the aspects of QoL that patients were mainly affected by were pain, distress, reduced functional levels (in ADLs particularly) and body image issues. Gait patterns and walking ability were reported to adapt by using a flexed knee and a walking aid in outdoor activities. Most patients were affected by ROM limitations in the form of extension lag or limited flexion. While understandable, more holistic outcomes must be considered if we are to fully understand recovery following LSS from a a biopsychosocial and patient-centred perspective. This scoping review highlighted inconsistencies and confounding factors that emphasise the importance of evidence-based guidance to support and inform healthcare providers during clinical decision-making.



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Author contributions: NAMD conceptualised the topic and conducted the literature search and analysis of the literature.

CO provided content from a specialist physiotherapy perspective, provided a critical review and helped refine the manuscript for publication.

MDH provided perspective from a health psychology viewpoint and provided critical review prior to submission of the manuscript.

CM provided guidance during the review process, refined and finalised the manuscript for publication.

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Table 1: PICO Table to define the research question and support the inclusion and exclusion criteria for the review.

|  |  |
| --- | --- |
| **Population** | Adult and paediatric population diagnosed with bone or soft tissue malignant tumour around the knee |
| **Intervention** | Limb salvage surgery (LSS) |
| **Comparison** | None |
| **Outcome** | Functional levels, physical activities, gait, mobility, quality of life, and return to work |

Table 2: Search terms included for the review.

|  |  |
| --- | --- |
| **Term** | **Keywords/Synonym** |
| Sarcoma | Or Bone cancer  Or Malignan\*  Or Osteosarcoma |
| AND | |
| Knee | Or Distal femur  Or Proximal tibia  Or Patella |
| AND | |
| Limb salvage | Or Limb sparing |
| AND | |
| Functional outcomes | Or Rehabilitation outcomes  Or Physical activity  Or Gait  Or Mobility  Or Participation  Or Return to work (RtW)  OR Quality of life (QoL) |

Table 3: Inclusion/exclusion criteria for the review.

|  |  |
| --- | --- |
| **Inclusion** | **Rationale** |
| English language literature | Non-English papers require translation, which is not practical due to limited time and resources. |
| 2009 and onward | To focus on the quality of articles concerned with limb salvage after publication of the clinical recommendations from the European Society of Medical Oncology in 2009, which are widely accepted by global committees and institutions. |
| Full access available | Limited resources to access the unavailable articles. |
| Limb salvage for primary bone tumours | The scope of this literature review focuses on outcomes of limb salvage with patients who were diagnosed with cancer; therefore, other conditions such as vascular, trauma and diabetes must be excluded. |
| Mixed qualitative and quantitative in form of experimental and observational studies, randomised control trials, quasi-experimental research, cohort studies, case-control studies, cross-sectional studies and retrospective chart reviews | Both qualitative and quantitative outcomes were presented in the literature. Qualitative studies were included to consider the outcomes from a population point of view.  As the scope of this literature review focused on exploring the outcomes of limb salvage intervention, observational longitudinal studies were limited to cohort studies, case-control studies and high-quality retrospective chart reviews in order to obtain valuable data from such studies (22).  Case series, case reports and expert opinions were excluded so as to focus on high-quality evidence-based practice articles. |
| Limb salvage procedures including allograft, endoprostheses and both techniques | This literature review focused on limb salvage techniques intended to remove the tumour, as defined in this literature review, with interventions for resuming functional levels. Articles that focused on outcomes or efficacies of procedures or interventions other than limb salvage techniques (which are supposed to reconstruct the limb or enhance the surgical procedure of the limb salvage) were excluded, as they are not the main objective of this literature review. |
| Limb salvage/sparing procedures | Other procedures which are considered ablative such as amputation and rotationplasty involve wearing an external prosthesis. These were excluded as they are not within the scope of this review.  However, articles that included ablative surgery as a comparison group were included. |
| Articles with more than one measure for functional, physical or QoL outcomes | Single-outcome measurement scores do not provide sufficient context for functional, physical or QoL outcomes, as they might be either a patient-oriented or an objective measure. Therefore, more than one outcome measure was required in the articles concerned with non-oncological outcomes to provide sufficient data for inclusion. |

Table 4: Review results: Articles identified from methods described.[[1]](#footnote-2)

| **Reference, Date of Publication & Location** | **Sample** | **Type of Study** | **Method of Research** | **Outcome Measure** | **Procedure Type** | **Key Findings** | **Limitations** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 1. (17)   *2017*  *Netherlands* | N = 20  Gender: Not specified  Mean age = 22.3 (18.2–31.6) | Prospective cohort | Long-term study comparing functional outcomes of participants at 2- and 7-years post-operation | * TESS * MSTS * Baecke questionnaire * Time up & down stairs (TUDS) * Various walking activities (VWA) * 6 minutes walking test (6MWT) | * LSS = 15   (Allografts= 6)  (Endoprostheses= 9)   * Ablative surgery (Amputation and Rotationoplasty) = 5. | The study is an extension to a previous study concerned with young adults’ functional outcomes after surgical intervention (LSS or ablative) for bone sarcoma.  Patients reached plateau phase at 2 years follow-up (f/u). No significant changes in functional outcome scores between 2 years and 7 years f/u.  No deterioration noted in functional outcomes at 7 years f/u despite the presence of 1 or 2 complications.  Mean score of covered walking distance outcome measure was 514 meters (471–556), which is lower than the mean score (593) of healthy adult individuals.  ***MSTS***: Mean score = 83%, CI (37-100) | Small sample size, as nearly half of the participants in previous study are deceased due to the disease prognosis.  The study did not compare the results of the major variables such as the ablative and salvage surgeries, type and technique of the procedure, which leads to the generalisability of the findings with chances of bias.  MSTS score was taken only at 7 years f/u. |
| 1. (35)   *2016*  *United Kingdom* | N = 76  (43 Male & 33 Female)  Mean age = 32 (9–74) | Retrospective cohort | Comparison between intra-articular resection and extra-articular resection in patients with bone and soft-tissue sarcoma | MSTS score  Knee ROM | LSS = 63  (EAR= 42)  (IAR=21)  Ablative surgery (Amputation and Rotationoplasty)= 13 | ***MSTS:*** Mean score in LSS = 26, with no significant difference between the intra-groups. However, both LSS intra-groups in general were significantly better than the ablative surgery group (P=0.04).  ***ROM:***  IAR mean flexion = 106 (70-130)  EAR mean flexion = 103 (60-130)  No significant differences between groups | Heterogeneous sample size in terms of surgical procedures, techniques and presence of adjuvant therapies without taking them into account as confounding factors during data analysis. This could lead to measurement or analysis bias.  No data reported in regards to extension lag, which is a predictable complication with extra-articular endoprostheses, as reported in other reviewed papers. |
| 1. (18)   *2014*  *China* | N= 15  (10 Male & 5 Female)  Mean age = 12 (9–16) | Retrospective cohort | Comparison of functional outcomes between two groups of patients: limb preservation with physeal distraction and limb preservation with knee arthroplasty (endoprostheses) | MSTS score  TESS score  ROM | Physeal distraction (PD) = 6  Knee arthroplasty KA= 9 | ***MSTS:*** Excellent to good overall functional scores. PD Mean MSTS = 86.67% KA Mean MSTS = 74.67%. No significant difference found between groups  ***TESS:***  PD score = 82.33%  KA score =76.33%  No significant differences of MSTS and TESS scores between groups  ***ROM:*** PD group has significantly better ROM than KA group (*P* = 0.05) | Small sample size.  Confounding factors as associated complications were not taken into account in the statistical calculations of functional outcomes. |
| 1. (42)   *2013*  *Germany* | N= 59  (36 Male & 23 Female)  Mean age = 33 (11–74) | Retrospective cohort | Comparison of functional outcomes between extra-articular resection and intra-articular resection groups | MSTS score  ROM  Oxford knee score | EAR = 55  IAR= 4 | ***MSTS:*** Assessed in only 46 patients; 13 patients were excluded due to post-operative failure episode within 1st year  Mean MSTS score = 22 (10–29) which is considered widely variable  ***Oxford knee score:*** Completed at latest f/u by 21 participants only; mean score = 32 (10–48), which is considered widely variable.  ***ROM:*** Recorded in only 38 patients  Mean flexion = 72 degree (10–100)  Nearly a third of patients had < 90 degree of flexion with one patient reporting gross limitation due to peri-prosthetic infection and revision. | Lack of data on functional outcome scores leading to possible selection, measurement and analytical bias.  Weak study design and statistical analysis of functional outcomes.  Small sample size of IAR in comparison with EAR due to convince sampling method.  Use of only univariate statistical analysis in some other outcome measures. |
| 1. (19)   *2012*  *USA* | N = 20  (12 Male & 8 Female)  Mean age = 34 (15–76) | Retrospective cohort | Comparison of functional status and QoL between limb salvage and above knee amputation groups | Physiological Cost Index (PCI)  Reintegration to Normal Living Index  SF-36  TESS | LSS = 14 all with endoprostheses  AKA = 6 | ***RNL***: Scores in LSS group significantly > than AKA group (P = 0.03)  ***PCI:*** Significantly better gait performance in LSS group than AKA (P = 0.02)  ***TESS & SF-36:*** Similar scores in both groups, with no significant differences  Overall, high QoL scores were observed in both groups. | Small sample size.  Limited and no access of participants to advanced prostheses options such as C-Leg in the AKA group.  Confounding factors such as chemo-induced cardiovascular toxicity were not taken into consideration with appropriate statistical tests, especially with the use of PCI as objective outcome measure, which measures cardiovascular performance in relation to gait.  The heterogeneity of the LSS group can lead to measurement bias. |
| 1. (37)   *2018*  *Spain* | N= 45  (22 Male & 23 Female)  Mean age:  DF = 19.7 (10–49)  PT = 23.8 (12–55) | Case-control | Comparison of allograft-prostheses composite for reconstruction between distal femur and proximal tibia groups | MSTS score  Western Ontario and McMaster  Universities (WOMAC) score for QoL  Visual Analog Scale (VAS) for pain | DF = 24  PT = 21 | Standardised healthcare plan, surgical technique and rehabilitation protocol  ***MSTS:*** Good overall outcome score  Mean of DF & PT = 24  No significant difference found between the groups  ***ROM:*** Extension lag outcomes:  PT Median = 7 degrees (SD 4.0)  DF Median =5 degrees (SD 1.0)  PT group has significantly worse extension lag than DF group (*P* = 0.029).  ***WOMAC & VAS:***  All patients reported either mild to no pain.  No significant differences found between groups.  All patients required permanent cane to walk except two patients in PT group who used no walking aid.  Only one patient from DF group and four patients from PT group reported a return to previous level of activity. | Possible selection bias due to the retrospective nature and convenience sampling.  Limited statistical analysis of functional outcome measures with associated variables such as demographics, stage of disease and surgical technique (e.g., extensor mechanism reconstruction with PT). |
| 1. (20)   *2009*  *Australia* | N = 20  (10 Male & 10 Female)  Mean age at surgery = 16.1  Control N = 10.  Mean age= 24.9 | Case–Control | Retrospective evaluation of disease-specific impairment and disability in patients who underwent LSS around the knee due to sarcoma | MSTS  TESS  ROM  Muscle power “knee extensors” | DF= 17  PT = 3  All DF & PT with intra-articular endoprostheses replacement | ***MSTS:*** Good to excellent overall score  Mean = 25 (SD 3.0)  The emotional acceptance and functional ability components ranked the lowest.  ***ROM:*** Knee flexion was significantly worse in cases when compared to control group (*P* < 0.01).  Mean flex = 120 (85–140)  ***Muscle Power:***Knee strength was significantly reduced in cases in comparison with control (*P* = 0.04)  ***TESS:*** Overall mild disability score  Mean = 86% (SD 3.5)  Lowest components of TESS score were kneeling movements, followed by sport participation, then walking upstairs and uphill.   * TESS score has moderate positive correlation with knee flexion movement and knee extensor strength * TESS score has moderate positive correlation with MSTS sub-score of walking capacity (*P*= 0.02), followed by emotional acceptance (*P* = 0.01)   No statistically significant differences between the prosthetic design and subjective outcome measures for impairment and disability | Small sample size.  Lack of recruitment information on control group, their demographics and generally a small number “Half number of the cases included”.  Study design does not match the methodology; the methods used in the study are more like a case-series instead of case-control. |
| 1. (38)   *2018*  *Malaysia* | N= 20  (8 Male & 12 Female)  Mean age = 22.75  (8–44) | Cross-sectional study design with objective and subjective measures | Evaluation of gait pattern with patients who underwent endoprosthetic reconstruction after tumour resection and comparison of the objective data from gait assessment with subjective data from MSTS score | Gait analysis for collecting data on temporal parameters-preferred walking velocity, stride length and duration of stance phase + goniometry of the knee during walking  MSTS score | DF = 15  PT = 5 | ***MSTS:*** Good to excellent score levels  Mean = 21 (13–25)  80% of participants (21–25) - Good to excellent  20% of participants (13–20) - Fair to good  Lowest component = “Walking ability”; only two patients gave a normal gait score after the surgery while the rest who scored the lowest in walking required a walking aid in outdoor activities.  ***Gait analysis***: The participants walked slower when compared with normal gait parameters (*P* < 0.05), indicating reduced stride length, velocity and stance after the surgery.  Comparison between affected and non-affected limb indicated symmetrical stride length & velocity. Asymmetrical stance phase was found significantly reduced (*P* = 0.00)  ***Knee goniometry during gait analysis:***  80% of participants exhibited stiff knee gait  10% of participants had flexed knee gait  10% of participants had normal knee gait  ***ROM:*** Despite the stiff and flexed knee gait pattern revealed by gait analysis, ROM in all patients was within normal actively and passively:  Active ROM mean = 2.25–105  Passive ROM mean = 0–105  No statistically significant difference found between affected and non-affected knee ROM (*P* > 0.05)  Overall MSTS score had significant relationship with velocity aspect in gait analysis (*P* < 0.05) | Small sample size.  No clear recruitment process described, which may lead to selection bias.  Age varied widely and was not statistically tested with outcome measure variables.  No bivariate or multivariate statistical analysis done in regards to location of resected tumour (distal femur or proximal tibia) with other variables. |
| 1. (21)   *2011*  *Netherlands* | N = 82  (41 Male & 41 Female)  Mean age= 16.9 (8–25) | Cross-sectional study with objective measures | Evaluation of functional ability and physical activity among children and young adults who underwent limb salvage and ablative surgeries for treating sarcoma around the knee | TESS score  Time up & go (TUG)  Time up & down stairs (TUDS)  6 minutes walking test (6MWT)  Lie down and stand up (LDSU)  Various walking activities (VWA)  Baecke questionnaire  Activity monitor by ActiLog device | Limb salvage = 39  (Allograft= 24)  (Endoprostheses= 15)  Ablative surgery = 43  (Amputation= 27) (Rotationoplasty= 16) | ***TESS:*** Mean score = 85.3 indicating moderate disability; no significant differences found between the LSS and ablative surgery groups  ***Baecke questionnaire:*** Mean score= 7.4 indicates moderate limitation  No significant statistical difference between the LSS and ablative groups in physical activity aspects of the Baecke Questionnaire and activity monitor measure  ***Performance tests:***  TUDS & VWA:  LSS group had better scores than ablative surgery (*P* = 0.003, *P* = 0.004, respectively).  Other performance tests showed no statistical difference between the groups. | The study f/u period ranged between 1–5 years, which is relatively short when considering long-term aspects.  Heterogeneous treatment protocols may lead to possible procedural or measurement bias. |
| 1. (13)   *2017*  *China* | N = 108  (69 Male & 39 Female)  Mean age = 25.3 (15–67) | Retrospective chart review | Retrospective study on long-term functional outcomes of cemented mega-prostheses | MSTS  ROM | DF= 72  PT= 36 | ***MSTS:*** Good to excellent overall score  Overall mean = 22.9  DF mean =25.4  PT mean = 20.95  No statistical test was done in this regard.  ***ROM:***  Knee flexion range (90–120) in patients who developed patella alta, with no mean calculated in this regard nor any statistical tests done with other variables. | Weak and lacking statistical approach in regard to functional outcome measures.  No mention of ROM in the cases who did not develop patella alta.  Heterogeneous sample for age, tumour type, stage, treatment protocol and surgical procedures. |
| 1. (40)   *2014*  *Japan* | N = 14  ( 9 Male & 5 Female)  Mean Age:  EAR = 44.4 years (23–65)  IAR = 22.4 years (11–58) | Retrospective chart review | Comparison of extra-articular functional outcomes to intra-articular endoprostheses procedures | MSTS  ROM | EAR= 6  IAR= 8 | ***MSTS:***  EAR mean = 21  IAR mean = 26.5  EAR was significantly worse than IAR (*P* < 0.01)  Lowest MSTS components: “walking ability” and “support”  4 patients in EAR group required walking aids, and all patients of IAR walked with no aid  ***ROM:*** (EAR < IAR)  EAR flexion = 84 (60–95)  IAR flexion = 95 (90–110)  Extension lag < 10 degrees was present in four cases | Small sample size.  The mean age of both groups varied noticeably.  Possible bias due to confounding factors such as the use of different types of endoprostheses, variable follow-up period and presence of adjuvant treatment in some cases. |
| 1. (41)   *2012*  *China* | N = 120  (75 Male & 45 Female)  Mean age = 18.9 (5–48) | Retrospective chart review | Evaluation of functional outcomes | MSTS  ROM | (DF= 78)  (PT= 42) | ***MSTS:*** Good to excellent overall score  DF mean = 25.7 (SD 2.9)  PT mean = 25.0 (SD 2.8)  No significant difference (*P* = 0.21)  Lowest components: “functional” and “emotional capacity”  ***ROM:***  Knee flexion in DF was worse than PT but with no statistical significance (*P*= 0.12)  DF = 103 (SD 27)  PT = 112 (SD 30)  Extension ROM was significantly worse regarding lag in PT group (18 patients) compared to DF group (nine patients) (*P* = 0.03)  DF = 8 (SD 3)  PT = 14 (SD 7) | Lack of rehabilitation program between the patients lead to procedural bias.  The authors stated that due to healthcare financial aspects, many osteosarcoma patients underwent amputation surgery because they could not afford the neo-adjuvant therapies required for LSS, which can affect the sampling.  Heterogeneous chemotherapy protocols delivered in the study could be highly considered as confounding factors, leading to procedural or measurement bias. |
| 1. (43)   *2010*  *Australia* | Case N= 20    (17 DF & 3 PT) all with intra-articular endoprostheses replacement    Mean age at surgery = 16.1    Control N= 10. | Case-Control Retrospective outcome study. | Electromyo-graphic assessment of Gait function following limb salvage procedures for bone sarcoma. | Electromyo-graphy.  Energy Consumption Measurement (Cosmed KB4 system). | Assessment and comparison of locomotor patterns in Osteosarcoma patients who went intra-articular knee limb salvage surgery via electromyographic and energetic measurement techniques. | EMG:  *Stance Phase*:  prolonged activation of rectus femoris and prolonged co-contraction of the rectus femoris and hamstring muscles in the affected limb  of the LSS group compared to a control group (p > 0.05).  Higher Quadricepts to Hamstring co-contraction index in affected limb than unaffected when compared to control group (P=0.01).  *Energy Measure:* Gross Energy Expenditure + Net Energy Expenditure + Energetic Cost Measurements were all significantly higher in LSS group (P < 0.01) indicating higher amount of energy used by LSS group during walking activity when compared to control group. | Small Sample Size and uneven comparison between case and control groups.  Study design is not well developed and executed.  Confounding factors which lead to cardiopulmonary issues in cancer patients such as adjuvant therapies were not taken into account especially with the use of Energy Consumption Measures. |

Table 5: Summary review of articles with respect to three themes.

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| --- | --- | --- | --- |
|  | **Functional Outcomes** | **Quality of Life** | **Gait and Knee Goniometry** |
| **Bekkering et al.**  2011 (21) | **✓** | **✓** | **✓** |
| **Carty et al.**  2009 (20) | **✓** | **✓** | **✓** |
| **Hardes et al.**  2013 (42) | **✓** |  | **✓** |
| **Ieguchi et al.**  2014 (40) | **✓** |  | **✓** |
| **Malek et al.**  2012 (19) | **✓** | **✓** | **✓** |
| **Puerta et al.**  2018 (37) | **✓** | **✓** |  |
| **Shaihd et al.**  2017 (35) | **✓** |  | **✓** |
| **Singh et al.**  2018 (38) | **✓** |  | **✓** |
| **Tan et al.**  2012 (41) | **✓** |  | **✓** |
| **Van Egmond-van Dam et al.**  2017 (17) | **✓** | **✓** | **✓** |
| **Zhang et al.**  2014 (18) | **✓** | **✓** | **✓** |
| **Zhang et al.**  2017 (13) | **✓** |  | **✓** |
| **Carty et al.**  2010 (43) | **✓** |  | **✓** |

1. Abbreviations: LSS = Limb salvage surgery; AKA = Above knee amputation; PT = Proximal tibia; DF = Distal femur; IAR = Intra-articular replacement; EAR = Extra-articular replacement. [↑](#footnote-ref-2)