# Advances in the Functional Assessment of Patients with Sarcoma

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**Abstract**

Functional assessment of patients with osteosarcoma may yield unique insights into the guide and advance treatment. A range of patient-reported outcomes has been validated, including general health and condition-specific measures as well as computer adaptive testing. Health state utility measures, which facilitate comparative-effectiveness research, are also available. Beyond these surveys, and laboratory-dependent gait analyses, is the potential for real-world evaluation through research-oriented and consumer-oriented accelerometers. Initial studies have shown promising validity of these activity trackers and may also have implications for traditional oncologic outcomes.

**Keywords**

Osteosarcoma · Sarcoma · Activity monitoring · Patient-reported outcomes · Health-related quality of life · Health state utilities · Computer adaptive testing · Accelerometers · Gait analysis

## Introduction

Osteosarcoma is a malignant process of bone-forming mesenchymal cells. It is the most common primary bone malignancy, with an estimated annual incidence of approximately 4.7 per million persons in the 0- to 20-year-old age group [1].Five-year overall survival for osteosarcoma is approximately 68%, though this ranges from 40% to 80% depending on the stage at diagnosis [2]. The advent of neoadjuvant chemotherapy led to a large improvement in survival and potentiated local treatment with limb salvage and reconstruction [3].

Many questions remain in the management of osteosarcoma, including indications for limb salvage versus amputation, optimal chemotherapy regimens, and posttreatment surveillance protocols [4, 5].Patient's baseline health-related quality of life (HRQL) evaluation itself may provide oncologic prognostic information and/or necessitate inclusion as a variable in predictive models

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[6]. Improved understanding of physical function measures and HRQL has the potential to answer ongoing questions and facilitate the evaluation of treatment strategies.

In this chapter, we provide an overview of functional assessment strategies. These include provider and patient completed surveys, questionnaires that are normalized by combining with preference data, gait lab testing, and directly tracking patients' free-living activity.

## Quality of Life Measures

Measurement of health-related quality of life is paramount in the evaluation of disease states, treatment effectiveness, comparative effectiveness research, and economic analysis. Central to evaluating HRQL is a patient-reported outcome (PRO).

PROs are evaluations of a patient's health status obtained directly from the patient through self-reporting. This is in juxtaposition to more traditional physician- or other clinician-reported outcomes. PROs elucidate the patient's subjective experience of health without mediation or interpretation by a clinician. In oncology patients, they provide information on the patient's subjective experience separately from, though perhaps complementary to, oncological outcomes of survival and recurrence or objective physical examination findings. PROs are vital tools for estimating HRQL.

Any PRO instrument ideally meets several minimum requirements [7].Above all, it should show *validity*; that is, it should convey the most meaningful aspects of health that it seeks to address. It should be r*esponsive* (i.e., sensitive to change). Floor and ceiling effects should be avoided, as these indicate a lack of discriminating ability between patients at the extremes of health states. It should further be *reliable* and *reproducible*, meaning that random error is minimized. Finally, a survey should be as brief as possible to reduce "survey fatigue," which is burdensome for the patient and is known to deteriorate the statistical power and accuracy of surveys [8]. This is particularly a concern in situations where patients are asked to complete multiple questionnaires.

PROs can measure general health status or focus on a specific disease or anatomic location. There are myriad PROs available, and selecting the ideal measure(s) can be challenging. Ultimately, whether for research, quality improvement, or symptom reporting, it is the specific question that must drive instrument selection. Because PROs evaluating general health may lack sensitivity to change due to a specific disease, they should ideally be validated for the diseases in question. Translations of PRO instruments should also be validated in the target language and/or cultural subgroup to whom it is being applied [9].

A shortcoming of HRQL measures (PRO or otherwise) is that they do not take health state *preference* into account. How much value does a patient place in an improvement of $x$ points on a given HRQL scale? Do three points of improvement in the mental component score of the SF-36 equate to three points in the physical component? Is a decline from 25 to 20 points on a 0–100 point scale as valuable as a decrease from 85 to 80? Without taking preference into account, separate health states are not directly comparable, limiting their use in comparative effectiveness research and economic analysis.

One way to resolve the problem of preference is through the use of health state utilities (HSUs). HSUs are PROs that incorporate a patient's or population's self-evaluation of their health state and the population's preference for this health state. HSUs are represented by a single numeric value, usually between 0 and 1.HSUs are generally validated in a population by asking respondents to imagine being in a particular health state. They may be arrived at by *direct* and *indirect* methods. Direct methods include the standard gamble approach and time trade-off approaches [10].In the standard gamble, a subject is presented with two options: the first is that they live out their remaining $x$ years in a state of suboptimal health. Alternatively, they can gamble on a return to a state of perfect health for $x$ years with probability $p$ but risk immediate death with probability $(1 - p)$. The time trade-off method asks a respondent how much of their lifetime they would sacrifice to trade their current state of health for a better one. For instance, if one had a remaining life expectancy of 5 years in their current suboptimal state of health (say, with daily severe arthritis pain), how many of those 5 years would they sacrifice to ensure that the remaining time was free of arthritic pain? Indirect methods of utility estimation require defining a function that maps a HRQL measure such as a PRO onto a utility instrument. An example of this is the EQ-5D, which is discussed below [11].

HSUs are HRQL measures in their own right, yet they are also suited for economic analysis. The resulting utility values can be used to compare health states within a single disease (such as osteosarcoma) or across multiple diseases, allowing both comparative effectiveness research and cost-utility analyses.

HRQL measures will have greater importance in the future. The Center for Medical Technology Policy issued a guidance document recommending, among other things, the use of PROs in all prospective comparative effectiveness research trials in oncology. It also recommended consideration of metrics amenable to cost-utility analysis [12].Of note, the Musculoskeletal Tumor Registry Pilot study will require PRO data as well, in the form of the Musculoskeletal Tumor Society score (MSTS) and the Toronto Extremity Salvage Score (TESS) [13].Corroborating the emphasis on this research is over $379 million awarded by the Patient-Centered Outcomes Research Institute in 2016 [14].

## HRQL Measures

### TESS

The Toronto Extremity Salvage Score (TESS) is a disease-specific PRO for assessing functional outcomes in bone and soft tissue sarcomas of the upper and lower extremity [15].It solicits information on the difficulty of various activities of daily living on a 5-point Likert scale and combines this with an evaluation of the importance of each activity to the patient. An aggregate final score from 0 to 100 is returned. There are separate upper and lower extremity activities, and it takes 12–15 minutes to complete [16]. It has been validated with high reproducibility in multiple languages and has excellent inter- and intra-relater reliability in lower extremity sarcoma [16, 17].

The TESS has been widely used in bone and soft tissue sarcomas, elucidating outcomes concerning a variety of clinical questions [18–20]. Notably, Robert et al. used the TESS in a comparison of limb salvage versus amputation in juveniles [21]. They showed that quality of life was related to limb functionality, regardless of whether they had undergone amputation or salvage. The TESS has also been used to demonstrate the similarity between primary osteosarcoma and radiation-induced bone sarcoma and demonstrated similar functional outcomes in osteosarcomas regardless of whether they presented with pathological fractures [22, 23].

The validity and reliability of the TESS are sufficiently high that it has been used to validate other HRQL scores for use in sarcomas [24]. It has also been used to evaluate and validate other functional assessments including wearable activity monitors, which will be discussed below [25].

### MSTS

The Musculoskeletal Tumor Rating Scale (MSTS) is another disease-specific HRQL measure for bone and soft tissue sarcomas of the extremity as well as metastatic bone disease. In contrast to the TESS, however, it is a *provider-determined* score. While it has been completed by patients in some series, it was not designed as a PRO measure. It was initially developed by Enneking in 1987 and revised in 1993 [26, 27]. The revised version has six areas of evaluation (pain, function, emotional acceptance, general functional ability, gait handicap, and the use of gait aides), each scored on a 0–5 Likert scale.

Two significant disadvantages of the MSTS have been widely reported. The first, as noted, is its provider reporting. Discrepancies between provider and patient-reported measures resulting from reporting bias have been widely reported across medical and surgical disciplines [28, 29]. In a comparison of patient and provider-rated MSTS scores in patients with bony metastatic disease, Janssen et al. found a statistically significant 8-point increase when scored by providers [30]. Furthermore, it has been noted to have significant ceiling effects, suggesting a lack of sensitivity to minor insults to health states [16]. It is convenient due to its brevity of only six questions and has shown validity in upper extremity bone tumors [31]. However, an analysis by Davis et al. evaluating multiple functional outcome scores in lower extremity sarcoma patients concluded that the MSTS "did not meet the standards of measurement." [16] Nevertheless, it continues to be widely reported.

## SF-36

The 36-Item Short Form Health Survey (SF-36) is a proprietary PRO instrument created by the Rand Corporation [32]. It is a measure of general health and covers eight general categories. It is often partitioned into physical and mental components. The SF-36 is one of the most common PRO instruments for general health and is often reported in sarcoma research. The SF-36 has been used to study limb salvage versus amputation for bone sarcomas in multiple studies and generally has shown slightly improved scores for limb-sparing surgery in the physical (but not necessarily mental) scores [33, 34].

By virtue of being a general health measure, it may lack sensitivity to changes in health states due to a specific disease. Because it was created for a general, community population it may also have difficulty detecting differences between patients with a significant disability; indeed, there is some evidence for floor effects with the SF-36 [35]. For these reasons, the instrument comparison by Davis et al. [16] concluded that the TESS is superior to the SF-36 in sarcoma studies. A shorter 12-question version (the SF-12) exists, as well, that similarly returns physical and mental functional scores.

## SF-6D

The Short Form-6D (SF-6D) is an HSU instrument based on the SF-36. It was made to transform full SF-36 data into HSUs, enabling the large swath of SF-36 datasets to take advantage of the benefits of utilities, such as economic analysis and more accurate comparative effectiveness research [36].The SF-6D utilizes 11 questions from the SF-36 and maps the responses to a six-dimensional health state that is then assigned a utility score between 0 and 1 based on a general population sample ranking health states using the standard gamble technique.

An examination of the SF-6D in bone and soft tissue sarcoma patients demonstrated a mean utility score of 0.59, similar to the morbidity of chronic obstructive pulmonary disease or chronic kidney disease in US populations. It further showed good convergent validity to the TESS without demonstration of floor or ceiling effects [24]. It has been used to evaluate wearable activity monitors in bone malignancies (see below) and cost-effectiveness examinations of radiation therapy and osteoarticular allograft in bone and soft tissue sarcoma [37, 38].

## EQ-5D

The EuroQol-5D (EQ-5D) is an HSU instrument developed by a multi-national, multi-disciplinary team.

It has been translated into at least 130 languages and validated in many of these [11, 39]. It is one of the most widely-used HSU instruments available. The EQ-5D (also called EQ-5D-3 L) evaluates HRQL using a self-valuation in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The respondent rates their health in each of these dimensions with a "1" (no problems), a "2" (some problems), or a "3" (extreme problems). This yields a five-digit number with $3^5$ possible values that is then mapped to a single utility value between 0 and 1.

It has been used extensively in solid cancers [40, 41].The first utility values reported in metastatic bone and soft tissue sarcomas used the EQ-5D instrument [42]. It provided baseline utility values for these patient populations and showed that the ED-5D was able to discriminate between certain subsets of patients based on disease progression. This set the stage for its use in later economic studies.

The EQ-5D has been shown to demonstrate substantial ceiling effects, questioning its sensitivity to detect changes in health status [35]. One study found profound ceiling effect in a cohort of breast, prostate, and colorectal CA patients, 13% of whom scored perfect states of health despite having end-stage cancer [41]. A new edition (EQ-5D-5 L) was created in 2009 to attempt to mitigate some of these ceiling effects [43]. Though more study is needed, there is evidence that the magnitude of the ceiling effects in cancer is somewhat decreased with the EQ-5D-5 L. [44]

## PROMIS

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a PRO instrument developed by the National Institutes of Health intended as a measure of general health over many domains of mental, physical, and social well-being [45]. It employs computer adaptive test (CAT) methods to generate the most informative next question based on previous answers. It then maps raw scores onto *T*-scores with a fixed mean and standard deviation that can then be used to make comparisons across domains, disease states, and the population at large. It is non-proprietary and free to the public to use.

PROMIS physical function scores have been shown to be reliable and valid in oncology populations [46, 47]. Because of the CAT methodology it employs, PROMIS questionnaires tend to be short; a comparison with upper and lower extremity TESS questionnaires in an orthopedic oncology population found that PROMIS questionnaires required a mean of 16.8 questions (versus 31 and 32 for the lower and upper extremity TESS questionnaires) [47].

PROMIS has been employed in many aspects of sarcoma research, including outcomes of planned versus unplanned sarcoma resections (which showed no difference in any PROMIS domains tested) [48]. It has also been used to examine limb salvage versus amputation, in which limb salvage outperformed amputation in physical function scores as well as showed higher emotion health scores than the US population at large (PMID 30958808). Another evaluation of postoperative non-metastatic sarcoma patients found improved depression domain scores than the general population, suggestive of a re-evaluation of goals and priorities with sarcoma diagnoses (PMID: 30799982).

## Objective Functional Assessment

Despite the usefulness of PROs and other questionnaire-based HRQL scores, it has been asked whether true assessment of quality of life and functional status can be fully captured in surveys or questionnaires [49]. Health events unrelated to function may influence function PRO scores, as has been shown with depression and arthroplasty outcomes [50, 51]. Objective measures of physical activity have consistently been shown to have a modest correlation to PROs and other HQRL scores, suggesting significant functional information exists that is not being captured by them. A 2016 systematic review of objective measures of physical function in sarcoma patients noted a deficit in literature quantifying “balance, gait, and physical activity” in lower extremity sarcoma patients [52]. Hence, objective measures of real-world patient activity may helpfully elucidate the patient experience in terms of physical function.

### Metabolic and Gait Analysis

Gait and ambulatory ability can be evaluated by metabolic measurements estimating energy efficiency or by gait parameters such as velocity, stride, and strength. Energy efficiency is often estimated by oxygen consumption, via direct measurement of patient blood oxygenation or rebreather mask techniques.

Ambulation and gait efficiency can be significantly affected by amputation of limb salvage procedures. Gait efficiency is well-known to be altered by amputation level: Waters et al. classically showed a strong trend of decreased gait velocity, increased oxygen consumption, and increased metabolic cost with a higher level of amputation [53].

Bernthal et al. studied energy consumption strength in a cohort of 69 long-term survivors of endoprosthetic reconstruction for a lower extremity bone sarcoma [54]. Energy consumption was estimated by oxygen consumption using a breath-by-breath exchange unit. A comparison to healthy control subjects showed no difference in energy consumption or walking speed, although proximal tibia replacements showed reduced knee flexion and extension strength. Kawai et al. provided baseline data on stride velocity, cadence, and energy consumption for proximal and distal femoral replacements; they demonstrated less optimistic gait efficiency estimates and attributed some variation in consumption to the level of resection [55].

Rotationplasty has received particular attention in laboratory gait analysis, with multiple studies showing rotationplasty gait analysis and kinematics to be superior to above-knee amputation and similar to both endoprosthetic reconstruction and healthy controls [34, 56, 57].

A slightly more convenient method of measuring energy efficiency (albeit still requiring a laboratory) is the *physiological cost index*(PCI). PCI is calculated using only walking heart rate, resting heart rate, and distance walked as inputs [58, 59]. It has been used to compare gait efficiency in lower extremity bone cancer patients that underwent amputation versus limb-sparing surgeries; the latter showed superior PCI scores (though notably, TESS and SF-36 scores were similar) [60].

Though a useful comparative tool, laboratory analyses of gait and energy efficiency can be invasive and costly and require bulky equipment or labs, decreasing their usefulness for many treatment centers and patients. Furthermore, it is not clear that differences found in controlled laboratory settings correlate with real-world physical activity [54].

## Real-World Functional Assessment

The impracticality of these physiological measurements has ushered innovation in real-world functional assessment across medical disciplines, including osteosarcoma and extremity sarcoma patients. Wearable activity monitors such as pedometers or accelerometers have shown promise in orthopedic patient functional evaluation [61]. Pedometers are electric or mechanical devices usually worn on the hip that count steps taken. They have proven to be accurate, low-cost alternatives to manually counting steps [62]. Accelerometers such as the Step Watch Activity Monitor (SAM, Modus Health, Washington, DC) are instruments that measure acceleration in space relative to a gravitational field. These devices have been used to evaluate activity in a variety of patient types including COPD [63], low back pain [64], hip and knee arthroplasty [65–67], and numerous others. Furthermore, baseline data for the general population are available in adult and pediatric populations [68, 69].

Unlike pedometers that estimate steps taken, accelerometers worn on the ankle are able to estimate the *intensity* of activity at any given time. Furthermore, steps may be underestimated by pedometers, especially in obese/heavy pts. [61, 67]. In a meta-analysis examining activity monitoring in arthroplasty patients, Naal et al. concluded that accelerometers were the most accurate and appropriate means of estimating activity when compared to oxygen consumption measurements, pedometers, PROs or other HRQL instruments, or activity logs [67].

A cross-sectional study of 29 lower extremity sarcoma patients validated the use of the SAM accelerometer and showed a significant positive correlation ($r = 0.56$) between daily steps taken and the TESS [70]. Interestingly, the osseous tumor subgroup took fewer steps than the soft tissue subgroup did.

A prospective study following that validation examined 25 separate patients that underwent limb salvage for lower extremity osseous tumor [25]. This showed a strong correlation between steps taken and time from surgery, and moderate correlation between steps taken and the SF-6D and SF-36 physical (but not mental) scores, strengthening the validity of accelerometers as an instrument to evaluate physical function in sarcoma patients.

Rosenbaum et al. used a wearable accelerometer to evaluate 22 patients that had undergone lower extremity limb salvage with modular endoprostheses for sarcomas of bone [71]. Interestingly, no significant correlation was found between gait and locomotion parameters and either MSTS or TESS scores.

They noted activity of a similar magnitude as with successful (non-oncologic) hip arthroplasty patients.

They further warned that the higher than expected step counts could have significant implications for (endo)prosthesis design [71].

Ranft et al. evaluated functional activity of long-term survivors of Ewings sarcoma using the Step Watch Activity Monitor [72]. They similarly reported that total daily steps exceeded 10,000 [73]. They also demonstrated a low ($r < 0.30$) correlation between step and TESS and that pelvic tumors showed worse physical scores.

## Real-Time, Real-World Monitoring

Wearable devices such as these have shown promise beyond passive data analysis for effectiveness or outcomes research; accelerometers have also shown promise in real-time activity monitoring in cancer patients. For instance, a pilot study was conducted in elderly adults with solid tumors who were monitored with accelerometer-equipped cell smartphones while receiving chemotherapy [74]. The method proved feasibility even with the elderly population; more importantly, results showed that patients were more likely to have experienced severe chemotherapeutic toxicity on days with substantial decline in daily steps. Many of these toxicities were managed over the phone, avoiding unnecessary hospital visits. A similar study that provided adult hematopoietic cell transplant recipients with pedometers showed a significant correlation between daily steps and worsening symptoms, pain, and PRO scores [75].

Wearable physical activity monitors are now low-cost and user-friendly. They show promise in objective functional assessment of sarcoma patients both as an adjunct to PROs and utility scores or as an objective evaluation in their own right, as they seem to convey information not contained in HRQL scores like ED-5Q and TESS. Though in its preliminary stages, the potential for proactive surveillance of activity through these devices as a surrogate for complications or impending poor outcomes shows significant potential.

Real-world tracked activity may have a significant role beyond the observational as described above; there is emerging evidence that physical activity may have an effect on *oncological* outcomes. Mouse animal models of Ewing sarcoma have found that the addition of an exercise regimen to doxorubicin therapy altered local vascular permeability, resulting in greater drug penetration and more efficiently inhibiting tumor growth [76]. The same mouse model showed that an exercise regimen was able to decrease acute and chronic cardiotoxic effects of doxorubicin-treated mice [77]. If these results prove consistent in human trials, tracking real-world activity in the peri-operative and chemotherapeutic period may become a vital adjuvant treatment from an oncologic perspective as well as from a functional one.

## Conclusion

A firm understanding of HRQL measures is crucial to evaluating patients' quality of life, well-being, and disability beyond oncological outcomes. Soliciting health information directly from patients through PRO measures allows for improved patient counseling concerning both their prognosis and the effect that their treatment may have on their health. They also enable comparative effectiveness research and economic and cost-utility analysis. Survey responses aggregate multiple streams of data, which may or may not be applicable to the specific question under consideration. Contrariwise, some functional information may not be captured properly by a questionnaire, urging evaluation of real-world activity. Free-living activity monitoring provides easily understandable data for assessing disability or advising patients. Real-time monitoring may even predict or alert clinicians of impending complications or poor outcomes.

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