Functional Outcomes in Musculoskeletal Oncology

Aaron Gazendam, MD

Thesis Abstract

In musculoskeletal oncology, limb salvage surgery is now the standard of care for most patients with bone or soft tissue tumors of the extremities. There has been an increased interest in quantifying functional outcomes following limb salvage with both physician reported and patient reported outcome tools utilized. However, due to the rarity of the disease and lack of prospective data, there remains significant gaps in the literature surrounding functional outcomes in this population. This thesis proposes minimal important difference values for commonly used functional outcome measures and created a predictive model for postoperative function for musculoskeletal oncology patients following lower extremity limb salvage and endoprosthetic reconstruction.

The data for this thesis was retrieved from the Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) trial database and included patients undergoing lower extremity surgical resection and endoprosthetic reconstruction for bone or soft tissue tumors. Utilizing this data, we provided answers to two important clinical questions 1) establishing minimal important difference (MID) values for commonly utilized functional outcome scoring systems and 2) determine patient and tumor factors predictive of postoperative function.

We developed both anchor-based and distribution-based MID values for both the Musculoskeletal Tumor Society Score and the Toronto Extremity Salvage Score, the two most utilized functional outcome tools in the field. Secondly, we characterized the longitudinal changes in function following endoprosthetic reconstruction and identified patient and tumor predictors of postoperative function. On average, patient function improved significantly from their preoperative baseline to 1-year follow-up, exceeding the predefined MID values. Older age, poor preoperative function, and endoprosthetic reconstruction for soft tissue sarcomas were associated with worse outcomes; reconstruction for giant cell tumors were associated with better post-operative function.

Overall, these two studies aim to provide a deeper and more meaningful understanding of functional status in musculoskeletal oncology patients.

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Glossary of Abbreviations

AR – Absolute risk

CI – Confidence Interval

CIHR – Canadian Institutes of Health Research

DFR – Distal Femur Replacement

GCT – Giant Cell Tumor

HRQL – Health Related Quality of Life

IQR – Interquartile Range

MD – Mean Difference

MID – Minimally Important Difference

MSTS – Musculoskeletal Tumor Society Score

OR – Odds Ratio

PARITY -- Prophylactic Antibiotic Regimens in Tumor Surgery

PFR – Proximal Femur Replacement

PTR – Proximal Tibia Replacement

ROC – Receiver Operating Characteristic

SD – Standard Deviation

STROBE – Strengthening the Reporting of Observational Studies in Epidemiology

STS – Soft Tissue Sarcoma

TESS – Toronto Extremity Salvage Score

CHAPTER 1: BACKGROUND

Epidemiology

The scope of musculoskeletal oncology primarily involves the treatment of malignant tumors occurring in the bone and surrounding soft tissues. Sarcoma is an umbrella term comprised of a heterogenous group of tumors of mesenchymal origin and represents the most commonly encountered primary malignancy in musculoskeletal oncology. Sarcomas are a rare and varied malignancy that can be broadly divided into bone sarcomas and soft tissue sarcomas with approximately 70 histologically distinct subtypes recognized by the World Health Organization[1].

Sarcomas represent less than 1% of all adult malignancies and 8% of pediatric solid organ malignancies[1,2]. Soft tissue sarcomas are more prevalent than bone sarcomas and represent approximately 85% of new sarcoma diagnoses each year[3,4]. Epidemiologic research from Europe has demonstrated the age-standardized incidence rates between 1.5-3.0/100,000/year and 0.5-2.0/100,000/year for soft tissue and bone sarcomas, respectively[3].

An increasingly important part of musculoskeletal oncology involves the management of metastatic bone disease. Given advances in systemic cancer therapies, the number of patients living with metastatic bone disease is rapidly increasing. Bone is a the third most common site of metastasis of many primary malignancies and surgical management is indicated when patients have impending or realized pathologic fractures or have failed nonoperative measures[5,6].

Treatment

The systemic treatment options of soft tissue and bone sarcomas varies widely based on histologic subtype and is outside of the scope of this thesis. Regardless of subtype,

surgery remains a cornerstone of treatment for sarcoma management[7]. The goal of surgical management is local disease control through wide excision with negative margins. Historically, amputation was the gold standard surgical option to achieve satisfactory oncologic outcomes. However, due to advances in systemic therapies, imaging modalities and implant prostheses, limb salvage surgery has become the contemporary standard of care for patients with localized sarcomas of the appendicular skeleton[7]. Limb salvage surgery has demonstrated similar disease free survival and overall survival while improving function when compared to amputation[8,9].

In patients with metastatic bone disease, there is a wide variety of both operative and nonoperative treatment options that vary based on tumor size, location, and type. Given the poor bone healing potential due to abnormal tumor biology, patients who have impending or realized fractures secondary to metastatic bone disease often undergo surgical management[10]. Patients with a solitary metastasis may undergo surgical resection and reconstruction with curative intent, depending on the primary tumor type[5].

For peri-articular bone or soft tissue tumors invading bone, wide resection with endoprosthetic reconstruction has become the most commonly utilized reconstruction technique[11]. An endoprosthesis is a metallic joint replacement that fills the bony defect left by the tumor resection and aims to replicate normal joint movement. Historically, endoprosthesis were custom made, which limited their utility. The advent of modular endoprostheses which are readily available has led to widespread adoption in the orthopaedic oncology community[12].

Functional Outcomes

Given the shift from amputation to limb-salvage surgery, there has been an interest in quantifying the functional outcomes and abilities of patients in musculoskeletal oncology.

In 1981, the International Symposium on Limb Salvage surgery identified the lack of standardized reporting as a gap in the literature and Enneking et al proposed the first musculoskeletal oncology focused functional outcome tool in 1987 called the Musculoskeletal Tumor Society Score 87 (MSTS-87)[13].

Musculoskeletal Tumor Society Score

The MSTS-87 was updated in 1993 to its current form (MSTS-93) and is more limb specific[14]. The MSTS-93 is a subjective system based on physician ratings that encompasses seven sub-domains of pain, range of motion, function, emotional acceptance, use of supports, walking ability, and gait. Each item is scored from 0 to 5 with a maximum score of 35 that is converted to scale from 0-100 with higher scores indicating better function. When evaluated using the Nottingham Health Profile, the Short Form-36 (SF-36), and the EuroQol protocol, the MSTS had acceptable reliability and construct validity in measuring in patients with malignant musculoskeletal tumors[15]. The MSTS scoring system is the most widely reported functional outcome tool in the musculoskeletal oncology literature[16].

The MSTS has several weaknesses that must be acknowledged. Firstly, the MSTS is a physician led questionnaire and cannot be considered a patient reported outcome which leads to inherent biases. It has been shown to overestimates function compared to patient reported outcomes[17]. Finally, the MSTS has been shown to not be an adequate measure of overall health-related quality of life[18].

Toronto Extremity Salvage Score

The Toronto Extremity Salvage Score (TESS) was designed to address the World Health Organization's definitions of Disability, Impairment, and Handicap[19]. It is a 30-item, patient-reported questionnaire that focuses on the ability to perform activities of daily living in a variety of daily settings. The TESS is converted to a scale of 0-100 with higher

scores indicating better function. The TESS has both a lower extremity and upper extremity specific questionnaire, with the lower extremity questionnaire utilized in the current study. It has been shown to be responsive, reliable, and valid as a measure of physical function following limb salvage surgery over time[20]. It has also been widely used in studies of limb salvage surgery across multiple populations and has been validated in several languages[21–23]. However, the TESS has demonstrated a ceiling effect in certain patient populations which may limit its widespread use[24].

Gaps in the Current Literature

Although both the TESS and MSTS are widely reported throughout the literature, there remains significant gaps in our understanding of functional outcomes in oncologic patients undergoing endoprosthetic reconstructions.

Firstly, there are a lack of defined minimally important differences (MID) for both the TESS and MSTS in patients undergoing endoprosthetic reconstruction. Minimal important differences represent "*the smallest difference in score in the domain of interest which patients perceive as beneficial*"[25]. Establishing MIDs is imperative as it allows clinicians and researchers to evaluate if differences in treatment are important and relevant to patients. This is of particular importance in orthopaedic oncology as surgical interventions are extensive and carry significant risks[26].

The calculation of MIDs can be broadly divided into two categories: anchor-based methods and distribution-based methods. In anchor-based methods, the outcome score is anchored to another subjective scale that is independently interpretable. Changes in the anchor are correlated to changes in the outcome score to derive MID values[27]. Distribution-based methods rely on variability in the outcome score in the sample population to derive their values[28].

Secondly, the majority of clinical studies report functional outcomes at a single time point postoperatively[16]. Assessing function at multiple timepoints, including preoperatively, allows for an understanding of the impact of the intervention over time. Due to the invasive nature of oncologic resections and reconstructions, normal function may not be restored to many patients, some of whom may not even return to their preoperative baseline. It is important to capture these changes in function in order to provide both patients and clinicians realistic expectations about the expected rehabilitation course following endoprosthetic reconstruction[29].

Finally, there is a paucity of data evaluating the impact that patient, tumor, and surgical factors have on functional outcomes after endoprosthetic reconstruction. Studies that do propose predictive models fail to incorporate baseline function, missing a key potential predictor of postoperative function[30].

CHAPTER 2

Data Sources

All data in this manuscript has been queried from the Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) trial prospective database. PARITY was a multicentre, blinded (surgeon, assessor, and patient), RCT, using a parallel two-arm design to investigate whether long duration (5 days) postoperative prophylactic antibiotics would decrease the rate of post-operative surgical site infection compared with short duration (24 h) among patients undergoing surgical excision and endoprosthetic reconstruction of lower extremity bone tumors[31]. This trial was registered [NCT01479283] and received ethics approval from the Hamilton Integrated Research Ethics Board (REB# 12-009). The PARITY trial consisted of 48 actively enrolling sites in 12 countries, 6 continents with over 150 investigators. The trial database was created and managed by the Methods Centre at the Centre for Evidenced-based Orthopaedics at McMaster University.

Specific Objectives

1) To define minimal important difference values for the Musculoskeletal Tumor Society Score and Toronto Extremity Salvage Score in musculoskeletal oncology patients undergoing surgical resection and endoprosthetic reconstruction of the lower extremity.
2) To describe patient-reported function over time and identify predictors of postoperative function in musculoskeletal oncology patients undergoing lower extremity endoprosthetic reconstruction.

Ethics Statement

Both studies obtained approval from Research Ethics Board at Hamilton Health Sciences (REB# 12-009) and from the local ethics boards of participating PARITY sites

CHAPTER 3: Defining Minimally Important Differences in Functional Outcomes for Musculoskeletal Oncology Patients Undergoing Lower Extremity Endoprosthetic Reconstruction

Aaron M. Gazendam, MD[1,2], Patricia Schneider, BSc[1], Mohit Bhandari, MD, PhD[1,2], Jason W. Busse, DC, PhD[1,2,3,4], Michelle Ghert, MD, FRCSC[1,2]

On behalf of the PARITY Investigators

1. Division of Orthopaedic Surgery, McMaster University, Hamilton, Ontario, Canada
2. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
3. The Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Ontario, Canada
4. Department of Anesthesia, McMaster University, Hamilton, ON, Canada
5. The Chronic Pain Centre of Excellence for Canadian Veterans, Hamilton, ON, Canada

Corresponding Author:
Aaron M. Gazendam
Division of Orthopaedics
Department of Surgery, McMaster University
St. Joseph's Hospital
Room G522
50 Charlton Avenue East
Hamilton, ON, Canada L8N 4A6
aaron.gazendam@gmail.com

Abstract

Background: Functional outcomes are commonly reported in studies of musculoskeletal oncology patients undergoing limb salvage surgery; however, interpretation requires knowledge of the smallest amount of improvement that is important to patients – the minimally important difference (MID). We established the MIDs for the Musculoskeletal Tumor Society Rating Scale-93 (MSTS-93) and Toronto Extremity Salvage Score (TESS) in patients with bone tumors undergoing lower limb salvage surgery.

Methods: This study was a secondary analysis of the recently completed PARITY (Prophylactic Antibiotic Regimens in Tumor Surgery) study. We used MSTS-93 and TESS data from this trial to calculate: (1) the anchor-based MIDs using an overall function scale and a receiver operating curve analysis, and (2) the distribution-based MIDs based on one-half of the standard deviation of baseline scores and one-half the standard deviation of the change scores from baseline to 12-month follow-up.

Results: There were 591 patients available for analysis. The Pearson correlation coefficients for the association between changes in MSTS-93 and TESS scores and changes in the external anchor scores were 0.71 and 0.57, indicating “high” and “moderate” correlation. The anchor-based MID was 12 points for the MSTS-93, and 11 points for the TESS. Distribution-based MIDs were larger; 16-17 points for the MSTS-93, and 14 points for the TESS.

Discussion: The current study has established MIDs for the MSTS-93 and TESS, based on 591 patients with bone tumors undergoing lower extremity endoprosthetic reconstruction. These thresholds will optimize interpretation of the magnitude of treatment effects, which will facilitate shared decision-making with patients in trading off desirable and undesirable outcomes of alternative management strategies.

Conclusions: Two methods for determining MIDs for the MSTS-93 and TESS for musculoskeletal oncology patients undergoing lower extremity endoprosthetic reconstruction yielded quantitatively different results. We suggest use of anchor-based MIDs which are grounded in changes in functional status that are meaningful to patients. These thresholds can facilitate responder analyses and inform if statistically significant differences following interventions are clinically important to patients.

Background

Primary bone sarcomas of the lower extremity have historically been treated with amputation; however, advances in imaging, chemotherapeutic regimens, and surgical techniques now facilitate limb salvage and reconstruction in approximately 95% of patients[32]. Limb salvage allows for early mobility, increased satisfaction, improved quality of life, better emotional acceptance, and enhanced cosmetic appearance[33–35].

Functional outcome instruments are designed to assess the impact of a treatment on a patient's health-related quality of life (HRQL)[36]. These instruments may be general or disease-specific, and should be self-reported (i.e., patient reported outcomes or PROs). In clinical trials, functional outcome instruments capture essential patient-centered outcomes that may be poorly correlated with surrogate outcomes, such as clinical, physiological, or radiographic tests. As perioperative and surgical techniques evolve, the measurement of functional outcomes and the impact on HRQL is an essential requirement for understanding their impact in this complex patient population[20].

In large clinical trials, small treatment effects may be statistically significant without demonstrating patient-important benefit [25]. The minimal important difference (MID) refers to the smallest effect that patients perceive as sufficient to pursue a course of treatment [25,37,38]. The Musculoskeletal Tumor Society Rating Scale (MSTS) and Toronto Extremity Salvage Score (TESS) are commonly administered to orthopaedic patients to capture functional status; however, MIDs for these instruments have not been established[26]. The proposed study aims to define MIDs for the MSTS and TESS in patients undergoing surgical excision and limb salvage surgery of the lower extremity for bone tumors.

Methods

This study was a secondary analysis of the PARITY (Prophylactic Antibiotic Regimens in Tumor Surgery) study. PARITY was a multicentre, blinded, randomized controlled trial, using a parallel two-arm design to investigate the effect of long (5 days) vs. short duration (24 hours) postoperative prophylactic antibiotics on the rate of post-operative surgical site infection among patients undergoing surgical excision and endoprosthetic reconstruction of lower extremity bone tumors. Patients, treatment providers and outcome assessors were all blinded to treatment allocation. This trial was registered [NCT01479283] and received ethics approval from the Hamilton Integrated Research Ethics Board (REB# 12-009). The PARITY trial consisted of 48 actively enrolling sites in 12 countries, 6 continents, with over 150 investigators. The trial completed enrolment in 2019 recruiting 604 patients. We used the functional outcome data collected from this trial to establish MIDs for the MSTS and the lower extremity TESS instruments.

Functional Outcome Instruments

The MSTS is a widely used instrument that was developed in 1987 by expert consensus to evaluate physical function after limb-salvage surgery[13,14]. It was revised in 1993 to reduce the number of domains evaluated and expand the range of potential outcomes for each domain [15,39]. The MSTS-93 is a subjective system based on physician ratings that encompasses seven sub-domains of pain, range of motion, function, emotional acceptance, use of supports, walking ability, and gait. Each item is scored from 0 to 5 with a maximum score of 35 that is converted to scale from 0-100, with higher scores indicating better function. When assessed using the Short Form-36 (SF-36) and the EuroQol protocol, the MSTS-93 had acceptable reliability and construct validity in measuring the quality of life in patients with malignant musculoskeletal tumors [15].

The TESS was designed to address the World Health Organization's definitions of Disability, Impairment, and Handicap[19]. It is a 30-item, patient-reported questionnaire that focuses on the ability to perform activities of daily living in a variety of settings. The

TESS is converted to a scale of 0-100, with higher scores indicating better function. The TESS has both a lower extremity and upper extremity specific questionnaire; data acquired from the lower extremity questionnaire were utilized in this study. The TESS has been shown to be responsive, reliable, and valid as a measure of physical function following limb salvage surgery[20]. It has also been widely used in studies of limb salvage surgery across multiple populations[21–23]. Both the MSTS-93 and the lower extremity TESS were administered in the PARITY study, in translated and culturally adapted forms based on the patient's native language, at baseline (preoperatively) and at 3, 6 and 12 months postoperatively.

Determination of Minimal Important Differences

There are two widely utilized approaches to establishing the MID; distribution-based and anchor-based methods[27]. Distribution-based methods rely solely on the statistical characteristics of the study sample. Distribution methods rely on measurements of variability in the scores, such as the standard deviation, and consider these to be the MID. In the current study, the distribution-based MIDs were calculated utilizing the one-half SD of baseline scores and the one-half SD of change scores within the groups from baseline to 12 month follow-up.

In anchor-based methods, the MID is established by relating a difference in outcome scores to a patient-important improvement or deterioration that is captured by an independent measure (the anchor) that is itself interpretable[27]. For the purpose of this study, both distribution-based methods and anchor-based methods were utilized to calculate MIDs. For our anchor, we used the functional activity scale, which is a subscore of the original MSTS-87 a questionnaire that captures graded change in overall function. The response options are: *no restrictions, recreational restrictions, partial disability,* and *total disability*, which we assigned numeric values of 1, 2, 3 and 4. When evaluating the

credibility of this anchor, it satisfies the criteria set out by Devji et al[27]: the outcome is patient centered, easily understandable and relevant to patients.

This questionnaire was administered pre-operatively and 3, 6 and 12 months after surgery, to allow for an evaluation of change over time. We considered that patients who reported changes from one adjacent score to the next (ie total disability to partial disability) represented a small but meaningful change equivalent to the MID. We correlated changes in the MSTS-93 and TESS to changes in the functional scale to determine MIDs for each instrument. Change scores for both the external anchor and MSTS-93/TESS were calculated and utilized for all time points in which patient data was available. For example, to evaluate the change in scores from baseline to 3 months, the 3-month scores were subtracted from the baseline scores and a positive score indicated an improvement in function over that time interval. The study intervals evaluated for changes in function were baseline to 3 months, baseline to 6 months, baseline to 12 months, 3 to 6 months, 3 to 12 months, and 6 to 12 months.

Statistical Analysis

To further determine the appropriateness of the anchor item to record change in the MSTS-93 and TESS scores was assessed by examining the correlation in changes between the anchor item and changes in the MSTS-93/TESS scores over the same interval. Pearson's correlation coefficients were calculated between each instrument change score and the corresponding change score for the functional activity scale at each of the study intervals. Because one can expect an external anchor to provide a valid estimate of MID only if the correlation between the target instrument and the anchor is sufficiently high, we considered the MIDs to be valid only from those instruments for which Pearson's correlation coefficients were 0.5 or greater, indicating moderate correlation[40,41].

For the anchor-based approach, the relationship between changes in the external anchor and changes in MSTS-93 and TESS scores were examined using receiver operating characteristic (ROC) curve analysis[42]. The ROC method plots the sensitivity against 1-specificity for the range of MSTS-93 and TESS scores in relation to the probability of detecting improvement as judged by a change score of one point on the external anchor. The ROC analysis was performed to differentiate between patients with MSTS-93 and TESS scores who reported a change score of 0 on the external anchor and those who had change score of +1 on the external anchor. The MID cut-offs were estimated by calculating the Youden Index which balances the sensitivity and specificity of the MSTS-93 and TESS change thresholds based on the external anchor. Youden's Index provides an overall indicator of test performance and is recommended when establishing MIDs based on the ROC analysis[42].

The distribution-based approach to estimate MID was performed in two commonly utilized methods. Firstly, it was calculated by computing one-half the standard deviation of measurement at the baseline[28]. Secondly, the distribution based MID was obtained by using one-half of the SD of the change scores within each group from baseline to 12-month follow-up [43].

Source of funding
The PARITY Trial received funding through research grants from the Canadian Institutes of Health Research, the Canadian Cancer Society Research Institute, the Canadian Orthopaedic Foundation J. Édouard Samson Award, the Orthopaedic Research and Education Foundation in conjunction with the Musculoskeletal Tumor Society, and the Physicians' Services Incorporated Clinical Research Grant. JWB is funded, in part, by a Canadian Institutes of Health Research Canada Research Chair in the prevention and management of chronic pain. MB receives institutional support from the Canadian Institute of Health Research, National Institute of Health, Michael DeGroote Institute for

Pain Research and Care and is an advisory board member for the Mayo Clinic Core Center for Clinical Research.

Results

Study Population Characteristics

Of the 604 patients included in the PARITY trial, 591 patients had functional outcome scores available for analysis. Of these 591 patients, 589 of them also had data pertaining to the external anchor score at one or more time points. The most common diagnosis was a primary bone malignancy followed by metastatic bone disease and soft tissue sarcoma. The mean follow-up time was 334 days (range 2-366) from surgery with 72 patients dying prior to final 1-year follow-up (Table 1).

Functional outcomes

Functional outcomes were recorded preoperatively and at 3, 6 and 12 months postoperatively. There were 535 (91%) patients with preoperative MSTS-93 scores and 551 (93%) patients with preoperative TESS scores. Final follow-up was at 12 months with 422 (71%) patients completing follow-up scores for the MSTS-93 and 431 (73%) providing a complete TESS (Table 2).

Anchor-based Evaluation

The Pearson correlation coefficients for changes in the MSTS-93 and TESS and changes in the external anchor scores were 0.71 and 0.57, indicating “high” and “moderate” correlation[41]. The ROC analysis demonstrated that the area under the curve (AUC) for the change in MSTS-93 and TESS in distinguishing between patients with no functional change and a change score of +1 were 0.75 (MSTS) and 0.70 (TESS) (Figure 1). The optimized cut off scores were 12 points (sensitivity, 0.60; 1-specificity, 0.24) for the MSTS-93 and 11 points (sensitivity, 0.66; 1-specificty, 0.36) for the TESS (Table 3). This indicates that a MID cutoff of 11 points for the TESS has a test sensitivity of 0.66 and

specificity of 0.64 in its ability to accurately predict whether patients had a meaningful improvement in function.

Distribution based

The MID calculated from 0.5SD of the mean preoperative baseline scores were 16 points for the MSTS-93 and 14 points for the TESS. When calculated utilizing the 0.5SD of the change score from baseline to final follow-up, the MIDs were 17 points for the MSTS-93 and 14 points for the TESS (Table 3).

Discussion

Summary of Findings

The current study proposes MID scores for both the MSTS-93 and the lower extremity TESS outcome measures based on 591 patients undergoing lower extremity endoprosthetic reconstruction for an oncologic diagnosis. Anchor-based MIDs were 12 points for the MSTS-93 and 11 points for the TESS. The distribution based MIDs ranged between 16-17 points for the MSTS-93 and was 14 points for the TESS.

Relation to Previous Literature

The use and prevalence of MIDs has grown exponentially within the orthopaedic surgery community and reference values have been calculated for most outcome scores across multiple patient populations [43,44]. However, there remains a paucity of data and literature evaluating patient important differences in musculoskeletal oncology[26]. The MSTS-93 and TESS represent the most frequently utilized functional outcome scores in this population and reference standards are needed to optimize interpretation of treatment effects [14]. To our knowledge, this study is the first to establish MIDs for the MSTS-93, which is the most widely utilized functional outcome score in musculoskeletal oncology[16]. Ogura et al previously calculated MIDs for the lower extremity TESS score for patients with lower extremity sarcomas[45]. The authors determined the anchor-

based MID to be between 4-6.9 points and the distribution based MID between 10.6-11.6 points at 12-month follow-up. However, these findings were based on only 85 patients from a single country and included a variety of surgical interventions which may limit generalizability[45].

Implications

Our estimates of MIDs for the MSTS-93 and TESS will facilitate interpretation of the importance of treatment effects, which will enable informed decision-making in trading off desirable and undesirable outcomes of alternative management strategies. The MIDs will also guide sample size calculations for subsequent studies of interventions directed at improving health-related quality of life in musculoskeletal oncology[46] and facilitate a shift from a focus on statistical significance to patient-importance and value-based care in oncologic patients. These thresholds for minimally important improvement will also facilitate responder analyses. We urge caution with respect to using MIDs to interpret the importance of average effects. Specifically, concluding that average effects just below the MID are unimportant and those just at or above the MID are important. This approach assumes that all patients experience comparable functional gains and fails to consider the distribution around the mean and the proportion of patients who achieve the minimally important difference.

There remains debate regarding the optimal method of calculating MIDs[27]. Some authors advocate for anchor-based MIDs as they are grounded in changes that are important and relevant to patients[27]. However, poorly crafted external anchors can be misleading and may not accurately represent changes that are important to patients[27]. Secondly, external anchors that are administered at a single time point are limited by recall bias. On the other hand, distribution-based approaches to estimating MIDs are not grounded in changes that are meaningful and relevant to patients, which may limit their clinical applicability[47]. In the current study, the anchor scores were administered over

time and the changes in the external anchor were well correlated with changes in the outcome scores, strengthening our confidence in the MID values obtained. Given that the anchor-based methods reflect changes that are meaningful to patients, we recommend use of our MIDs derived through this approach over distribution-based methods.

We explored two functional outcome measures in our study. The MSTS-93 is a physician derived scoring system, which overestimates function when compared to patient reported function[17]. Secondly, the MSTS-93 may not adequately assess health-related quality of life and may be limited by ceiling effects[18]. However, the MSTS-93 remains the mostly widely utilized functional outcome score and it is important to define MIDs for this instrument to evaluate the existing the literature. The TESS is a patient reported outcome that has been validated and has been shown to be responsive to change. Importantly, the TESS has been reliably translated and culturally adapted making it widely generalizable[21–23].

Strengths and Limitations

This study has several strengths. First, we included patients from 48 different clinical centers in 12 countries from a range of health care systems making our results highly generalizable. Secondly, the outcome scores were administered several times over the follow-up period enabling the calculation and inclusion of change scores across a number of different time intervals. Given the rarity of bone and soft tissue tumors, the majority of studies reporting functional outcomes are small, retrospective, single center case series. The current study represents a large, prospectively collected sample population increasing the certainty of the findings.

This study does have some limitations. All patients underwent lower extremity endoprosthetic reconstruction and the MIDs obtained may not be applicable to other patient populations in musculoskeletal oncology or patients undergoing endoprosthetic

reconstruction for non-oncologic pathologies. For example, it may not be appropriate to extrapolate the findings of the current study to patients undergoing amputation or alternative reconstruction options (ie rotationplasty) as those patients were not evaluated in the current studies and MIDs for these populations have not been established. Furthermore, once MIDs for these populations are established, the choice of if and how to perform a reconstruction must account for factors beyond the MIDs. There are differences in complication rates and oncologic outcomes among surgical treatment options for this population that must be taken into consideration alongside any potential differences in functional outcomes[34,48]. As evidenced by other orthopaedic populations, MIDs differ between surgical and nonsurgical patients and future research is required to define MIDs for nonoperative patients with bone tumors[49,50]. The proposed MIDs allow for an evaluation of patients undergoing endoprosthetic reconstruction and provide meaningful values to identify predictors of postoperative function and the impact of different surgical techniques, endoprosthetic designs, postoperative rehabilitation protocols, and complications following reconstruction. Secondly, our final follow-up at 1 year may not reflect longer-term functional outcomes in this population.

Conclusions

We established MIDs for the MSTS-93 and TESS for musculoskeletal oncology patients undergoing lower extremity endoprosthetic reconstruction. We recommend use of anchor-based MIDs, over distribution derived thresholds, as they are grounded in changes in functional status that are relevant and meaningful to patients. These values can provide the basis for determining if statistically significant differences following interventions are important to patients.

Table 1. Patient Characteristics

Variable	Number (%) (n=591)
Age (SD)	40.9 (21.8)
Gender (M/F)	354/237
Implant	
Proximal Femur	148 (25%)
Distal Femur	271 (46%)
Total Femur	10 (1.5%)
Proximal Tibia	100 (17%)
Distal Femur + Proximal Tibia	6 (1%)
Diagnosis	
Primary Bone Malignancy	425 (72%)
STS	54 (9%)
Metastatic Bone Disease	55 (9%)
GCT	44 (7.5%)
Other	13 (2.2%)
Tumor Grade	
I	62 (10.5%)
II	112 (19%)
III	252 (42.6%)
IV	109 (18.4%)
Not recorded	56 (9.5%)
SD = standard deviation, M=male, F= female, DFR = distal femur, PT = proximal tibia, STS = soft tissue sarcoma; GCT = giant cell tumor	

Table 2. Functional Outcome Scores

Functional Score	Included Patients	Mean Score (SD)
MSTS-93		
Baseline	535	56.5 (30.3)
3 months	487	60.7 (22.3)
6 months	449	71.9 (21.5)
12 months	422	78.2 (20.0)
TESS		
Baseline	551	63.6 (27.9)
3 months	478	67.4 (21.5)
6 months	460	75.3 (19.4)
12 months	431	80.9 (17.8)
SD = standard deviation; MSTS-93 = Musculoskeletal Tumor Society Score; TESS = Toronto Extremity Salvage Score		

Table 3. Distribution and Anchor-Based Minimal Important Differences in MSTS-93 and TESS scores

Outcome Measure	Distribution Based MID		Anchor-based MID
	0.5 SD of Preoperative Scores	0.5 SD of change scores from baseline-12 months	
MSTS-93	15.8	16.8	11.7
TESS	14.2	14.2	10.8
MID = minimal important difference; MSTS-93 = Musculoskeletal Tumor Society Score; TESS = Toronto Extremity Salvage Score; SD = Standard Deviation			

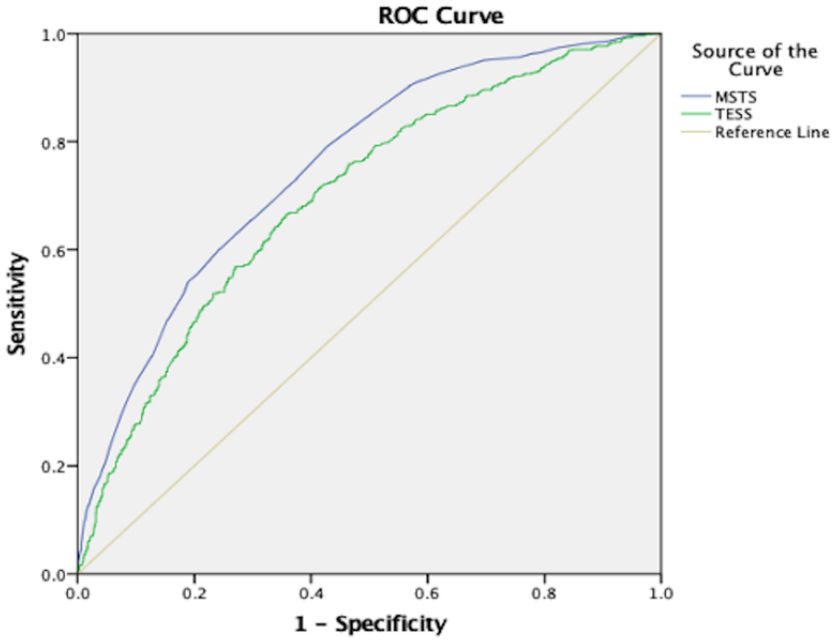

Figure 1. Receiver operating characteristic curve analysis for the TESS and MSTS-93 differentiating between patients with no change in function and an improvement of +1 in function based on the external anchor.

CHAPTER 4: Predictors of Functional Recovery Among Musculoskeletal Oncology Patients Undergoing Lower Extremity Endoprosthetic Reconstruction

Aaron M. Gazendam, MD[1,2], Patricia Schneider, BSc[1], Diane Heels-Ansdell, MSc[2], Mohit Bhandari, MD, PhD[1,2], Jason W. Busse, DC, PhD[1,2,3,4], Michelle Ghert, MD, FRCSC[1,2]

On behalf of the PARITY Investigators

1. Division of Orthopaedic Surgery, McMaster University, Hamilton, Ontario, Canada
2. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
3. The Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, Ontario, Canada
4. Department of Anesthesia, McMaster University, Hamilton, ON, Canada
5. The Chronic Pain Centre of Excellence for Canadian Veterans, Hamilton, ON, Canada

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Corresponding Author:
Aaron M. Gazendam
Division of Orthopaedics
Department of Surgery, McMaster University
St. Joseph's Hospital
Room G522

50 Charlton Avenue East
Hamilton, ON, Canada L8N 4A6
aaron.gazendam@gmail.com

Abstract

Background and Objectives: Functional outcomes are important for oncology patients undergoing lower extremity reconstruction. The objective of the current study was to describe patient reported function after surgery and identified predictors of postoperative function in musculoskeletal oncology patients undergoing lower extremity endoprosthetic reconstruction.

Methods: We acquired functional outcome data from the recently completed *Prophylactic Antibiotic Regimens in Tumor Surgery* (PARITY) trial; specifically, the 100-point Toronto Extremity Salvage Score (TESS) which was administered preoperatively and at 3, 6 and 12 months postoperatively. Higher scores indicate better physical functioning, and the minimally important difference is 11-points. We calculated mean functional scores at each timepoint after surgery and developed a logistic regression model to explore predictors of failure to achieve excellent postoperative function (TESS ≥80) at 1-year after surgery.

Results: The 555 patients included in our cohort showed important functional improvement from pre-surgery to 1-year post-surgery (mean difference 14.9 points, 95% CI 12.2 to 17.6; $p<0.001$) and 64% achieved excellent post-operative function. Our adjusted regression model found that poor (TESS 0-39) preoperative function (odds ratio [OR] 3.3, 95%CI 1.6 to 6.6); absolute risk [AR] 24%, 95%CI 8% to 41.2%), older age (OR per 10-year increase from age 12, 1.32, 95%CI 1.17, 1.49; AR 4.5%, 95%CI 2.4% to 6.6%), and patients undergoing reconstruction for soft-tissue sarcomas (OR 2.3, 95%CI 1.03 to 5.01; AR 15.3%, 95%CI 0.4% to 34.4%), were associated with higher odds of failing to achieve an excellent functional outcome at 1-year follow-up. Patients undergoing reconstruction for giant cell tumors were more likely to achieve an excellent

functional outcome postoperatively (OR 0.40, 95%CI 0.17 to 0.95; AR -9.9%, 95%CI -14.4% to -0.7%).

Conclusions: The majority of patients with tumors of the lower extremity undergoing endoprosthetic reconstruction achieved excellent function at 1-year after surgery. Older age, poor preoperative function, and endoprosthetic reconstruction for soft tissue sarcomas were associated with worse outcomes; reconstruction for giant cell tumors were associated with better post-operative function.

Level of Evidence: Therapeutic Level IV

Background

Surgical intervention with wide excision and negative margins is the mainstay of treatment for patients with malignant bone tumors[51,52]. With improvements in imaging modalities, chemotherapeutic agents and surgical techniques, limb-salvage surgery has become the standard of care for the majority of patients diagnosed with malignant bone tumors of the extremity[53]. Limb-salvage surgery allows for the same oncologic control as amputations with potential improvements in function and quality of life[8]. In skeletally mature patients with tumors centered around the hip and knee, endoprosthetic reconstruction has become the reconstruction technique of choice[11].

There has been an increased interest in functional outcomes following limb-salvage surgery;[54–57] however, there remains important knowledge gaps. The majority of the literature consists of small, single center, retrospective reviews with the inherent biases such study designs carry[16]. Further, functional outcomes are most commonly reported at a single time point postoperatively, which does not allow for an assessment of change over time[58–60]. Due to the invasive nature of oncologic resections and reconstructions, some patients may experience prolonged functional impairment after surgery. This information is critical to inform patients and clinicians about the expected rehabilitation course following endoprosthetic reconstruction[29].

This study aimed to: 1) describe changes in patient-reported functional outcomes preoperatively to 1 year postoperatively following lower extremity endoprosthetic reconstruction, and 2) identify preoperative patient and tumor variables associated with postoperative function.

Methods

Study Design and Setting

This was a secondary analysis of the recently completed PARITY (Prophylactic Antibiotic Regimens in Tumor Surgery) trial[61]. PARITY was a multicenter randomized controlled trial (RCT), in which surgeons, patients and outcome assessors were blinded, that investigated the impact of 24h vs. 5 days of postoperative intravenous prophylactic antibiotics on surgical site infections among patients undergoing endoprosthetic reconstruction of lower extremity bone and soft-tissue tumors. This trial was registered [NCT01479283] and received ethics approval from the Hamilton Integrated Research Ethics Board (REB# 12-009). The PARITY trial consisted of 48 sites in 12 countries across 6 continents with over 150 investigators. The current study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies[62].

Participants

All patients who underwent a proximal femur reconstruction (PFR), distal femur reconstruction (DFR) or proximal tibia reconstruction (PTR) with an endoprosthesis as part of the PARITY trial were included in the current analysis.

Data Sources and Variables

Baseline patient demographic, tumor characteristics, surgical data and functional outcome scores were obtained from the prospectively collected PARITY trial database.

Functional Outcomes

The Toronto Extremity Salvage Score (TESS) was designed to address the World Health Organization's definitions of Disability, Impairment, and Handicap[19]. It is a 30-item, patient-reported questionnaire that focuses on the ability to perform activities of daily living in a variety of daily settings. Scores are translated to a 0-100 scale with higher

scores representing better function. In the PARITY trial, the TESS was administered preoperatively, and at 3, 6 and 12 months postoperatively. We categorized TESS values as poor (0-39), fair (40-59), good (60-79) or excellent (80-100). A TESS of ≥80 is commonly reported by unoperated healthy controls aged 30-69,[63] and the minimally important difference (MID) is 11 points[64].

Statistical Analysis

Demographic data was reported using descriptive statistics, with mean and standard deviation (SD) or median and interquartile range, depending on data distribution. Patient-reported functional outcomes were presented as means and SDs at all time points (preoperative, 3 months, 6 months and 12 months), both for the entire cohort and stratified by PFRs, DFRs and PTRs. Change scores were presented as mean differences (MD) and 95% confidence intervals (CI). We explored for statistical significance of functional changes pre-operatively to each post-operative follow-up using paired t-tests.

We constructed a multivariable logistic regression model to explore predictors of failure to achieve excellent functional outcome (TESS ≥80) at 1-year follow-up. We pooled patients into a single group for the current study as the PARITY trial was a no-difference study. All patients with complete data were included in our regression analysis. We selected six covariates previously reported as predictors or judged by our clinical experts to be related to functional outcomes: age, gender, tumor type (primary bone sarcoma, STS invading bone, metastatic bone disease, or giant cell tumor [GCT]), endoprosthetic reconstruction (PFR, DFR or PTR), systematic metastases at presentation, and preoperative TESS[30,65,66]. We also adjusted for antibiotic treatment (24h vs 5 day). We excluded independent variables with fewer than 40 observations, unless we were able to collapse them with other related variables to exceed this threshold, to provide reassurance that each variable had sufficient discriminant power to detect an association with functional outcome if such an association existed. To avoid over fitting, we required

at least 10 events and 10 nonevents per category of independent variable, for a minimum of 120 patients who achieved an excellent functional outcome, and 120 that did not by 1 year after surgery[67]. Model performance was evaluated using the Hosmer and Lemeshow statistic to assess for goodness-of-fit[68]. Outcomes of the binomial logistic regression were presented with odds ratios (OR) and 95% confidence intervals (CI). We calculated the absolute risk (AR) for each significant predictor and estimated the baseline risk for failure to achieve an excellent function outcome at 1-year by calculating the incidence amongst patients without any significant risk factors. All analyses were performed using SPSS (IBM SPSS Statistics for Mac, V26). A value of $P<0.05$ was considered to be significant for all analyses.

Sources of funding

The PARITY Trial received funding through grants from the Canadian Institutes of Health Research (CIHR), the Canadian Cancer Society Research Institute, the Canadian Orthopaedic Foundation J. Édouard Samson Award, the Orthopaedic Research and Education Foundation in conjunction with the Musculoskeletal Tumor Society, and the Physicians' Services Incorporated Clinical Research Grant. JWB is funded, in part, by a CIHR Canada Research Chair in the prevention and management of chronic pain. MB receives institutional support from the Canadian Institute of Health Research, National Institute of Health, Michael DeGroote Institute for Pain Research and Care and is an advisory board member for the Mayo Clinic Core Center for Clinical Research.

Results

Cohort Characteristics

Of 604 patients enrolled in the PARITY trial, 555 underwent endoprosthetic reconstruction of the proximal femur (n=144), distal femur (n=312) or proximal tibia (n=99), and had patient reported functional outcome data available for one or more post-operative time points. Of the 49 excluded patients, 15 had a non-eligible endoprosthetic reconstruction and 34 were missing TESS data at all follow-ups. The mean age of the cohort was 41 (SD±22) and 60% were male (332/555). The most common diagnosis was a primary bone sarcoma (n=407) followed by a STS (n=54), metastatic bone disease (n=51), and GCT (n=43). The mean follow-up was 333 days (range 2 – 366) with 51 (9%) patients dying from disease progression prior to final follow-up (**Table 1**).

Functional Outcomes

Mean functional outcome scores increased over time for the cohort, and the average TESS at 12-month follow-up was 81.1 (SD±17.8). There were statistically significant improvements in the TESS from preoperative to final follow-up that exceeded the MID of 11 (MD 14.9 [95% CI; 12.2,17.6] p<0.001) (**Table 2, Figure 1**). There were differences in improvement in pre-operative to 12-month TESS based on anatomic location, with PFR (MD 16.6 [95% CI; 10.6, 22.6], p<0.001) and DFR (MD 16.5 [95% CI; 13.0, 20.0], p<0.001) showing larger improvements than PTR (MD 8.2 [95% CI; 1.8, 14.6], p=0.013).

Binomial Logistic Regression Analysis

We included 397 patients with both preoperative and 12-month follow-up TESS in our regression analysis, of which 254 (64%) achieved an excellent (TESS ≥80) outcome. Our adjusted regression model found that poor (TESS <40) pre-operative function (OR 3.3, 95% CI 1.64, 6.60; AR 24%, 95% CI 8.0, 41.2), older age (OR per 10-year increase from age 12, 1.32, 95% CI 1.17, 1.49; AR 4.5% per decade, 95% CI 2.4, 6.6), and STS (OR 2.27; 95% CI 1.03, 5.01; AR 15.3%, 95% CI 0.4, 34.4) were less likely to achieve an

excellent functional outcome; patients presenting with GCTs were more likely to achieve an excellent functional outcome (OR 0.40, 95% CI 0.17, 0.95; AR -9.9%, 95% CI -14.4, -0.7). Patient sex, metastases at presentation, type of endoprosthetic reconstruction (PFR, DFR or PTR) and antibiotic duration group were not associated with excellent patient-reported function 1-year after surgery. (Table 4) Our model demonstrated goodness of fit according to the Hosmer and Lemeshow Test ($\chi^2 = 9.03$, p=0.340).

Discussion

We found that patients with bone tumors undergoing endoprosthetic reconstruction of the lower extremity demonstrate important functional improvement at 1-year follow-up, with approximately 2/3^{rds} achieving excellent functioning. Older patients, reporting poor pre-operative functioning, and presenting with STS were less likely to report excellent function at 1-year; patients presenting with GCT were more likely to achieve excellent long-term functional recovery.

Strengths of our study include a large, comprehensive analysis of prospectively collected functional scores in patients undergoing lower extremity endoprosthetic reconstruction. Second, we recruited patients from 48 clinical sites in 12 countries which increases the generalizability of our findings. Third, this is the first study to capture changes from preoperative function over the course of a patient's rehabilitation in this population. Fourth, we had very little missing data (6%) in our cohort. Our study does have some limitations. We captured functional outcomes up to 1-year after surgery and it remains possible that additional recovery may have been seen after this time, particularly among the 25% of patients that required re-operation.

Given the surgically complex nature of tumor resections and reconstructions, there may be concerns that patients are left with significant functional limitations;[69] however, the current study demonstrates that most musculoskeletal oncology patients achieve excellent long-term function at 1-year post-operatively. Compared to other types of reconstruction, patients undergoing PTRs showed a decrease in function at 3-months after surgery. The majority of patients undergoing PTRs require extensor mechanism reconstruction, typically through gastrocnemius rotation flap with wire or suture fixation to reconstruct the patellar tendon[70,71]. The postoperative rehabilitation protocol for these patients generally involves a prolonged period of immobilization which was likely a contributing factor in the significant reduction in function noted at the 3-month follow-up visit[71].

Patients with poor preoperative functional scores (TESS <40), were at a higher risk of not achieving optimal postoperative functional status, independent of age, tumor type or anatomic location. Similar findings have been demonstrated in other orthopaedic populations, including patients undergoing total hip arthroplasty[72].

Patients with a STS requiring bone resection and endoprosthetic reconstruction were significantly less likely to achieve optimal function in this cohort. Bony invasion in STS is relatively rare and often indicates a larger, more aggressive tumor[65]. Soft-tissue sarcomas often necessitate more soft tissue and muscle resection than primary bone tumors to achieve negative margins which has the potential to negatively impact postoperative function. High-grade STSs are also generally managed with peri-operative radiotherapy. Given the risk of wound healing and periprosthetic infection associated with preoperative radiation, some clinicians opt for postoperative radiation [73,74]. However, postoperative radiation is associated with soft tissue fibrosis, stiffness and lymphedema which may negatively impact functional outcomes[74].

Older age was a risk factor for failure to achieve excellent postoperative function, and this has been shown in previous studies of primary bone tumor resection and endoprosthetic reconstruction[75] and lower extremity limb salvage surgery[30]. With increasing age, patients are more likely to present with frailty; representing an age-related decline in function, sarcopenia and energy which impacts their ability to recover postoperatively[76]. Similarly, older patients are more likely to have medical comorbidities which may impact their ability to rehabilitate. Further research evaluating the utility of prehabilitation to optimize post-operative functional recovery is warranted, perhaps particularly in older patients and those with lower pre-surgical functioning[77].

Identifying predictors of postoperative function regain function following lower extremity endoprosthetic will allow both patients and physicians to make evidenced-based decisions when discussing alternative management strategies. Additionally, recognizing patients at highest risk of failure allows clinicians to appropriately allocate resources to ensure high risk patients are given the best chance at success. For example, high risk patients may benefit from additional pre and postoperative rehabilitation to ensure their postoperative function is optimized.

Conclusions

Most patients with tumors of the lower extremity undergoing endoprosthetic reconstruction achieved excellent function at 1-year after surgery. Older age, poor preoperative function, and endoprosthetic reconstruction for soft tissue sarcomas were associated with worse outcomes; reconstruction for giant cell tumors were associated with better post-operative function.

Table 1. Patient characteristics

Variable	Entire Cohort (n=555)	Proximal Femur Reconstruction (n=144)	Distal Femur Reconstruction (n=312)	Proximal Tibia Reconstruction (n=99)
Age (SD)	40.7 (21.6)	51.3 (20.4)	37.1 (20.9)	36.6 (20.6)
Gender (M/F)	332/223	91/53	177/135	
Diagnosis				
Primary Bone Sarcoma	407	97	239	71
Soft tissue sarcoma	54	11	33	10
Metastatic Bone Disease	51	32	16	3
Giant Cell Tumor	43	4	24	15
Preoperative TESS				
Poor (0-39)	113	44	58	11
Fair (40-59)	96	22	53	21
Good (60-79)	140	23	96	21
Excellent (80-100)	180	45	92	43
Missing	26	10	13	3
Systemic Metastases				
Yes	97	42	45	10
No	458	102	267	89
Death from disease progression	51	23	24	4

SD = standard deviation; M = male; F = female; TESS = Toronto Extremity Salvage Score

Table 2. Functional outcome scores over time.

Functional Score	Overall Mean Score (SD)	PFR Mean Score (SD)	DFR Mean Score (SD)	PTR Mean Score (SD)
TESS				
Preoperative	63.5 (27.7)	57.1 (31.2)	64.2 (26.0)	69.5 (26.2)
3 months	67.9 (21.3)	62.2 (21.7)	71.6 (20.0)	64.0 (26.2)
6 months	75.7 (19.2)	72.8 (19.3)	76.8 (19.0)	76.0 (19.0)
12 months	81.1 (17.8)	77.3 (18.5)	83.0 (16.2)	80.2 (20.1)

TESS = Toronto Extremity Salvage Score; SD = standard deviation; PFR = proximal femur reconstruction; DFR = distal femur reconstruction; PTR = proximal tibia reconstruction.

Table 3. TESS change scores over time.

Functional Score	Mean Differences (95% CIs)					
	0– 3 months	P-value	0 – 6 months	P-value	0 – 12 months	P-value
TESS						
Overall	3.4 (0.7, 6.2)	0.015	10.0 (7.4, 12.6)	<0.001	14.9* (12.2, 17.6)	**<0.001**
PFR	2.7 (-3.7, 9.0)	0.410	12.3* (6.1, 18.6)	<0.001	16.6* (10.6, 22.6)	**<0.001**
DFR	7.1 (3.8, 10.5)	**<0.001**	10.8 (7.5, 14.0)	<0.001	16.5* (13.0, 20.0)	**<0.001**
PTR	-7.0 (-13, -0.5)	0.034	4.8 (-1.1, 10.7)	0.11	8.2 (1.8, 14.6)	0.013

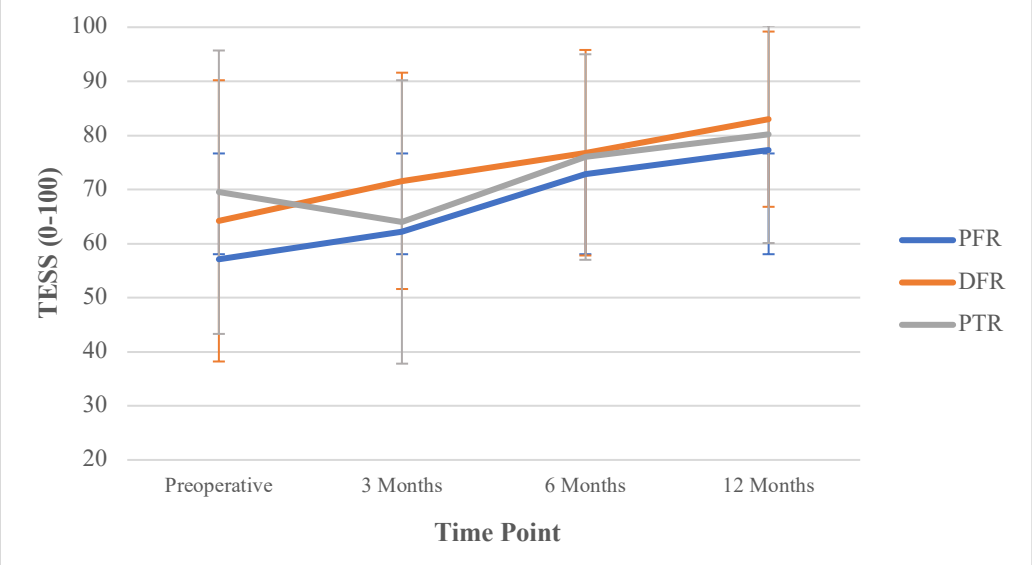
TESS = Toronto Extremity Salvage Score; CI = confidence interval; PFR = proximal femur reconstruction; DFR = distal femur reconstruction; PTR = proximal tibia reconstruction; **bolded** = statistically significant when evaluated with paired t-tests; *exceeds minimal important difference cut-off.

Table 4. Binomial logistic regression analysis evaluating factors associated with failure to achieve excellent post-operative function at 1-year (n=397)

Factor	OR (95% CI)	P-value	Absolute risk, % (95% CI) *
Age (per 10-year increase from age 12)	1.32 (1.17, 1.49)	<0.001	4.5 (2.4, 6.6)
Sex			
Female	reference category		
Male	1.00 (0.63, 1.60)	0.999	
Tumor Type			
Bone sarcoma	reference category		
Soft-tissue sarcoma	2.27 (1.03, 5.01)	0.042	15.3 (0.4, 34.4)
Metastatic bone disease	0.78 (0.28, 2.20)	0.628	
Giant cell tumor	0.40 (0.17, 0.95)	0.038	-9.9 (-14.4, -0.7)
Type of reconstruction			
Distal femur	reference category		
Proximal femur	0.98 (0.55, 1.75)	0.947	
Proximal tibia	1.3 (0.72, 2.4))	0.368	
Preoperative TESS Score			
Excellent (80-100)	reference category		
Good (60-79)	1.04 (0.57, 1.91)	0.889	
Fair (40-59)	1.83 (0.96, 3.50)	0.068	
Poor (0-39)	3.30 (1.6, 6.60)	0.001	24.0 (8.0, 41.2)

Metastases at presentation	1.30 (0.61, 2.62)	0.537	
Antibiotic Duration 24h regime 5-day regime	 Reference 0.91 (0.58, 1.42)	 0.668	
OR = odds ratio, CI = confidence interval, * absolute risks are reported for significant factors in the adjusted model, bolded = statistically significant			

Figure 1. Changes in the TESS scores over time with points indicating means and error bars indicating standard deviations



PFR: proximal femur reconstruction, DFR: distal femur reconstruction, PTR: proximal tibia reconstruction

CHAPTER 5: Discussion and Conclusions

Thesis Summary

This thesis utilized functional outcome data from a large clinical trial to address unanswered questions in musculoskeletal oncology research. We developed MID values for both the MSTS and the TESS, the two most commonly utilized functional outcome tools in the field. Secondly, we characterized the longitudinal changes in function following endoprosthetic reconstruction and identified patient and tumor predictors of postoperative function. On average, patient function improved significantly from their preoperative baseline to 1-year follow-up, exceeding the predefined MID values. Older age, poor preoperative function, and endoprosthetic reconstruction for soft tissue sarcomas were associated with worse outcomes; reconstruction for giant cell tumors were associated with better post-operative function.

Clinical Implications

Establishing MIDs for functional outcome instruments in patients undergoing limb salvage surgery is critically important and timely. These estimates allow for easy and meaningful interpretations of the magnitude of treatment effects which enables rational decision making in trading off desirable and undesirable outcomes of alternative treatment strategies. It will also guide sample size calculations for subsequent studies of interventions aimed at improving functional outcomes in musculoskeletal oncology. Ultimately, this work will enhance the methodologic rigour of clinical research in the field.

This thesis is the first to describe functional outcomes in a longitudinal manner in this patient population. In the context of the aforementioned MIDs, evaluating function over time provides an understanding of if (and when) patients make patient important improvements in their function. This longitudinal analysis involves over 500 patients

from 12 different countries, providing the most comprehensive understanding of function available to date. Identifying predictors of postoperative function regain function following lower extremity endoprosthetic will allow both patients and physicians to make evidenced-based decisions when discussing alternative management strategies.

Research Implications

The results of this thesis are important additions to the current musculoskeletal oncology literature. The PARITY trial represented the first surgical trial in the field and was a momentous effort including over 150 clinical investigators spanning almost 10 years[78]. The robust, prospectively collected database that was generated is unique in this patient population and provides an opportunity to address unanswered questions in the field. Given the resources required to perform an international RCT in musculoskeletal oncology, data of similar quality and generalizability will likely not be generated in the near future.

The results from this thesis provide novel opportunities for knowledge dissemination and translation. We plan to collaborate with relevant academic societies including the Musculoskeletal Tumor Society (MSTS), the American Academy of Orthopaedic Surgeons (AAOS), the European Musculoskeletal Oncology Society and the International Society of Limb Salvage to ensure that results from this thesis are incorporated into future research and practice guidelines. For example, the MSTS and AAOS have recently created a national database for musculoskeletal oncology patients that includes both the MSTS-93 and TESS outcome scores. We will work with the MSTS and AAOS to ensure that future studies derived from this database are grounded in patient important differences utilizing the MIDs developed here.

Conclusion

In this thesis, we established MID values for both the TESS and MSTS functional outcome instruments in musculoskeletal patients undergoing lower extremity endoprosthetic reconstruction for the first time. We characterized the change in function throughout the pre and postoperative course and identified predictors for postoperative function. The results of this thesis provides a valuable addition to the literature and ultimately aims to improve the outcomes of musculoskeletal oncology patients worldwide.

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