DIPLOMARBEIT

Sarcomas of the ankle region: QOL and functional outcome of limb-salvage vs. amputation

eingereicht von

Martin T.P. Kapper

zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Orthopädie und Traumatologie

unter der Anleitung von

Univ.-Prof. Dr. Andreas Leithner

Dr.med.univ. Maria Anna Smolle

Graz, am 15.07.2021

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 15.07.2021 *Martin T.P.Kapper eh*

Acknowledgements

I would like to express my appreciation to my supervisors Univ.-Prof. Dr.med.univ. Andreas Leithner, head of the Department of Orthopaedics and Trauma and Dr.in med.univ. Maria Smolle for their valuable and constructive suggestions during the planning and development of this thesis, as well as their willingness to provide their time. Furthermore, I would especially like to thank my good friend Lennart for proofreading this thesis. I would also like to extend my thanks to the technicians of the Digital Culture Laboratories Hirikilabs for their help in offering me the resources needed. Finally, I would like to express my special thanks to my family and friends for their support and encouragement throughout my studies.

Contents

Glossary and abbreviations

AG	Amputation group
AJCC	American joint committee on caner
BMI	Body mass index
BS	Bone sarcoma
COSS	Cooperative osteosarcoma study group
CT	Computed tomography
CTX	Chemotherapy
ES	Ewing sarcoma
ESMO	European society of medical oncology
EURACAN	European reference network on rare adult cancers
EUROBOSS	European bone over 40 sarcoma study
EWS-FLI1	Ewing's sarcoma gene-friend leukemia integration 1 transcription factor
FDG	2-Deoxy-2-fluoro-D-glucose
FNCLCC	French fédération nationale des centres de lutte contre le cancer
LR	Local recurrence
LS	Liposarcoma
LSG	Limb salvage group
MFS	Myxofibrosarcoma
MRI	Magnetic resonance imaging
mTOR	Mechanistic target of rapamycin
NCI	United states national cancer institute
OS	Osteoscarcoma
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PET-CT	Positron emission tomography-CT
ROM	Range of motion
RTX	Radiotherapy
SD	Standard deviation
SS	Synovial sarcoma
STS	Soft tissue sarcoma
TNM	Tumour nodes metastasis
US	Ultrasound, Ultrasonography

EQ-5D-5L	Euroqol group-5D version-5-level
EQ-VAS	Euroqol group-visual analogue scale
FLZ	Fragebogen zur Lebenszufriedenheit
MWAS	Modified weight activity score
PLUS-M	Prosthetic limb users survey of mobility
PROMIS	Patient-reported outcome measurement information system test
TESS	Toronto extremity salvage score
UCLA	Rating-system university of california at los angeles

List of figures

List of tables

Zusammenfassung

Einleitung: Zieht man die Größe der betroffenen Region in Betracht, ist es kaum verwunderlich, dass Sarkome der Knöchelregion zu den seltensten der muskuloskeletalen Tumoren zähen. In vergleichbaren Studien die postoperative Unterschiede zwischen Extremitätenerhalt und Amputation untersuchen, bestand zumeist ein Fokus auf die postoperative Funktionalität des Gelenks. Allerdings wurde der Lebensqualität der Patienten und Patientinnen bisher wenig Aufmerksamkeit geschenkt. Diese Diplomarbeit behandelt erhobene Parameter über postoperative Funktionalität, Lebensqualität, und Lebensstil von Patienten und Patientinnen die an einem tertiären Sarkomzentrum (Univ. Klinik für Orthopädie und Traumatologie, Medizinische Universität Graz) behandelt wurden. Darüber hinaus wurden Daten aus dem Tumorregister für Sarkome in Graz retrospektiv analysiert, wobei ein besonderer Fokus auf postoperative Komplikationen gelegt wurde.

Material und Methoden: Alle zwischen 1998 und 2017 im Studienzentrum behandelten Patienten und Patientinnen mit primären Knochen- und Weichteilsarkomen der Knöchelregion wurden retrospektiv in die Analyse einbezogen. Insgesamt wurden die Daten von 24 Patienten und Patientinnen analysiert, unter besonderer Berücksichtigung der postoperativen Komplikationen. Ein p-Wert <0.05 wurde als statistisch signifikant angenommen. Darüber hinaus wurden die Patienten und Patientinnen zur Teilnahme am prospektiven Teil dieser Studie gebeten, bei dem eine einmalige Untersuchung und Befragung mittels Fragebögen durchgeführt wurde, um Parameter über Lebensqualität, Lebensstil und funktionelles Outcome zu erheben. Insgesamt wurden 7 Personen inkludiert.

Ergebnisse: Die im Zuge dieser Arbeit ausgewerteten retrospektiven Daten zeigen, dass 91,7% der postoperativen Komplikationen nach der ersten Operation in der Gruppe der Patienten und Patientinnen auftraten, die durch ein extremitätenerhaltendes Verfahren behandelt wurden. Die häufigsten postoperativen Komplikationen waren Weichteilkomplikationen (46%) und mechanische Komplikationen (27%). Aus der Datenerhebung ist ersichtlich, dass alle Patienten und Patientinnen mit primären postoperativen Komplikationen noch einmal operiert werden mussten. Im prospektiven Teil wurde im Vergleich der beiden Studiengruppen (LSG=limb salvage surgery group vs. AG=amputation group) bei der Analyse der Fragebögen kein signifikanter Unterschied zwischen Extremitätenerhalt und Amputation gefunden. Allerdings wurden verschieden Tendenzen beobachtet. In T-Werte umgerechnet zeigen die erhobenen Daten einen überdurchschnittlichen Unterschied (von ungefähr einer Standardabweichung) zwischen den zwei Vergleichsgruppen LSG versus AG bei den Ergebnissen der Fragebögen

die auf Bewegung (PROMIS), Einschränkungen der Mobilität (TESS) und generelle Lebenszufriedenheit (FLZ) testeten. Allerdings erreichten diese tendenziell besseren Ergebnisse in der LSG keine statistische Signifikanz (alle $p>0.05$).

Schlussfolgerung: Zusammenfassend lässt sich sagen, dass postoperative Komplikationen von Weichteilen und mechanische Komplikationen bei Patienten und Patientinnen mit Extremitätenerhalt häufiger aufgetreten sind und in den meisten Fällen zu einer Reoperation führten. In Bezug auf die postoperative Funktionalität scheint kein signifikanter Unterschied zwischen den beiden Studiengruppen (LSG vs. AG) zu bestehen. Hinsichtlich der Funktionsfähigkeit des Gelenks und der allgemeinen Lebenszufriedenheit der Patienten und Patientinnen wurden bestimmte positive Tendenzen für extremitätenerhaltende Verfahren beobachtet. Folglich sollten bei Patienten und Patientinnen mit Sarkomen in der Knöchelregion Risiken und Nutzen eines Extremitätenerhalts vs. Amputation sorgfältig gegeneinander abgewogen werden, um das Risiko operationsbedingter Komplikationen zu minimieren, das onkologische Ergebnis zu verbessern, die funktionellen Ergebnisse zu optimieren und die Lebensqualität zu erhalten.

Abstract

Introduction: Considering the dimension of the affected region, ankles sarcomas are relatively rare within the group of musculoskeletal tumours. Most studies only focus on surgical and functional outcome when comparing limb-salvage surgery versus amputation in treatment of ankle sarcomas. Yet, little attention has so far been paid to patients' quality of life. This thesis outlines parameters for quality of life, lifestyle and functional outcome of patients treated for sarcomas of the ankle region at a tertiary sarcoma centre (Department of Orthopaedics and Trauma, Medical University of Graz). In addition, the data collected from the database of the study centre were retrospectively analysed with the focus on postoperative complications.

Material and Methods: All patients treated at the study centre between 1998 and 2017 for primary bone and soft tissue sarcomas of the ankle region were retrospectively included, resulting in 24 patients eligible. Rate of postoperative complications was analysed. A p-value < 0.05 was accepted as statistically significant. In addition, patients were invited to participate in the prospective part of the study, consisting of a medical consultation, clinical examination and questionnaire survey at the study centre to collect data about quality of life, lifestyle and functional outcome. In total, 7 patients were prospectively enrolled.

Results: The retrospective data evaluated in this thesis shows that 91.7% of postoperative complications after the first surgery occurred in the group of patients treated by limb-salvage procedure. The most common postoperative complications were soft tissue complications (46%) and mechanical complications (27%). In addition, all patients with postoperative complications needed revision surgery. In the prospective part of the current study, no significant difference in quality of life between patients treated with limb-salvage procedure versus patients undergoing amputation was found. However, certain tendencies were observed: A difference beyond average (approximately one *standard deviation* (SD)) in the T-score between the two study groups *limb salvage group* (LSG) and *amputation group* (AG) was present in the questionnaires testing for physical ability (PROMIS), physical disability (TESS) and patients' overall life satisfaction (FLZ). However, these per tendency favorable outcome scores for patients in the LSG did not reach statistical significance (all $p>0.05$).

Conclusion: In conclusion, postoperative complications such as soft tissue complications and mechanical complications occur more frequently in patients with limb-salvage surgery and most commonly require re-operation. Furthermore, there seems to be no significant difference between patients with limb salvage and those with amputation with regards to functional outcome. Regarding the patients' physical ability, physical disability and overall life

satisfaction, certain tendencies in favor of limb salvage surgery were present, though. Consequently, risks and benefits of limb salvage vs. amputation should be carefully weighed against each other in patients with sarcomas of the ankle region, in order to minimise the risk of surgery-associated complications, improve oncological outcome, optimize functional results, and maintain quality of life.

Disclosures

Findings of the current diploma thesis have been in part included in the following publication:

Smolle MA, Leithner A, Kapper M, Demmer G, Trost C, Bergovec M, Windhager R, Hobusch GM. Complications, mobility, and quality of life in ankle sarcoma patients. Bone Joint J. 2021 Mar;103-B(3):553-561.doi:10.1302/0301-620X.103B3.BJJ-2020-1308.R1. PMID: 33641415.

1 Introduction

About 5 to 10% of all musculoskeletal tumours arise in the ankle region, although the ankle region itself accounts for 3% of the entire body mass only. (1) As sarcomas of the ankle region are outnumbered by benign tumours at this anatomic site, malignant tumours are at risk of being mistaken as benign lesions. (2) Thus, unplanned excisions of sarcomas of the foot and ankle region are not uncommon, potentially necessitating more radical re-resections and adjuvant *radiotherapy* (RTX), which may adversely affect surgical as well as oncological outcome. (3) Due to the distinctive anatomic structure of the foot with close proximity of different functional units, limb salvage surgery is not always possible. (4) The authors of recent studies have discovered that there is no difference in survival rate for patients with limb salvage surgery or amputation for sarcomas of the ankle region. However, amputations seem to be associated with poorer functional outcomes. (5) In this diploma thesis, parameters for the postoperative quality of life and the functional outcome of patients treated for sarcomas of the ankle region by limb-salvage or amputation at a single study centre were examined. For this purpose, all patients treated at the *Department of Orthopaedics and Trauma, Medical University of Graz*, between 1998 and 2017 for primary bone and soft tissue sarcomas of the ankle joint (including talus, calcaneus, ankle joint and distal tibia/fibula) were retrospectively analysed. Factors associated with development of postoperative complications and the likelihood of appearance were retrospectively explored. Furthermore, standardized questionnaires (see appendix) were used and parameters for postoperative functionality and mobility identified by clinical examination. For this purpose, patients from the retrospective part were invited to participate in the prospective questionnaire-based part of the study.

1.1 Soft tissue sarcomas (STS)

As the ratio between benign soft tissue tumours and soft tissue sarcomas (STS) is around 100:1, it is not surprising that malignant soft tissue tumours are often misdiagnosed as benign lesions. (6) STS account for less than 1% of all primary malignant tumours (e.g. breast, lung). (2) They have an unknown aetiology, they tend to occur in extremities – any body region may be affected – and are more often observed in later life periods, mirrored in a median patient age of 65 years. (2) STS commonly present as painless masses, thus often leading to misinterpretation and delayed diagnosis. (7) Moreover, due to the rarity of STS, physicians usually lack experience in properly handling these tumours. STS are classified depending on their morphology, histological appearance, immunohistochemical profile, and molecular genetic changes. Of note, a variety of STS types and subtypes exists, with over 50 subtypes defined by the *World Health Organisation*. (2) This makes the interpretation of biopsy results more difficult. Biopsy should be performed in any case with suspected malignancy. (8)

1.2 Bone sarcomas (BS)

Bone sarcomas (BS) occur with an incidence of 0.8 per 100.000 females and 1.1 per 100.000 males per year. (9) The life time risk of being diagnosed with primary BS is estimated at 0.1%. (9) Generally, two incidence peaks are present, with the first peak observed in younger patients, aged between 10 and 20 years. (9) The second peak occurs in patients over the age of 60. (10) This bimodal age-specific occurrence rate is different form STS. The majority of primary malignant bone tumours occur *de novo* and do not cause specific symptoms – despite gradually increasing, weight-bearing unrelated, deep and dull pain. (2) Furthermore, general discomfort, swelling and pain unresponsive to analgesics can frequently be observed. Pain may initially present neuralgia-like, occurring mostly at rest. (11) It then intensifies over time, often spreading into nearby joints and thus additionally complicating early diagnosis. Furthermore, limited mobility is an important clinical sign. Finally, pathological fractures due to none to minimal trauma may occur. In order to reach the correct diagnosis, a combination of clinical, histological and radiological measurements is usually required. (2) Concerning treatment, limb salvage procedures are performed as long as wide margins can be achieved. (12) Over the years, survival rates for children and adolescent with BS have improved significantly, particularly due to advances in neoadjuvant and adjuvant chemotherapeutic protocols. (13)

1.3 Diagnostics

1.3.1 Clinical Presentation

Both BS and STS show a variety of different clinical presentations. Therefore, a comprehensive physical examination and patient history are particularly important in patients who present with a soft tissue mass with or without local pain. As outlined above, STS-patients usually present with a mass or swelling with a tendency to grow. BS usually commonly cause pain, whilst this, in most cases, does not apply to STS. Sometimes symptoms such as fever, unplanned weight loss and fatigue can be observed, which is especially frequent in Ewing sarcomas (ES). (14) The tendency of STS to be painless often leads to delayed diagnosis. On the other hand, the indistinct symptoms of BS likewise impair early diagnosis. Patients might not seek medical consultations until the tumour has considerably grown in size or they note restrictions during their daily activities due to pain or mechanical discomfort. (14) It is therefore recommended that patients with either soft tissue lumps larger than 4 cm in size, (15) or unclear imaging findings as soft tissue shadows on x-rays, cortical bone changes or periosteal reactions, should be referred to a specialist tertiary sarcoma centre. (14)

1.3.2 Imaging

Radiological imaging plays a vital role in non-invasive diagnostics of STS and BS. It allows precise analysis of size, expansion, and localisation of the tumour. In addition, it can be used to detect local and distant spread. A variety of imaging techniques such as *ultrasound* (US), *magnetic resonance imaging* (MRI), *computed tomography* (CT) and *positron emission tomography-CT* (PET-CT) with their role in STS and BS will be discussed below.

US is frequently performed during primary assessment of both benign and malignant soft tissue tumours, as it is a simple and cheap method with broad availability. (16) For instance, US allows a simple differentiation between cystic and solid masses. (14) Nonetheless, it is hardly useful to diagnose bone lesions due to the lack of penetration through the bony cortex. (14) The “gold standard” for STS diagnosis is MRI with administration of a contrast medium. It allows precise measurements of the tumours’ expansion as well as differentiation between healthy structures and tumour tissue. (16) Furthermore, it has a high sensitivity with regards to detection of *local recurrences* (LR) in STS and BS. STS are usually surrounded by a capsule or pseudo-capsular structures that may be observed on T2 weighted images. (14)

Other imaging techniques such as CT are especially useful in order to detect changes of bony structures.(16) Hence, it is a commonly used tool in case of suspected BS, but may also be applied in large soft tissue tumours with potential involvement of adjacent bones. (14) CT-scan of the abdomen, chest and pelvis is used for initial staging and during follow-up in order to detect metastases in the lungs, pelvis, abdomen, or retroperitoneum. (14) Tumour size, involvement of lymph nodes (rarely seen in bone and soft tissue sarcomas) and metastases are key factors in the interpretation of oncological CT protocols. (17)

In addition, positron emission tomography (PET) helps to differentiate malignant structures from post-therapeutic residual structural abnormalities. (17) PET-CT scans of tumour masses combine functional and anatomical imaging findings.(14) Through positron emitting radionuclides the tumour´s metabolism can be evaluated. The most commonly used tracer for PET-CT is 2-Deoxy-2-fluoro-D-glucose (FDG). Through increased accumulation of radioactive substances in neoplasms, it can be used to detect metastases or LRs and may serve as an evaluation-tool regarding response to neoadjuvant chemotherapy. (14)

In paediatric patients, US and MRI imaging techniques should be primarily used during follow-up, due to the fact that children show a higher sensitivity to radiation exposure than adults, thus being at higher risk for radiation induces carcinomas. (16, 18) For the initial staging, CT-scans are inevitable, though.

1.3.3 Biopsy

Patients with suspected STS or BS should be referred to specialised tertiary sarcoma centres for further diagnostics and treatment. Subsequent biopsy is important to rule out differential diagnoses, and to plan further treatment strategies. (19) Histologically, primary sarcomas can be differentiated from other, clinically similar presenting soft tissue and bone “pathologies” as hematoma, metastasis or osteomyelitis. (14) The variety of different biopsy procedures include the following: fine needle aspiration biopsy, core needle biopsy and open surgical biopsy, all having different benefits and disadvantages. While needle biopsies only allow to obtain a limited amount of tissue with the advantage of reduced tissue damage, open surgical biopsy needs more pre- and intraoperative planning, whilst allowing to obtain more tumour tissue. (19) In any case, the aim is to extract a representative tissue sample with minimal tissue damage. (19) Of note, image-guided biopsies are increasingly replacing open surgical biopsies in STS and BS. (14) Imaging techniques such as CT and US can be useful in order to increase

the diagnostic accuracy by allowing a more precise biopsy of the desired region. (16) Additionally, necrotic areas and blood vessels can be avoided with the intention of decreasing the risk of unrepresentative samples and haemorrhage. (16) Of note, malignant cells may be seeded along the biopsy tract, wherefore resection of the biopsy tract during definite surgery is routinely performed. (14)

1.3.4 Grading

Histological grading provides information about the tumour's dignity and thus its overall aggressiveness. The most commonly used grading system for STS are the FNCLCC system by the *French Fédération Nationale des Centres de Lutte Contre le Cancer* and the NCI by the *United States National Cancer Institute*. (2) The FNCLCC system uses a score which evaluates three different parameters: The amount of tumours necrosis, mitotic rate and tumour differentiation. (20) Each parameter is scored independently. In order to obtain the final grading, the scores are summed up. (20) The histological grading of the FNCLCC-system reaches from Grade 1 (total score: 2, 3) to Grade 3 (total score: 6, 7, 8). (2)
The NCI-system likewise ranges from grade 1 to grade 3. To receive an individual grade, the combination of cellularity, histologic type, mitotic rate and pleomorphism is used. Sarcomas are classified as either grade 2 or grade 3, depending on the amount of necrotic cells, with the cu-off value being 15%. (21) In BS, the tumour grading frequently depends on the histological subtype. (2) Moreover, prognosis of BS as osteosarcoma and Ewing's sarcoma is also based on the histological regression grade following neoadjuvant chemotherapy. (22) This Salzer-Kuntschik regression grade subdivides response to chemotherapy by the extent of necrosis within the tumour, with higher amounts of necrosis being associated with a better patient outcome. (22)

1.3.5 Staging

Staging is based on histological and clinical parameters and provides information about the tumour's extension. The most commonly used staging system for prognostic staging groups of STS is shown in table 1. It was developed by the *International Union against Cancer* and the *American Joint Committee on Caner* (AJCC). (23) It is based on the TNM-system as well as tumour grading. (23) The TNM-system is generally determined by three major factors: First, the tumour's depth of infiltration and diameter (T), second, lymph node metastasis (N) and third, distant metastasis (M). The system is used as basis for staging of STS (Table 1) and primary BS (Table 2) with soft tissue involvement. (23) According to the AJCC, a special characteristic about the staging in STS and BS is that the histopathological grade (G) is likewise taken into account and the impact of N-stage is low. (23)

Furthermore, the staging system by *Enneking et al.* may be used to stage BS and STS, which is shown in table 3. (24) Musculoskeletal sarcomas are staged from I to III. The first two stages are determined by the surgical grade of the tumour. They are further separated into two subcategories depending on the local tumour extension. Tumours with distant metastases enter in stage III. Apart from histological features, also clinical and radiographic features are included. The evaluated tumour staging influences further surgical procedures and the extent of tumour resection. (24, 25) A general diagnostic strategy for BS as proposed by the ESMO *(European Society of Medical Oncology*) is summarised in figure 1. (26)

Stage	**Primary tumour (T)**	**Regional lymph node (N)**	**Distant metastasis (M)**	**Histologic grade (G)**
IA	T1	N0	M0	G1, GX
IB	T2, T3. T4	N0	M0	G1, GX
II	T1	N0	M0	G2, G3
IIIA	T2	N0	M0	G2, G3
IIIB	T3, T4	N0	M0	G2, G3
IV	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

Table 1: AJCC prognostic stage groups for soft tissue sarcoma in the trunk and extremity, Tanaka K, Ozaki T. New TNM classification (AJCC eighth edition) of bone and soft tissue sarcomas: JCOG Bone and Soft Tissue Tumor Study Group. Jpn J Clin Oncol 2019; 49(2):103–7. (23)

Stage	Primary tumour (T)	Regional lymph node (N)	Distant metastasis (M)	Histologic grade (G)
IA	T1	N0	M0	G1 or GX
IB	T2 or T3	N0	M0	G1 or GX
IIA	T1	N0	M0	G2 or G3
IIB	T2	N0	M0	G2 or G3
III	T3	N0	M0	G2 or G3
IVA	Any T	N0	M1a	Any G
IVB	Any T	N1	Any M	Any G
	Any T	Any N	M1b	Any G

Table 2: AJCC prognostic stage groups for bone sarcoma in the appendicular skeleton, trunk, skull and facial bones, Tanaka K, Ozaki T. New TNM classification (AJCC eighth edition) of bone and soft tissue sarcomas: JCOG Bone and Soft Tissue Tumor Study Group. Jp Clin Oncol 2019; 49(2):103–7 (23)

Stage	Grade	Site	Metastasis
IA	Low (G1)	Intracompartmental (T1)	No metastasis (M0)
IB	Low (G1)	Extracompartmental (T2)	No metastasis (M0)
IIA	High (G2)	Intracompartmental (T1)	No metastasis (M0)
IIB	High (G2)	Extracompartmental (T2)	No metastasis (M0)
III	Any (G)	Any (T)	Regional or distant metastasis (M1)

Table 3: Enneking staging for malignant musculoskeletal tumors based on surgical grade, local extent, and presence or absence of metastasis, Jawad MU, Scully SP. In brief: classifications in brief: Enneking classification: benign and malignant tumors of the musculoskeletal system. Clin Orthop Relat Res 2010; 468(7):2000–2.(25)

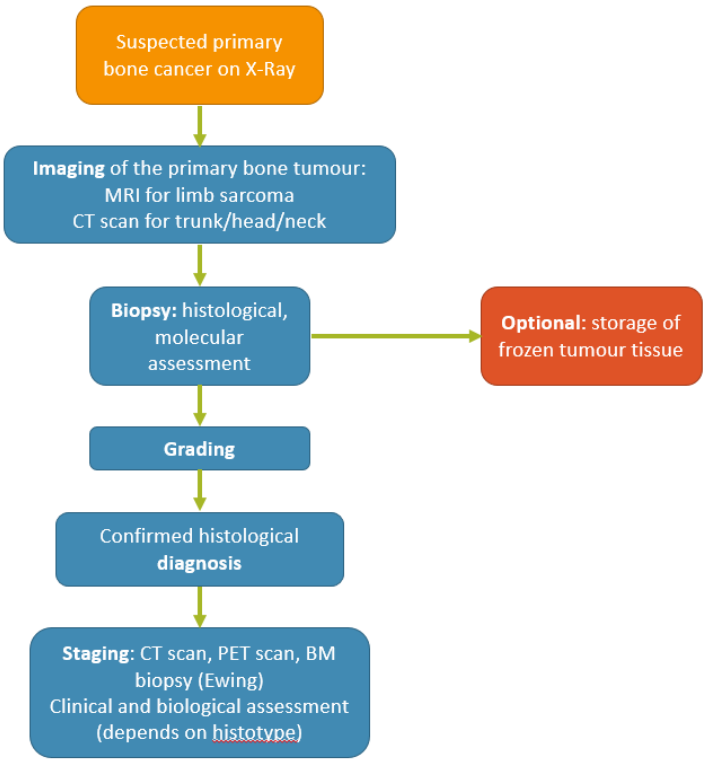


Figure 1: General diagnostic strategy for bone sarcomas. BM, bone marrow; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography. Casali PG, Bielack S, Abecassis N, Aro HT, Bauer S, Biagini R et al. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4):iv79-iv95. *(26)*

1.4 Tumour Entities

1.4.1 Osteosarcoma (OS)

Osteosarcoma (OS) is the most common primary malignant bone tumour, predominantly affecting children and young adults. (27) It constitutes an osteogenic tumour, producing osteoid or bony matrix. The tumour's subtypes are as follows: Conventional OS, telangiectatic OS, small cell OS, low grade central OS, high grade surface OS, periosteal OS, parosteal OS and secondary OS. (2) Out of these, conventional OS is the most frequent one. (2) The incidence is 4-5 cases per 1 million persons per year, with about 60% of patients being under the age of 25 years at the time of primary diagnosis. (28) OSs occur more frequently in men than women with a ratio of 1.3:1. They do not seem to be associated with any ethnic group or race. (29) The typical anatomical site is the metaphysis of long bones. OS frequently occurs in the distal femur, proximal tibia or proximal humerus. (27) Its exact aetiology is unknown. (2) Symptoms include local swelling, red skin, sleep-disturbing pain, pain not associated to weight-bearing or movement. (30) Other findings might include limited range of motion, localised hyperthermia or telangiectasia. (2) Sometimes, pathological fractures are the first "symptom". Radiographic appearance can be highly variable, ranging from osteoblastic to osteolytic, usually with periosteal reactions as Codman's triangle or sunburst phenomenon. (31) Around 15 to 20% of patients present with clinically detectable metastases at the time of diagnosis (32), with more than 85% of them being located in the lungs. Treatment strategies include neoadjuvant chemotherapy (CTX), followed by surgical removal of the primary tumour with wide margins as well as resection of metastases (if still present at re-staging). Subsequently, adjuvant CTX within internationally used treatment protocols, (27) like the EUROBOSS for patients older than 40 years or COSS , is applied. (33, 34)

1.4.2 Ewing´s Sarcoma (ES)

Sarcomas of the Ewing family are characterized by morphologically similar round neoplastic cells and include the ES, formerly Askin tumour (i.e. Ewing's sarcoma of the thoracic wall) and primitive neuroectodermal tumour. (2) Common chromosomal translocations – most frequently the t(11; 22) (q24; q12) – are observed, leading to specific gene fusions, as the Ewing's sarcoma gene with the Friend leukemia integration 1 transcription factor (EWS-FLI1). (35) The cellular origin of ES is still unknown. However, neuroectodermal cells or mesenchymal progenitor cells are currently believed to be the origin of these sarcomas. (35)

After OS and chondrosarcoma, ES is the third most common primary BS. Moreover, it is the second most frequent bone tumour in children and adolescents, accounting for about 10% of all primary malignant bone tumours in this age group. In addition, it occurs more often in males than in females with a ratio of 1.4:1. (36) Involvement of soft tissues is not uncommon. (36) ES typically arise in the diaphysis of long bones such as the femur or tibia, but can also be observed in flat bones. (35) Cases of ES in patients over the age of 40 are very rare, but also associated with less favourable prognosis. (37) Frequent symptoms include, pain, swelling and the development of a solid mass in an extremity. In addition, systemic symptoms as fever and night-sweat may be observed. In vicinity to neurovascular structures, ES may cause peripheral neurological symptoms (e.g. nerve palsy, hypesthesia). (36) Differential diagnoses in younger patients include osteomyelitis, rhabdomyosarcoma, medulloblastoma, neuroblastoma and lymphoma. (36) Delayed diagnosis is common. Typical misdiagnoses in young patients include coxitis fugax and osteomyelitis. (36) Treatment includes neoadjuvant CTX according to standardised protocols as the EURO-EWING 2012 protocol, followed by surgical removal and adjuvant CTX, again adhering to established protocols. Furthermore, radiotherapy is indicated in case of insufficient resection, irresectable tumours and tumours with poor chemotherapeutic response, as ES are considered radiosensitive. (35, 37)

1.4.3 Myxofibrosarcoma (MFS)

The term myxofibrosarcoma (MFS) refers to a connective tissue neoplasm of fibroblastic origin with variable myxoid stroma, pleomorphism and a vascularized pattern. (38) It shows a broad histological variety ranging from hypocellular myxoid tissue in low grade tumours to hypercellular fibrous histiocytoma-like tissue in high grade MFS. (39) They account for around 5% of all STS subtypes. (40) Moreover, MFS is most commonly seen in elderly patients, with a peak in the 7th decade of life. It mainly develops – similar to other STS subtypes – in the lower extremities (77%) and trunk (12%). (41) The tumour is described as a painless, slowly growing mass and may be either primarily superficial, later infiltrating through the fascia, or primarily deep, forming a distinct mass within the muscles. As with all STS and BS, MRI is used as the "gold-standard" diagnostic method as well as for preoperative planning. (40) As MFS have a high tendency to infiltrate surrounding tissues, resection should include a broader safety margin around the tumour than for other STS. (42) Resection with negative margins is indispensable. Surgery might involve vascular and plastic reconstruction in case vessels or large amounts of soft tissue have to be sacrificed. In rare cases, a limb-sparing procedure cannot

be performed, thus requiring amputation. Apart from surgery, radiotherapy can be used pre- or postoperatively, which may decrease the probability of later LR. (40)

1.4.4 Liposarcoma (LS)

Liposarcomas (LS) account for 9%-18% of STS cases and have the highest incidence around the 4th to 5th decade of life. (43) The anatomical sites most commonly affected are the extremities (52%) and retroperitoneal space (19%). (44) The tumour's characteristics and malignant potential differs strongly depending on the histological subtypes, being the following: Well-differentiated, dedifferentiated, myxoid, and pleomorphic liposarcoma. (43) Dedifferentiated and pleomorphic liposarcomas are regarded as high grade tumours, whilst the myxoid subtype is per tendency less aggressive. (44)

The dedifferentiated subtype accounts for nearly 18% of LSs and is characterised by a 12q14-15 amplification involving the MDM2 gene. (45) This subtype has a high risk to recur locally. (46) Metastases develop in about 18% of cases. (47)

The pleomorphic subtype accounts for less than 5% of all LSs, being the most infrequent subtype. It typically develops in elderly patients, with a slight male predominance. (48) Clinical examination shows a large, painless mass that develops over months, most commonly located in the lower extremity and underneath the muscular fascia. (48) This subtype sets metastases in 30% to 50% of patients. (48) Radiologically, it is described as a well-defined mass with heterogeneous appearance and necrotic areas. These areas of necrosis can also be seen microscopically, as well as pleomorphic epithelioid or spindled cells and adipocytic components. (48)

Microscopically, myxoid LS shows uniform round shaped non-lipogenic cells and small signet-ring lipoblasts with a branching vascular pattern. (49) This subtype is more prevalent in younger patients than the other subtypes, frequently occurring in the lower limbs. (50) Primary retroperitoneal origin is rarely seen (50) However, although most STS and LS-subtypes primarily spread to the lungs, the myxoid subtype also commonly sets metastases to rare regions as spine, bone, abdomen, or other soft tissues. (43)

1.4.5 Synovial Sarcoma (SS)

Synovial sarcoma (SS) is a mesenchymal spindle cell tumour with variable epithelial differentiation. (2) Of note, its appearance within a joint is very infrequent and, other than its name might suggest, it is not of synovial cellular origin. (51) In fact, the origin of synovial sarcoma is still unknown. (51) SS is defined by the presence of the t(X; 18) (p11.2; q11.2) translocation, which leads to the formation of SS18: SSX fusion proteins that can be detected in over 95% of cases. (52) SS account for 5% to 10% of STS with a slight tendency to occur more frequently in men, with a male to female ratio of 1.2:1. (53) It is most common in young adults under the age of 30 years, whilst in small children, SSs are a rarity. (52) The monophasic and biphasic subtypes appear with unequal age distribution. (51) SSs often grow slowly, causing pain and tenderness in over 50% of cases. Other symptoms might develop depending on the anatomical location of the tumour, as radiculopathies or restricted joint mobility. Upon radiological examination, it is described as a large and well-defined mass. (51) SS tends to recur locally and to develop metastases at a higher rate than other STS subtypes. (51) In detail, metastases are seen in up to 50% of SS-cases, especially affecting the lungs, pleura, bones and lymph nodes. (51) Multimodal treatment is the therapy of choice, combining surgery, CTX, and eventually radiotherapy. Due to the high recurrence rates even after several years of initial diagnosis, long term follow up is needed. (51) The 10 year survival rate is 10% - 30% and thus generally poorer than for other STS subtypes. (53)

1.5 Therapy

Treatment strategies of extremity sarcomas should be planned and discussed within a multidisciplinary team including orthopaedic sarcoma surgeons, radiologists, oncologists, pathologists, radiotherapists, physiotherapists and nurses. This team might seek further consultation with other specialists, if necessary. Treatment should be carried out by experienced specialists in tertiary sarcoma centres with a sufficiently high annual number of cases. (54) The abovementioned treatment options such as surgery, RTX, CTX, and targeted therapy are described in further detail in this chapter.

1.5.1 Surgery

Due to the variability of anatomical location of the tumour, patient's general condition and histological findings, surgical treatment strategies need to be adapted individually.

In STS, the main goal is surgical resection with wide margins. Exceptions include inoperable tumours, significant functional loss in case of limb salvage surgery, and patient's refusal. Wide, margin-negative resection is essential in order to reduce the risk of LR. (55) Within the group of extremity-STS, patients with superficial, low-grade tumours, smaller than 5 cm may be treated by surgical resection only. (56) In case of high-grade tumours, resection alone may not be adequate and should be accompanied by other treatment methods such as RTX or – in case of STS less frequently – CTX. (57) Amputations are rare, but may be necessary in case of extremely large tumours, anticipated functional loss of the affected extremity, or involvement of vital anatomical structures as main vessels and nerves. (55)

Similar to STS, the treatment goal of BS is to achieve en-bloc resection with negative margins while at the same time preserving functional abilities of the limb. Adequate resection is vital, as contaminated margin status is an important risk factor for LR. (58) Amputation used to be the standard treatment for BS until the 1970s. (59) Advancements in CTX protocols, imaging techniques, surgical approaches and endoprosthetic reconstructions have paved the way for increased limb salvage surgery rates. (59) Thus, nowadays limb salvage surgery can be performed in about 85% of OS in extremities, frequently followed by endoprosthetic reconstruction. (59, 60) Further reconstruction options include bone allografts and allograft–prosthetic composites. (12)

1.5.2 Radiotherapy (RTX)

In STS, radiotherapy is frequently used in combination with surgical resection. RTX can decrease the rate of LR and therefore allows for better local control. (57) The use of adjuvant or neoadjuvant RTX should especially be considered in intermediate and high-grade radio-sensitive STS as myxoid liposarcoma. (54) RTX may be applied preoperatively, intraoperatively, and/or postoperatively. (61) In preoperative settings, RTX is used in order to reduce the tumour's extent, therefore potentially facilitating later surgical resection. (55) Nonetheless, this setting is also associated with higher wound complication rates. (61) Postoperative RTX is generally associated with fewer postoperative complications due to better primary wound healing following surgery, but also causes higher local toxicity as the irradiated field is not resected, as it would be in case of neoadjuvant RTX. (55) In case of STS, it is still under debate when and who to administer RTX, and whether method or timing have a significant impact on the patient's prognosis. (61)

RTX plays a limited role in the treatment of primary BS. However, it and may be additionally used in cases of margin-positive resection or palliative settings. Furthermore, in ES, radiation alone can be an alternative to surgical resection, especially when surgery would lead to significant functional loss. (62)

1.5.3 Chemotherapy (CTX)

The role of CTX in BS and STS depends on the histological subtype, as biologic behaviour and the sensibility to CTX are variable. In general, however, CTX is far less effective in STS in comparison to BS, despite efforts to develop histology-tailored CTX and novel therapeutics. (63) Thus, CTX is currently far more often applied in BS than in STS, due to the better chemosensitivity. (64) However, according to the ESMO-EURACAN clinical practice guidelines as shown in the figure 2, CTX is the method of choice for the management of metastatic, primarily unresectable STS.

CTX is applied in two major settings. (65) Adjuvant CTX, coming from the latin word "adjuvare", i.e. to help or aid, is the name originally given to the postoperative treatment of micro-metastatic deposits of solid tumours with CTX. In contrast, neoadjuvant CTX complemented by the prefix "*neo*-", meaning "new", describes the chemotherapeutic treatment of primary solid tumours too large for primary surgical excision and is used preoperatively. (66) In selected cases, adjuvant CTX can improve disease free survival and overall survival, and can decrease LR rates. Neoadjuvant CTX, in combination with radiological imaging, is a

valuable tool for assessment of the tumour´s histological response to CTX. (65) Furthermore, surgical excision might be more feasible following neoadjuvant CTX, due to potential shrinking of the primary tumour. (65)

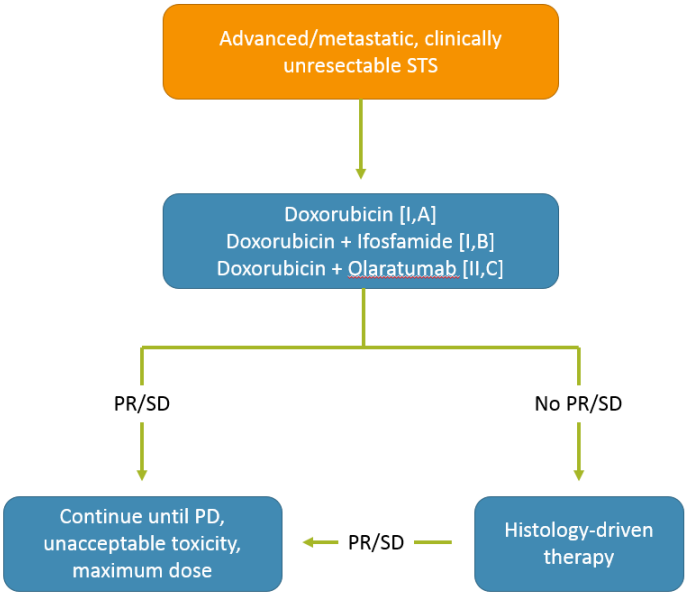


Figure 2: Management of advanced/metastatic, clinically unresectable STS. Olaratumab (if used) to be maintained as single agent after reaching the dose-limiting toxicity of doxorubicin. PD, progressive disease; PR, partial response; SD, stable disease; STS, soft; Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4):iv51-iv67. (67)

In contrast to metastatic STS, for localized, clinically resectable STS < 5 cm, the ESMO-EURACAN guidelines recommend primarily surgical resection with or without RTX. Patients with larger, grade II or grade III STS are at greater risk of LR or metastasis, thus preoperative CTX or RTX should be considered. (67) Concerning treatment of BS, CTX plays an important role in the primary therapy of ES and OS. On the other hand, the BS-subtype chondrosarcoma is insensitive to CTX. As an example, current treatment regimens for OS consist of multimodal neoadjuvant (preoperative) CTX, surgical resection and adjuvant (postoperative) CTX. Side effects of these highly-toxic therapeutic protocols might include azoospermia, subclinical renal insufficiency, and hearing impairment. (64) Previous to the routine administration of CTX, metastases were detected in about 85% of patients following curative resection, resulting in a long term survival rate below 20%. (68) Due to the introduction of multiagent CTX regimens, however, long term survival rates have increased to nearly 80%. (27)

1.5.4 Targeted therapy

Targeted therapy is an area of great interest in cancer research in general and has recently been discussed in numerous studies and reviews regarding their therapeutic role in sarcoma. (69) Recent advances in immunotherapy and targeted therapy offer exciting new strategies for cancer treatment. Despite the fact that CTX remains an essential backbone of sarcoma treatment strategies, new developments may offer a more personalized therapeutic approach. (69) In targeted therapy, treatment depends on the tumour's specific molecular characteristics rather than its histological or clinical appearance. (70) By interfering with specific molecules which are related to the tumour's development and progression, targeted therapeutic drugs block specifically the tumour's growth, progression or metastasis formation. Targets can be reached intracellularly, by small molecular drugs or extracellularly, by using monoclonal antibodies. Various targeted therapies have already proofed useful in cancer treatment, such as signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immune checkpoint inhibitors, and toxin-delivery molecules. (71) Common pathway inhibitors are receptor tyrosine kinase inhibitors, mTOR (mechanistic target of rapamycin) inhibitors or Hedgehog pathway inhibitors. (72) The current limitations of this type of treatment lie in the heterogeneity of response between the tumour types and even within the same tumour entities, as well as differing mechanisms of treatment resistance and the lack of predictive biomarkers. (73) As a result, combinations of chemotherapy with multi-targeted agents are currently investigated. The usage of immune checkpoint inhibitors in advances STS is an active area of research and could potentially expand current treatment options. (73) Immune checkpoint inhibitors against PD-1/PD-L1 draw a lot of attention, as PD-L1 overexpression is observed in about 65% of STS and BS subtypes. (74) Possible treatment options currently under research include Nivolumab, an IgG4 anti-PD-1 monoclonal antibody or Ipilimumab, an anti-CTLA-4 therapeutic monoclonal antibody. (74) The protein receptor CTLA-4 is expressed on T cells and downregulates T cell activation. Due to its similarity to CD28, it competes on binding to the same membrane proteins (CD80/86) of dendritic cells, therefore silencing immune response. (75)

1.6 Ankle region

The close contiguity between individual anatomic structures is a distinctive characteristic of the ankle region. Numerous bones, epiphyses, cortices and muscles with missing fascial barriers along with the vascular and lymphatic network complicate sarcoma surgery in the ankle region. Despite the fact that general management principles recommend a wide resection with 1-2 mm margins, this might not always be feasible in ankle sarcomas. (4) The ankle region consists of four main anatomical compartments, with the posterior tibial artery, vein and nerve in the medial compartment and the dorsalis pedis artery in the anterior compartment. The tibial nerve is predominantly responsible for the motoric innervation of the plantar area of the foot. Neurovascular structures of the foot and ankle have to be preserved in order to avoid neurological and vascular damage, or even functional loss. (76) Regarding the anatomical structures of the ankle region, one should also be aware of the anterior and posterior neurovascular bundle crossing the ankle joint. These two bundles regularly complicate surgical approaches as they contain nerves and vessels supplying the foot. (77) In case of an anterior surgical approach to the ankle, for example, a precise incision is very important as the anterior neurovascular bundle as well as the branches of the superficial peroneal nerve cross the ankle in proximity to the skin incision line. (78) Proximal to the ankle joint, the anterior neurovascular bundle (deep peroneal nerve and anterior tibial artery) is located between the tibialis anterior and extensor hallucis longus muscles. Distal to the joint, it runs along the extensor hallucis longus and the extensor digitorum longus tendons. The posterior neurovascular bundle is located between the flexor digitorum longus and flexor hallucis longus muscles. (77) Moreover, three groups of ligaments can be found around the ankle. The anterior talofibular ligament, a part of the lateral ligament complex, is the most commonly injured one and therefore frequently the cause for medical consultation. (79) During physical examination, common symptoms caused by ankle sarcomas include local pain during movement, neurological deficits and local swelling. (4) The authors of a recent study pointed out that the most prevalent malignant bone tumour types in their study group of ankle sarcomas were chondrosarcoma (48,6%), osteosarcoma (17,1%) and Ewing sarcoma (14,3%). (1) According to the same study, the most prevalent malignant soft tissue tumours in the foot and ankle region were synovial sarcoma (23,2%), myxofibrosarcoma (18,6%), and leiomyosarcoma (4, 9,3%). (1) With the intention of demonstrating the area affected by sarcomas of the ankle region, a 3D model of an OS affecting the ankle region, shown in figure 3, has been printed by the diploma student.

Figure 3:3D model, OS affecting the ankle region

2 Methodology

2.1 Research design and questions

The aim of the retrospective part of the present study was to collectively analyze all patients treated at the *Department of Orthopaedics and Trauma, Medical University of Graz, Austria*, for sarcomas of the ankle region with specific focus on postoperative complications. In the prospective part of this study, the case series was described analytically. The aim of the prospective part was to investigate the quality of life and functional outcome after surgery of ankle sarcomas in patients treated at the study centre (*Department of Orthopaedics and Trauma, Medical University of Graz, Austria*). Data was collected by using standardized questionnaires. In addition, parameters for postoperative functionality and mobility were collected through clinical examination. Of note, case studies are suitable for a patient group with a specific rare disease, but on the other hand, the lack of a control group makes this study type eligible for descriptive purpose only. (80)

2.2 Data collection

The data for the retrospective part was collected from the database of the *Department of Orthopaedics and Trauma, Medical University of Graz, Austria*. In total, 24 patients were included in the retrospective part, treated between 1998 and 2017. Data ascertained included personal details, contact information (both deleted after having had contact with patients for the prospective part), lifestyle indicators, BMI, diagnosis, tumour characteristics, date and type of surgery, neo-/adjuvant CTX, neo-/adjuvant RTX, postoperative immobilization and mobility, postoperative complications, second, third, fourth reoperation and/or complication, secondary metastasis, palliative treatment, last known condition (alive/death), and date of last follow up. In order to obtain the data depicted in the prospective part, patients were subsequently invited to another medical consultation, clinical examination and filling-in of questionnaires at the study centre. Each patient had to give consent in order to be invited to the study centre and needed to sign an informed consent form prior to clinical investigation. Clinical examination included gait analysis, joint mobility at the involved limb, analysis of scars, peripheral circulation, motor activity and sensibility. Based on the questionnaires mentioned below (and in the appendix), parameters indicative of postoperative functionality and quality of life were collected. For this purpose, the following questionnaires were used: TESS (Toronto Extremity Salvage Score), University of California Los Angeles activity scale (*UCLA*) Rating System, EQ-5D-5L + EQ-VAS, PLUS-M (Prosthetic Limb Users Survey-M), Modified weight activity score, PROMIS (Patient-Reported Outcome Measurement Information System) and FLZ (Fragebogen zur Lebenszufriedenheit). Questionnaires in English were orally translated if necessary.

TESS (Toronto Extremity Salvage Score): This score is patient-based and has been designed to assess the functional outcomes and physical disability of patients undergoing surgery for musculoskeletal tumours. (81)

UCLA Rating-System (University of California at Los Angeles): The UCLA Rating-System uses a questionnaire where patients have to tick one statement that fits best to their current situation, in order to describe their activity level reaching from 1. “Wholly inactive, dependent on others, and cannot leave residence” to 10, “Regularly participates in impact sports”. (82)

EQ-5D-5L: This test consists of two parts, namely the EQ-5D and the EQ-VAS (Visual analogue scale). The descriptive system comprises 5 dimensions with 5 levels each: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-VAS asks patients to fill in their self-related health on a vertical visual analogue scale from "The best health you can imagine" to "The worst health you can imagine".(83)

PLUS-M: The Prosthetic Limb Users Survey of Mobility was developed to assess the mobility of adults with lower limb amputation. There are 12 questions to be answered by the patient. The score can be applied several times in order to evaluate the patient's progress. (84)

MWAS: Modified weight activity score: (sports/hours per week): This score is measured by ascertaining all types of physical activity the patient practices. (85)

PROMIS: The Patient-Reported Outcome Measurement Information System test, has been designed to evaluate and monitor physical, mental and social health both in children and adults. (86)

FLZ: This test measures patient's satisfaction in various areas of their life, including: Health, working life, financial state, leisure time, partnership, relationship with your children, yourself, sexuality, social relations and residence. (87)

For statistical analysis, a scoring system in numbers was designed for some questionnaires: UCLA: according to the questionnaire (see appendix); TESS: according to the questionnaire (see appendix); PROMIS: according to the questionnaire (see appendix); PLUS-M: according to the questionnaire MWAS: according to the questionnaire (impact score x hours x times per week, see appendix); EQ-5D-5L:"I do not experience any problems" (5 points) – "not able to do" (1 point) FLZ: "very unsatisfied" (1 point) – "very satisfied (7 points); Concerning the FLZ, the score shown in table 9 equals the average mean of all sections which were answered by the patient.

2.3 Participant selection (retrospective and prospective part)

Potential study participants were selected from a prospectively maintained database at the study centre. The collected data included all patients treated between 1998 and 2017 at the study centre for primary bone and soft tissue sarcomas of the ankle joint (including talus, calcaneus, ankle joint and distal tibia/fibula). Patients had undergone either limb-salvage surgery or amputation. This long period of retrospective analysis was chosen due to the low incidence of ankle sarcomas. Table 4 depicts all cases that were included in the retrospective part.

In order to obtain the data discussed in the prospective part of the study, patients were invited to another medical consultation, clinical examination and questionnaire-completion. The study protocol was permitted by the Ethics Committee of the Medical University of Graz (EK-Nr. the 31-054 ex 18/19). At the time of consultation, out of 24 patients, 10 were no longer alive according to the database. These patients are marked in grey in table 4. In total, 11 patients were invited (first by letter, then by phone) to participate in the prospective part, out of which 7 agreed on participation. Out of the remaining possible candidates, two initially declined participation, whilst two did not attend the first study-specific appointment and refused to book another appointment. Furthermore, one patient did not respond to the given calls, and two could not be contacted due to missing contact information.

Tumour Type	**Grade**	**Size** (mm)	**Localisation (nearest anatomical region)**
Osteosarcoma	G3	25	Posterior calcaneus
Leiomyosarcoma	G2	20	Achilles tendon
Chondrosarcoma	G2	58	Calcaneus
Osteosarcoma	G3	62	Distal tibia
Ewing's sarcoma		50	Calcaneus
Ewing's sarcoma		38	Distal tibia
Ewing's sarcoma		55	Distal tibia
Atypical lipomatous tumour	G1	190	Lateral ankle region
Liposarcoma	G3	160	Distal lower leg + upper ankle joint
Chondrosarcoma	G1	15	Medial distal tibia
Myxoid liposarcoma	G2	60	Behind medial malleolus
Myxofibrosarcoma	G3		Upper ankle region
Synovial sarcoma, monophasic fibrous	G3	32	Sinus tarsi
Synovial sarcoma, monophasic	G3	40	Lateral ankle region

Osteosarcoma	G3	120	Distal tibial metaphysis
Synovial sarcoma, monophasic fibrous	G3	130	Planta pedis
Osteosarcoma	G3		Calcaneus
Spindle cell sarcoma	G3	140	Dorsal ankle region
Myxoid liposarcoma	G3	2	Distal tibia
Myxofibrosarcoma	G3	80	Distal of malleolus lateralis
Synovial sarcoma	G3	90	Malleolus lateralis
Fibroblastic osteosarcoma	G3	35	Calcaneus
Ewing's sarcoma		43	Distal tibia
Synovial sarcoma, monophasic fibrous	G3	45	Planta pedis (ventral of calcaneus)

Table 4: Retrospective case study data, showing tumour type, grading, size and location. Cases marked in grey are no longer alive.

2.4 Data Analysis

For data collection and statistical analysis, Microsoft Excel Windows 2013, and IBM SPSS Statistics, Version 26.0, respectively, were used. Results were accepted significant with a p-value of 0.05 or below. To evaluate the relationship between two categorical variables, Pearson's chi squared test and Phi/Cramer-V was used. Scalar, non-parametric variables were evaluated through the Mann-Whitney-U test. In order to define the mean, variance, SD, minimum and maximum of a continuous variable, explorative analysis was performed. With the aim of obtaining a T-score metric, the available data of the questionnaires was converted and standardized within itself using Microsoft Excel 2013. As such, a score of 40 is one SD lower, a score of 60 is one SD higher than the average mean of 50 in the T-score metric. Scores of the various questionnaires were converted into percentages to better illustrate the results. A Score of 100% therefore equals the best functional, mental or physical health status possible in each questionnaire. In addition to the data analysis, a 3D model of an OS affecting the ankle region with a size of 17cm, shown in figure 3, was printed by the diploma student, with the intention to demonstrate the potential area affected by sarcomas of the ankle region. Therefore, a CT scan, available on www.embodi3d.com has been converted into a 3D model (.slt file) and was later on adapted through Blender 2.8. With kind support of the Digital Culture Laboratories Hirikilabs, Donostia - San Sebastian, the 3D Model was printed using the scaling software Ultimaker Cura 4.0 and an Ultimaker 2+ 3D printer.

3 Retrospective Part

3.1 Study group

All patients treated for BS and STS of the ankle joint (including talus, calcaneus, ankle joint and distal tibia/fibula) between 1998 and 2017 at the *Department of Orthopaedics and Trauma, Medical University of Graz* were analysed. Patients had undergone either limb-salvage surgery or amputation. Participants were subsequently assigned to one of the two study groups depending on the surgical procedure, i.e. LSG (limb salvage group) and AG (amputation group).

		Limb-salvage	Amputation	Total
Female		6	7	13
	% within group	46.2%	63.6%	54.2%
Male		7	4	11
	% within group	53.8%	36.4%	45.8%
Total		13	11	24
	% within gender	54.2%	45.8%	100.0%

Table 5: Patient Cohort, Gender

			Limb-salvage	Amputation	
Sarcoma	Bone		7	4	11
		% within group	53.8%	36.4%	45.8%
	STS		6	7	13
		% within group	46.2%	63.6%	54.2%
Total			13	11	24
		% within Sarcoma	54.2%	45.8%	100.0%

Table 6: Patient Cohort, BS vs. STS

As visible in table 5, our study group included 13 (54.2%) female and 11 (45.8%) male patients, out of which 13 were treated with a limb-salvage procedure and 11 underwent amputation. Of note, one patient primarily underwent limb-salvage surgery, but later on required amputation due to postoperative complications. Furthermore, table 6 depicts treatment groups split by BS vs. STS. At the time of surgery, the average age of patients was 44 ± 26.6 years (range, 8 to 94) and the preoperatively measured BMI was 24.1 kg/m2 ± 4.8 (range, 14 to 30 kg/m^2).

3.1.1 Tumour Type, Grading, Size

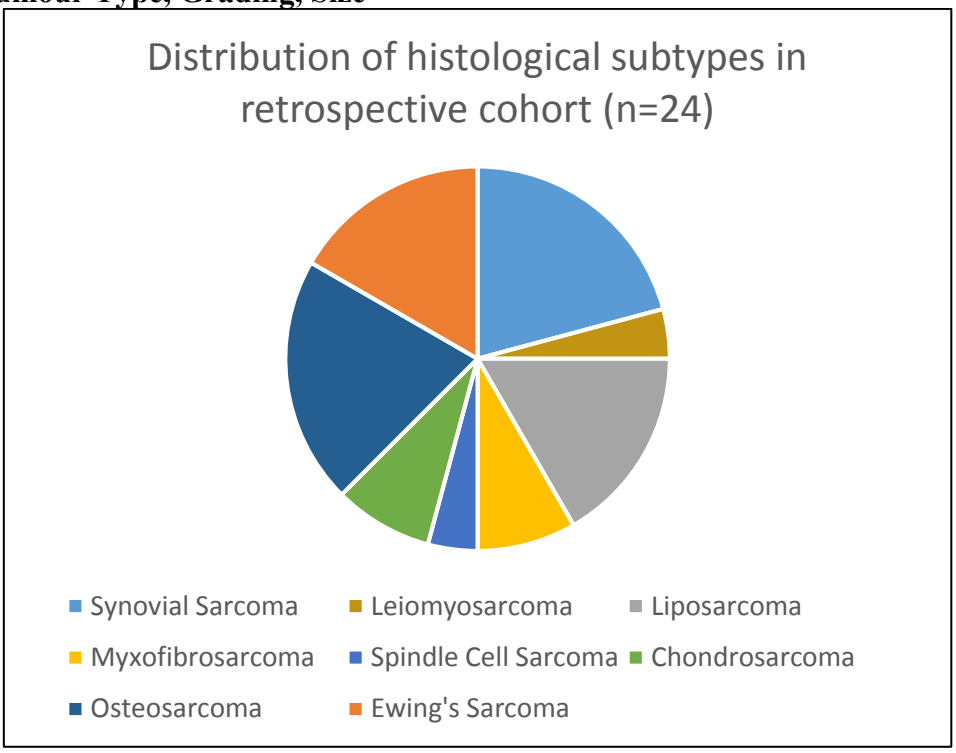


Figure 4: Distribution of histological subtypes in retrospective cohort

Figure 4 depicts the frequency of the histological subtypes. Synovial sarcomas (n=5) and osteosarcomas (n=5) accounted for 20.8% of cases each. Furthermore, 16.7% each were liposarcomas (n=4) or Ewing´s Sarcomas (n=4). Other tumour types including chondrosarcoma (n=2), myxofibrosarcoma (n=2), leiomyosarcoma (n=1) and spindle cell sarcoma (n=1) occurred less frequently.

	Grade				Total
	unknown	G1	G2	G3	
Limb salvage	3	2	2	6	13
Amputation	1	0	1	9	11
Total	4	2	3	15	24

Table 7: Patient Cohort, Grading

Table 7 depicts the distribution of tumour grade between the two study groups. In the amputation group, 9 tumours (81.8%) were G3, accounting for 60% of all G3 sarcomas. The overall average tumours size was 6.7 cm. Categorized into three groups, 11 tumours (45.8%) were < 5 cm, 6 tumours (25%) were between 5 - 10 cm, and five (20.8%) tumours were >10 cm. Furthermore, two sarcomas were of unknown size. Tumours in the calcaneus were the smallest, with an average size of 4.2 cm (SD ± 1.5 cm). The highest average tumour size was seen for sarcomas in the distal fibula with a mean of 9.0 cm and the ankle region itself with a

mean of 9.3 cm (SD ± 6.5 cm). Tumours in the distal tibia had an average size of 4.8 cm (SD ± 3.8 cm) and in the planta pedis an average size of 8.8 cm (SD ± 6.0 cm).

3.1.2 Survival

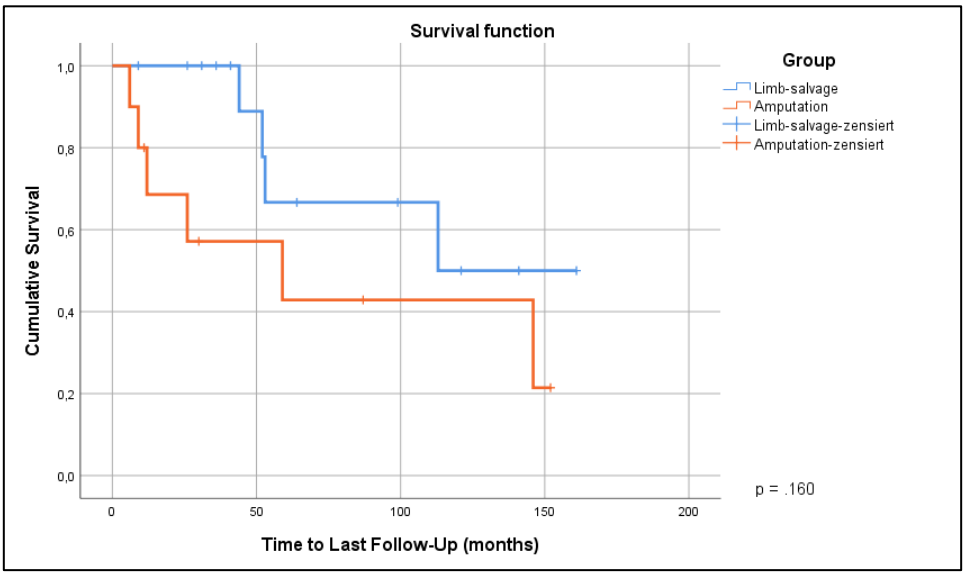


Figure 5:Kaplan-Meier survivorship curve showing difference in overall survival between Limb-salvage and Amputation.

After 5 years, 67% of patients in the LSG were still alive, as compared with 43% of patients in the AG. The shape of the graph indicates a per tendency better survival rate in the limb salvage group, although not statistically significant (p = .160, Log Rank Test).

3.2 Complications

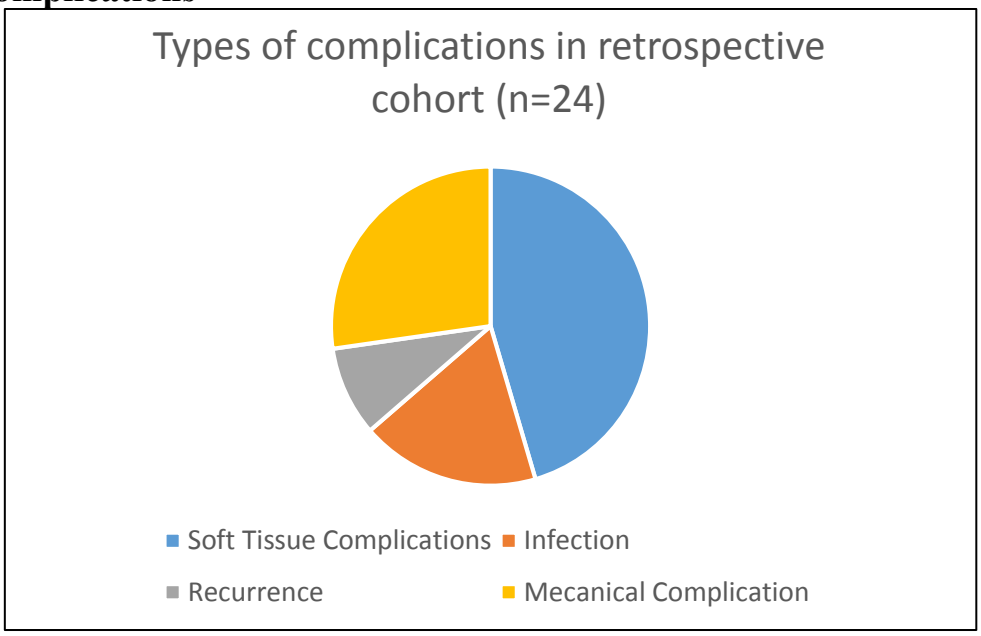


Figure 6: Patient Cohort, type of complication

Figure 6 shows the different postoperative complications after the first surgery, clustered into categories. 46% of complications were soft tissue complications (n=11) such as wound healing deficits, ulcerations, venous thrombosis and haematomas. Moreover, 27% were mechanical

complications (n=7) including postoperative joint luxation, pain, and pseudoarthrosis. Postoperative wound infection occurred in 18% of cases (n=4). Moreover, 9% of patients experienced a LR (n=2).

3.2.1 Primary complication risk

Cross tabulation					
			group		
			Limb-salvage	Amputation	Total
Complication	No	Count	3	9	12
		% within complication	25.0%	75.0%	100.0%
	Yes	Count	11	1	12
		% within complication	91.7%	8.3%	100.0%
Total		Count	14	10	24

Table 8: Chi-square test, analysis depicting primary complications after the first surgery within limb-salvage vs. amputation

Table 8 depicts the percentage of complications and reoperations for the two study groups (limb salvage vs. amputation). Of note, only complications and reoperations after the first surgery are presented. Overall, 91.7% of complications occurred in the LSG, signifying that patients in this group experience complications more often than patients in the AG ($p = 0.001$; Chi-square test: $\chi^2 = 10.791$; Large effect size: Phi = .676). Moreover, out of 12 patients who experienced complications after their first operation, 4 patients (33.3%) developed subsequent complications. Notably, all patients experiencing complications after their first surgery had to be operated again.

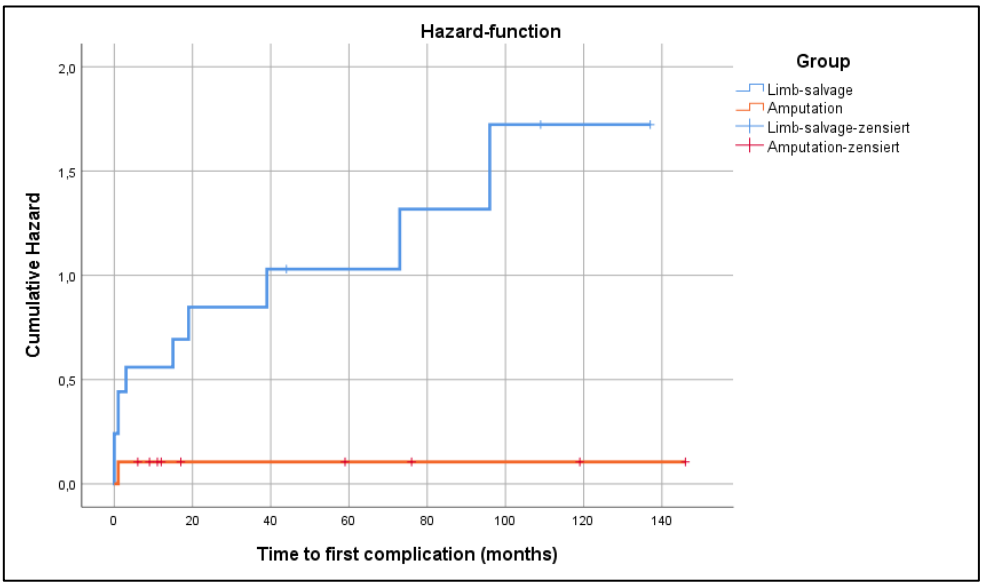


Figure 7: Kaplan-Meier curve depicting the hazard function of experiencing a complication.

The risk of experiencing the first postoperative complications after surgery was significantly higher in the LSG in comparison to the AG (p = .013, Log Rank Test, figure 7).

In order to assess whether factors other than the type of primary surgery may increase the risk of postoperative complications, several parameters were analysed. In the current study, two significant results – for margins and gender - were found.

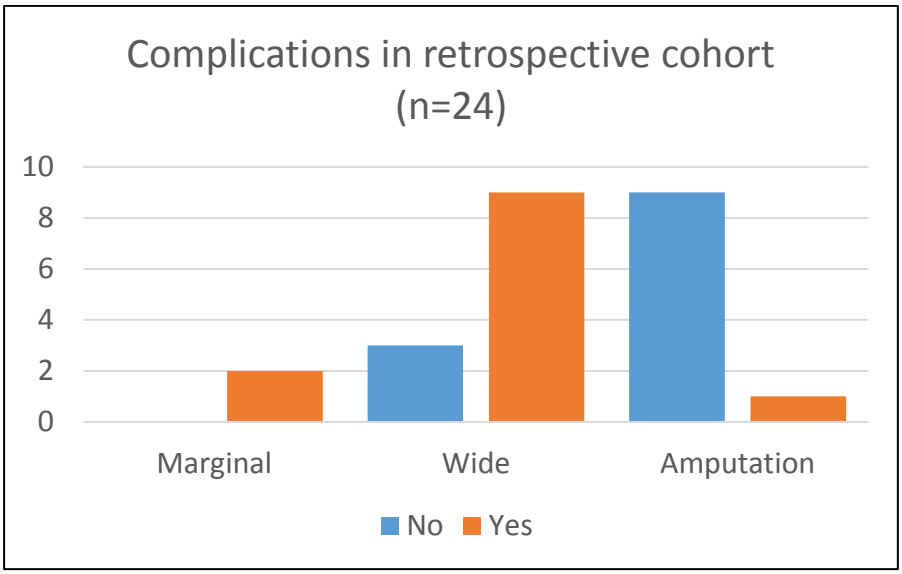


Figure 8: Diagram depicting the correlation between postoperative complication and margins.

Two patients had been treated through a marginal excision and later on developed complications (Figure 8). Furthermore, 9 out of 12 patients treated with wide resection developed postoperative complications. In contrast, this was true for only one out of 10 patients who underwent amputation. (p = .003; Chi-square test: $\chi^2 = 11.400$, Large effect sizes: Phi = .689)

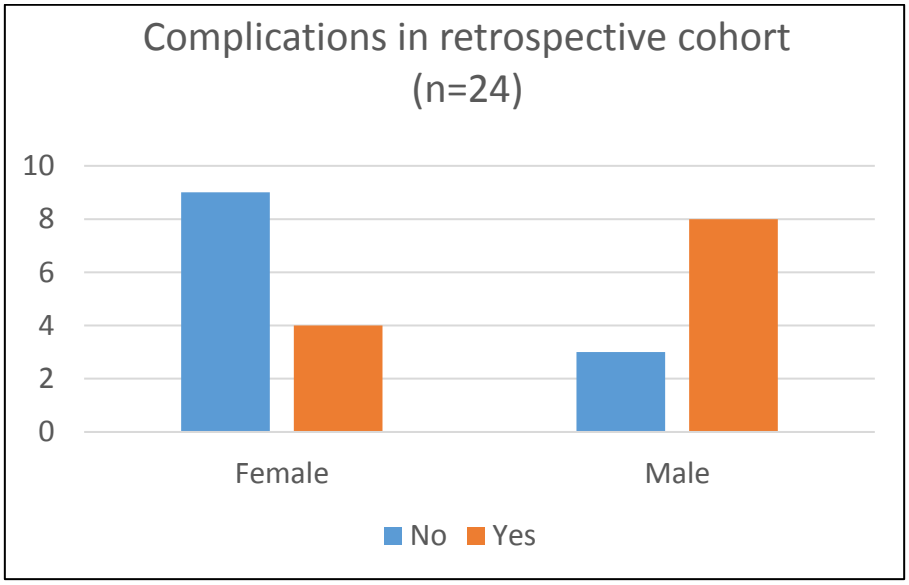


Figure 9: Diagram depicting the correlation between postoperative complication and gender.

There was also a gender-specific difference in terms of postoperative complications, with 8 of 11 males (72.7%) developing complications, in comparison to 30.8% of female patients (4 of 13; Figure 9; Chi-square test: $\chi^2 = 4.196$, $p = .041$; Medium effect sizes: Phi=.418).
Furthermore, the maximum number of potential re-operations in each patient was investigated (Figure 10).

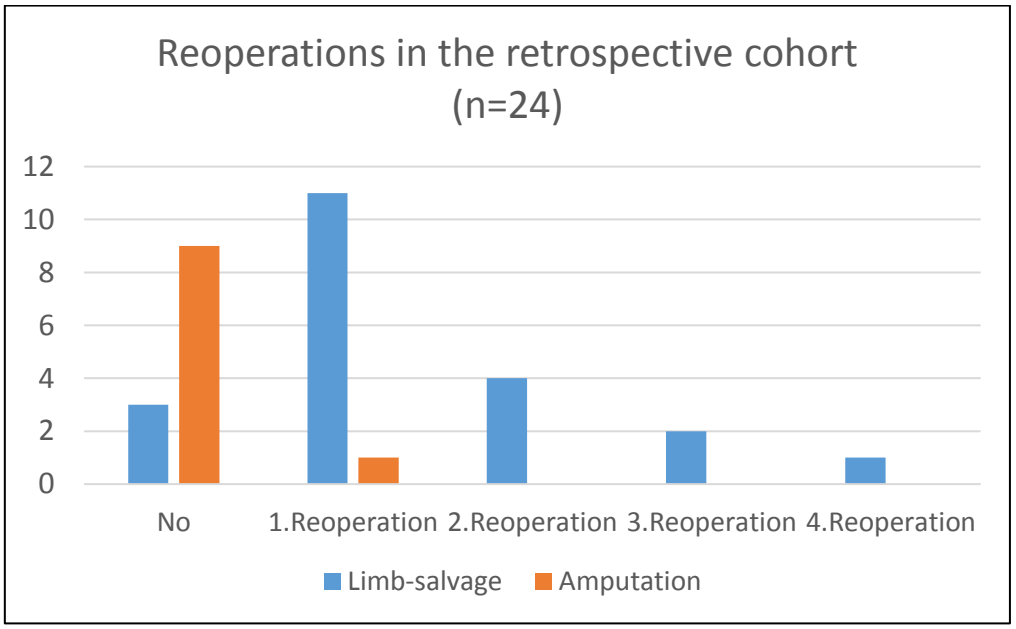


Figure 10: Diagram depicting the number of patients who underwent reoperations

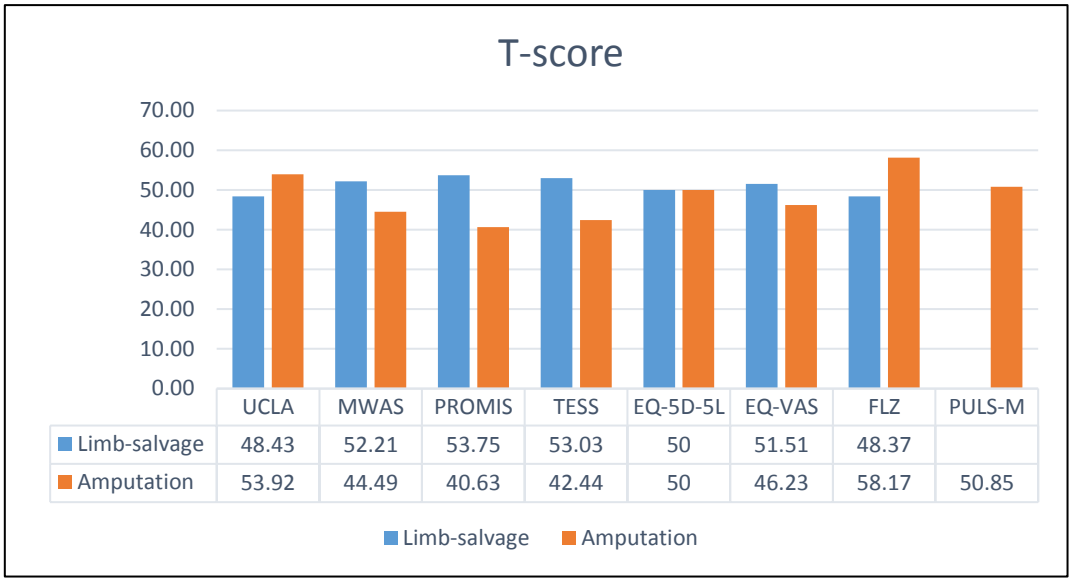
The vast majority of primary re-operations occurred, as mentioned above, in the LSG. Whilst patients with limb salvage required up to 4 further re-operations, none of the patients in the AG necessitated another revision surgery after the first one.

4 Prospective Part

4.1 Questionnaires

A significant correlation was found between TESS and PROMIS ($r = .91$; $p = .004$) as well as between the TESS and EQ-VAS ($r = .85$; $p = .016$). In addition, tendencies between the UCLA and MWAS ($r = .73$; $p = .06$), the MWAS and PROMIS ($r = .685$; $p = .089$), the MWAS and TESS ($r = .69$; $p = .087$), as well as the EQ-5D-5L and EQ-VAS were discovered ($r = .73$; $p = .063$). The overall mean value for each questionnaire was as follows: UCLA: 4.9 (SD ±1.8); MWAS: 4.6 (SD ± 3.6); PROMIS: 39.6 (SD ± 7.0); TESS: 77.3 (SD ±16.1); EQ-5D-5L: 22.0 (SD ± 3.2); EQ-VAS: 66.4 (SD ±18.4); FLZ 39.7 (SD ± 5.4).

4.2 Questionnaire results and analysis



	UCLA	MWAS	PROMIS	TESS	EQ-5D-5L	EQ-VAS	FLZ	PULS-M
Limb-salvage	48.43	52.21	53.75	53.03	50	51.51	48.37	
Amputation	53.92	44.49	40.63	42.44	50	46.23	58.17	50.85

Figure 11: Diagram showing results of both study groups on the T-score metric

As the T-scores rather served for viewing purposes, no statistical analyses were performed to assess differences between the limb salvage surgery- and amputation-groups. Figure 11 depicts the mean T-score metrics of the different questionnaires split by the study groups (LSG vs. AG). The UCLA Activity Score was average in both groups (LSG vs. AG; 48.4 vs. 53.9). Modified weight activity score was 52.2 in the LSG and 44.5 in the AG. For the PROMIS, a difference of one SD between the T-score of the LSG (53.7) and the T-score of the AG (40.6) was found. In addition, TESS scores did also differ by one SD between the LSG (53.0) and the AG (42.4). For the EQ-5D-5L, a mean T-score of 50.0 was found in both study groups. Slight differences were observed in the visual analogue scale with 51.5 in the LSG versus 46.2 in the AG. In the FLZ questionnaire, results showed a T-score of 48.4 in the LSG. In the AG, only one result was measured, which accounted for 58.2, equivalent to a difference of one SD. The PLUS-M questionnaire was developed to assess the mobility of adults with lower limb amputation and resulted in an average T-score of 50.9 for amputees in our cohort, which corresponds to the 53.4% percentile. To sum up, the data indicates a difference beyond average (of about one SD) between the median of the two study groups in the questionnaire results measuring physical ability (PROMIS: M_{LSG}=53.7 vs. M_{AG}=40.6), physical disability (TESS: M_{LSG}=53.0 vs. M_{AG}=42.4) and general life satisfaction of patients (FLZ: M_{LSG}=48.4 vs. M_{AG}=58.2).

4.2.1 Analysis

In order to detect significant differences between the crude questionnaire results in the LSG versus AG, Mann-Whitney-U tests were used. As shown in table 9 no significant difference between the two groups was found for the respective questionnaires.

	LSG median	**AG median**	**Range**	**p-value (Mann-Whitney-U-Test)**
UCLA	4.0	5.4	0 - 8	p =.381
MWAS	5.0	2.625	0 – 10.75	p = .571
PROMIS	44	33.5	31 - 49	p =.190
TESS	82.1	66.05	54.7 - 100	p = .381
EQ_5D_5L	24	22	18 - 25	p = .857
EQ_VAS	70	60	40 - 95	p = .571
FLZ	40.71	43.7	29.6 – 43.9	p = .667

Table 9: Median and range of questionnaire scores for LSG and AG, compared with Mann-Whitney-U test-

4.3 Physical status

Range-of-motion parameters for postoperative functionality and mobility were collected during clinical examination, focussing on the foot, ankle and knee (Table 10).

Range of Motion (ROM) (°)			
	Median	**Range**	**Standard Values**
Dorsal extension	20°	0 - 20°	20–30°
Upper ankle joint Neutral	0°	0	0°
Plantar flexion	20°	10 - 40°	40–50°
Pronation	10°	0 - 35°	15°
Neutral	0°	0°	0°
Supination	10°	0 - 40°	35°
Knee Extension	0°	0°	5–10°
Knee Neutral	0°	0°	0°
Knee Flexion	120°	100 - 140°	120–160°

Table 10: Range and median range of Motion (ROM) of patients in prospective patient cohort, Given in degrees (°). Standard values derive from the Waldeyer textbook and atlas of anatomy *(88).*

Wound conditions were inconspicuous in all 7 patients during clinical examination. All were fully weight bearing at final follow-up. One patient had a forefoot-elevation weakness, thus requiring an orthesis. Due to the small sample size (n=7), a comparison between groups with regards to range of motion was not performed. The standard values in table 10 are described according to the *Waldeyer textbook and atlas of anatomy*. (88) The calculated average mean ROM (°) in our group differed with regards to plantar flexion from standard values (median: 20° vs. standard: 20°-30°), supination (median: 10° vs. standard: 35°). Of note, values for ankle and foot mobility could only be assessed in patients with limb salvage surgery.

4.4 Case presentation

Patient ID 14

Patient 14 was a male, 77-year-old, patient undergoing amputation at the middle third of the lower leg due to myxoid liposarcoma, grade 2. The tumour was sized 6.0 cm and localized behind the medial malleolus of the right foot, with the pronounced soft tissue shadow visible on the x-ray. Amputation was chosen due to the proximity to neighboring structures. Gentle full mobilisation was possible directly after the operation. He did not develop any postoperative complications until the most recent follow-up, 3 years after surgery.

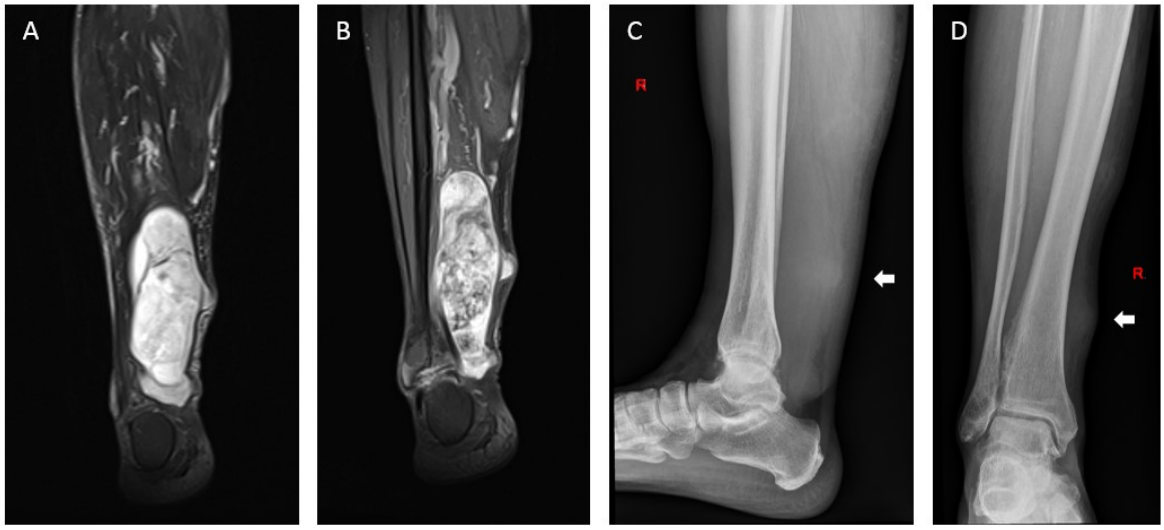


Figure 12: Sagittal T2-weightes fat-suppressed MRI scan (T2) of an myxoid liposarcoma at the right lower leg (A) and sagittal T1-weighted MRI scan with contrast agent (B). X-Ray of the lower foot, with the arrow pointing at the soft tissue shadow caused by the myxoid liposarcoma.(C, D)

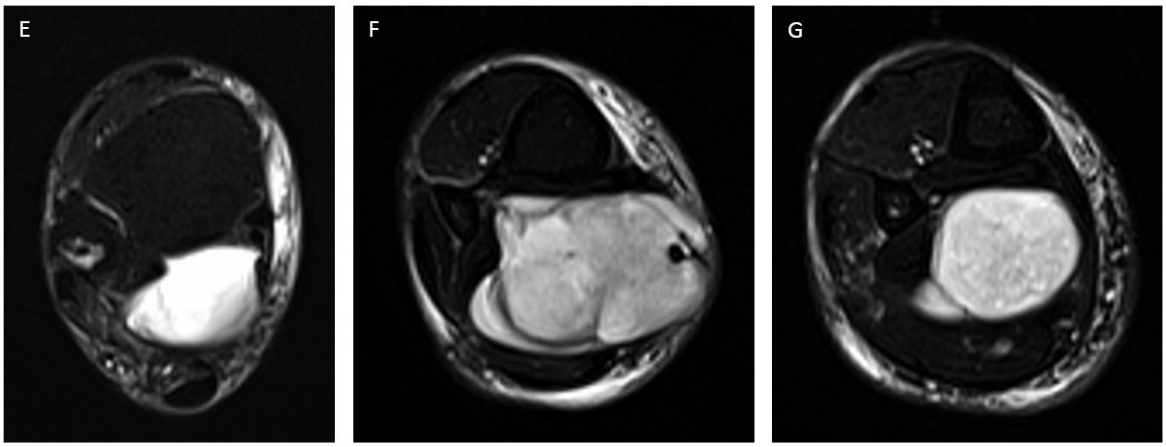


Figure 13: Transversal T2-weighted fat-suppressed MRI scan of the same patient at time of diagnosis (E). Transversal T2-weighted fat-suppressed MRI scans at the level of the "fungating" tumour area (F) and further proximal (G).

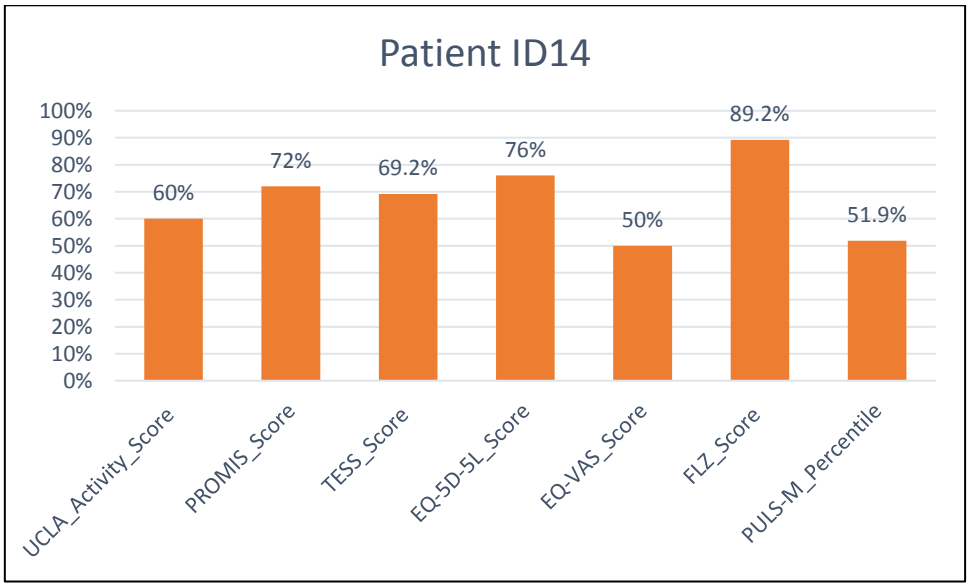


Figure 14: The diagram describes the percentage scored by the patient in reference to the maximum points (100%). The PLUS-M results are shown in percentile, which indicates the percent of the PLUS-M™ development sample that reported lower mobility than is reflected by the corresponding T-Score.

The UCLA Activity Score showed a physical activity level of 60% (crude value: 6) translating to "Regularly participates in moderate activities". The PROMIS Score was 72% (crude value: 36) and the TESS Score 69.2%. Furthermore, the PLUS-M Percentile of 51.9% (crude value: 45) demonstrated an intermediate mobility with amputation. The EQ-5D-5L was 76% (crude value: 19) and the visual analogue scale EQ-VAS 50%. According to the FLZ Score, the patient's overall satisfaction was 89.2% (crude value: 43.7), with highest outcomes in financial state and partnership and lowest outcomes in the categories work and sexuality. The Modified weight activity score was 5.25 points (range of the entire study cohort: 0 – 10.8). Regular activities mentioned by the patient were bicycling and gardening. On the one hand, the patient reported an intermediate rate of physical activity and mobility with amputation. On the other hand, the patient was in a good health status and had a high satisfaction in life. In comparison to other patients investigated, a result below average was observed for the EQ-5D-5L T-score. The remaining questionnaire results were comparable to the entire group. Furthermore, during physical examination, the range of motion of the knee was 0°/0°/100° (extension/neutral/flexion). At the last follow-up the wound condition was inconspicuous. The patient was full weight bearing the affected limb with a good-fitting prosthesis.

Patient ID_04

This 47-year-old male patient underwent amputation due to a monophasic fibrous synovial sarcoma, grade 3, localized at the sinus of the left foot with a size of 3.2 cm, with infiltration of the bone. He received adjuvant CTX. No postoperative complications emerged until the last follow up, 13 years after surgery.

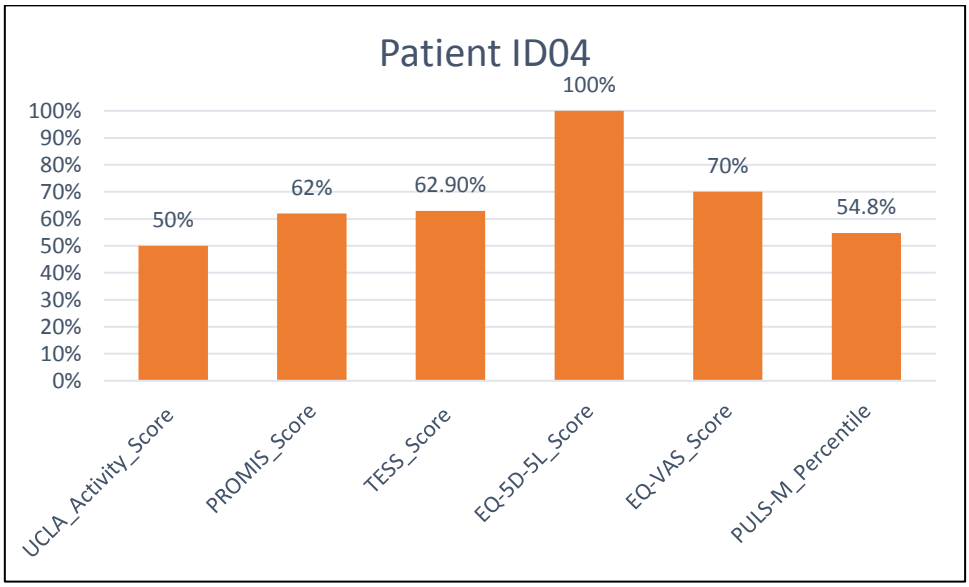


Figure 15: The diagram describes the percentage scored by the patient in reference to the maximum points (100%). The PLUS-M results are shown in percentile, which indicates the percent of the PLUS-M™ development sample that reported lower mobility than is reflected by the corresponding T-Score

UCLA Activity Score was 50% (crude value: 5) – "Sometimes participates in moderate activities such as swimming or could do unlimited housework or shopping". PROMIS Score was 62% (crude value: 31) and the TESS Score 63.9%. The Modified weight activity score was 0, as the patient stated not to perform any regular activities. Furthermore, the PLUS-M percentile of 54.8% (crude value: 46) demonstrated an intermediate mobility following amputation. The overall health status according to the EQ-5D-5L was 100%, (crude value: 25) and the EQ-VAS was 70%. In comparison to the other patients, results below average in the MWAS and PROMIS questionnaires were observed. The remaining questionnaire results were comparable to the entire study group. As this patient declined to participate in a physical examination at the study center, no data about the local wound status or ROM could be ascertained.

Patient ID_03

Patient 3 was a female patient, undergoing limb-salvage surgery at the age of 18 with wide resection, followed by plastic reconstruction with a muscular flap. She had initially been diagnosed with a monophasic synovial sarcoma, grade 3, with a size of 4.0 cm at the lateral right ankle region. At time of surgery, she had been a non-smoker, with a BMI of 27. After surgery, the patient received CTX as well as local RTX. No postoperative complications emerged. At last follow-up, 10 years after surgery, the patient was fully weight bearing without any limping.

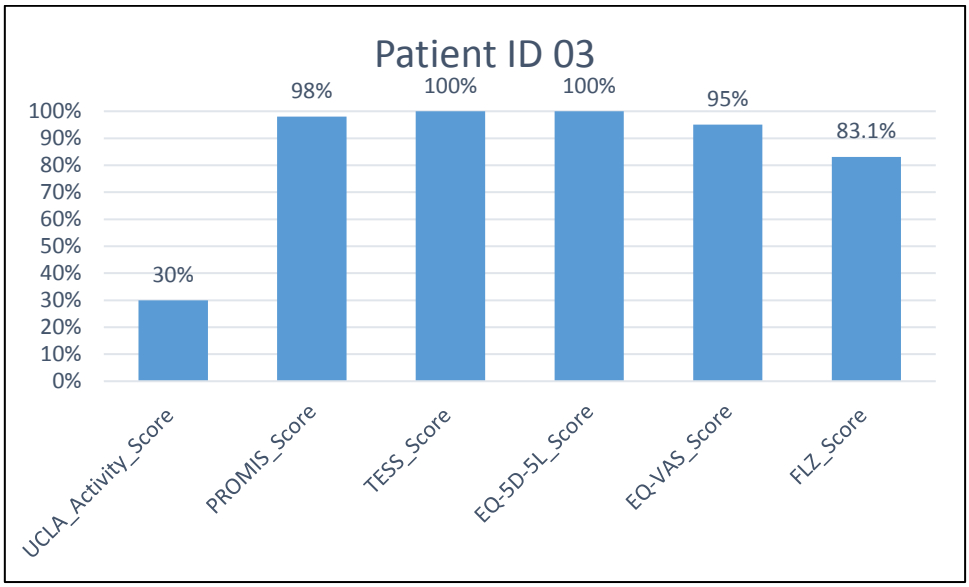


Figure 16: The diagram describes the percentage scored by the patient in reference to the maximum points (100%).

The UCLA Activity Score was 30% (crude value: 3) translating into "Sometimes participates in mild activities, such as walking, limited housework and limited shopping". PROMIS Score was 98% (crude value: 49) and TESS Score 100%. Overall health status in the EQ-5D-5L was 100% (crude value: 25) and EQ-VAS 95%. The patient's overall satisfaction according to the FLZ was 83.1% (crude value: 40.7). Highest satisfaction levels were measured in the categories self-image and social relations, the lowest in financial situation and leisure. Modified weight activity score was 4.0, as she stated to habitually do gardening. Figure 16 shows the patient's low physical activity, as well as a high physical functionality, nearly maximal health status and very high satisfaction in life. In comparison to the other patients, as assessed with the T-score, 4 out of 7 questionnaire results were above average: PROMIS, TESS, EQ-5D-5L and EQ-VAS. The UCLA test results were below average in this patient, though. Moreover, during the physical examination, the range of motion (°) for the upper ankle joint was 20°/0°/30°

extension/neutral/flexion, 30° pronation, and 40° supination. Knee extension/neutral/flexion was 0°/0°/120. The wound condition was inconspicuous at latest follow-up.

Patient ID 18

This male patient, aged 72 years, underwent limb-salvage surgery with wide resection due to a grade 2 chondrosarcoma of the right calcaneus, sized 5.8 cm. No infiltration of nerves or vessels was present. After surgery, the patient developed recurring wound infections, necessitating three revision surgeries altogether.

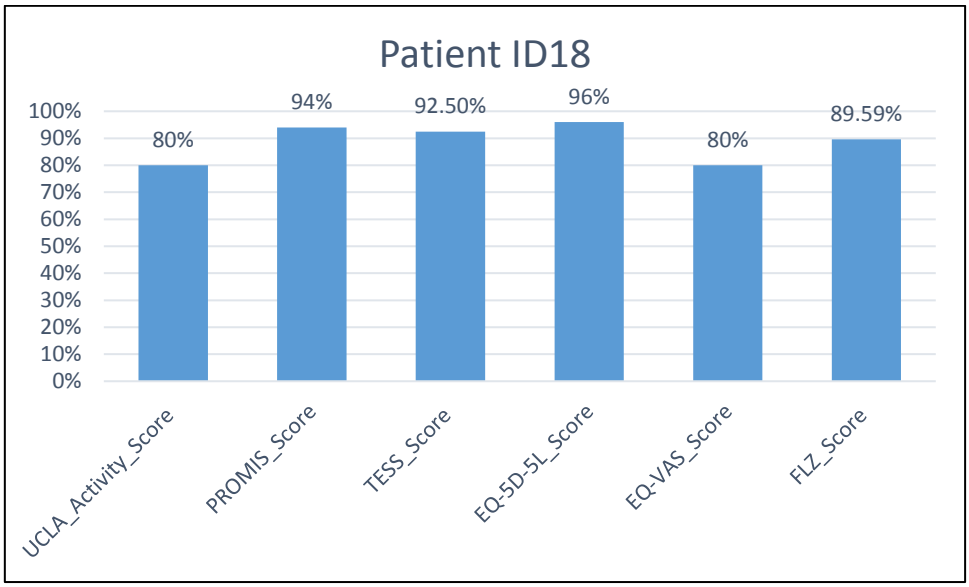


Figure 17: The diagram describes the percentage scored by the patient in reference to the maximum points (100%).

The UCLA Activity Score was 80% (crude value: 8), implying "Regularly participates in active events, such as golf or bowling". The PROMIS Score was 94% (crude value: 47) and the TESS Score 92.5%. The EQ-5D-5L score was 96% (crude value: 24) and the visual analogue scale EQ-VAS 80%. With the FLZ Score, an overall satisfaction level of 89.6% (crude value: 43.9) was measured. Highest values for the FLZ items financial state and work were found, whilst lowest values were reported for items self-image and sexuality. The MWAS was 10.8, being the highest score of the entire study group. The high MWAS score resulted from the patient's regular leisure activities as aerobics, bicycling, hiking and tennis. In comparison to the questionnaire-T-scores of the remaining patients, results were above average for the UCLA, MWAS, PROMIS and TESS (difference of one SD). During physical examination, the range of motion for the upper ankle joint was 20°/0°/40° (extension/neutral/flexion), 10° for pronation and 10° for supination. Knee extension and flexion were 0° and 120°, respectively. During latest follow-up 2 years after surgery, the patient's wound condition was inconspicuous. He was fully weight-bearing the affected limb with custom-made shoes.

Patient ID 08

Patient 8 was a 66-year-old male who underwent limb-salvage surgery for an atypical lipomatous tumour, grade 1. The tumour was sized 19 cm and extended from the middle left lower leg to the ankle region. He initially underwent marginal resection. Due to local recurrence, re-resection became necessary.

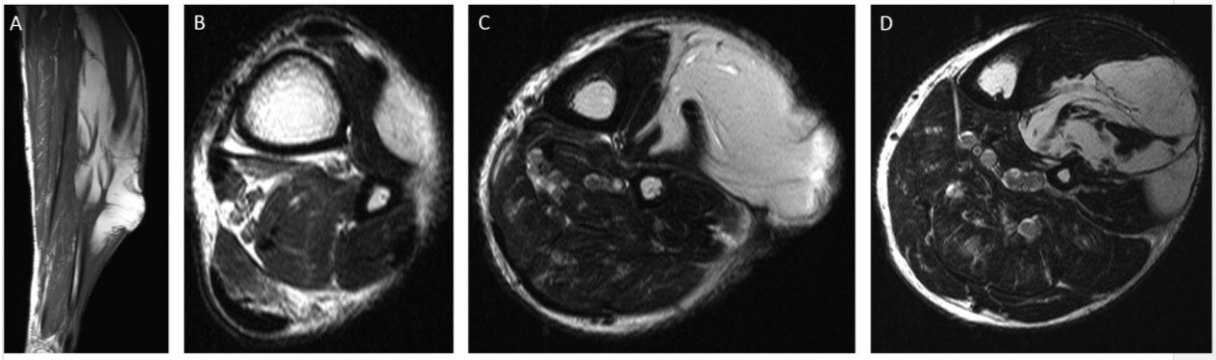


Figure 18: Sagittal T1-weigthed MRI scan of an atypical lipomatous tumour at the left lower leg with area of "fungation" (A). Transversal T2-weighted MRI scan of the same patient, at the level of the distal syndesmosis (B). Transversal T2-weighted MRI scans at the level of the "fungating" tumour area (C) and further proximal (D).

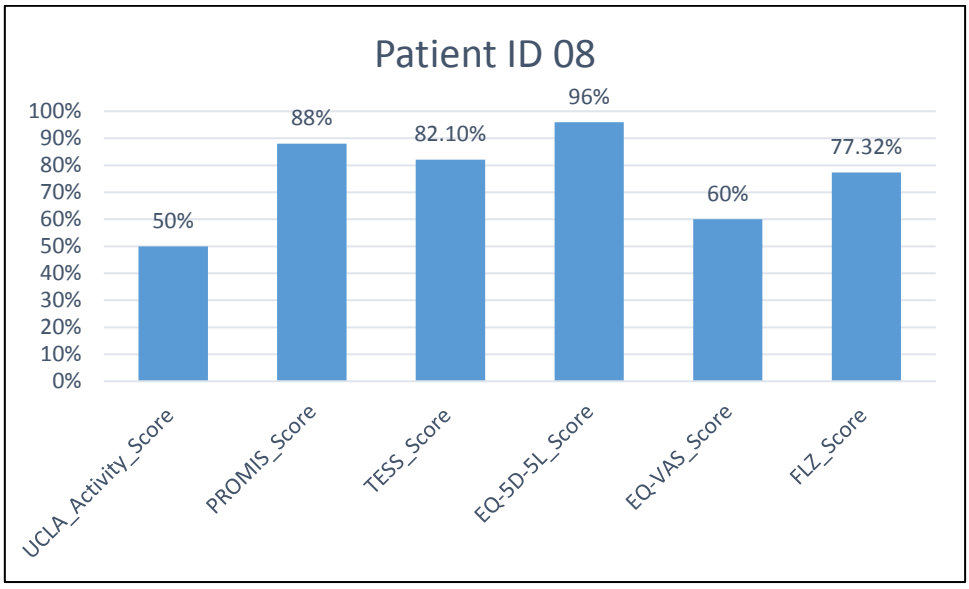


Figure 19: The diagram describes the percentage scored by the patient in reference to the maximum points (100%).

The UCLA Activity Score was 50% (crude value: 5), implying "Sometimes participates in moderate activities such as swimming or could do unlimited housework or shopping". PROMIS Score was 88% (crude value: 44) and the TESS Score 82.1%. The overall health status according to the EQ-5D-5L and EQ-VAS, respectively, was 96% (crude value: 24), and 60% (crude value: 60). The overall FLZ Score was 77.3% (crude value: 37.8), with highest

outcome for the item “relation to your children” and lowest outcome for the FLZ items “health”, “housing” and “sexuality”. The Modified weight activity score was 5.8. Regular activities mentioned by the patient were bowling, dancing and swimming. Results of all questionnaires were comparable to the entire study group. During physical examination, the range of motion of this patient was 20°/0°/40° extension/neutral/flexion for the upper ankle joint, as well as 10° pronation and 10° supination. Full ROM of the ipsilateral knee joint was present (extension/neutral/flexion; 0°/0°/140°). The patient was fully weight bearing the affected limb without any limping at latest follow-up 10 years after surgery.

Patient ID_11

This female patient underwent limb-salvage surgery at the age of 53 with wide resection for a chondrosarcoma grade 1, sized 1.5 cm that was located at the medial distal left tibia. No infiltration of nerves or vessels was present. Until the last follow-up, 14 years after surgery, no postoperative complications had emerged. Notably, she had to non-weight-bear the left lower limb for six weeks following surgery to allow healing.

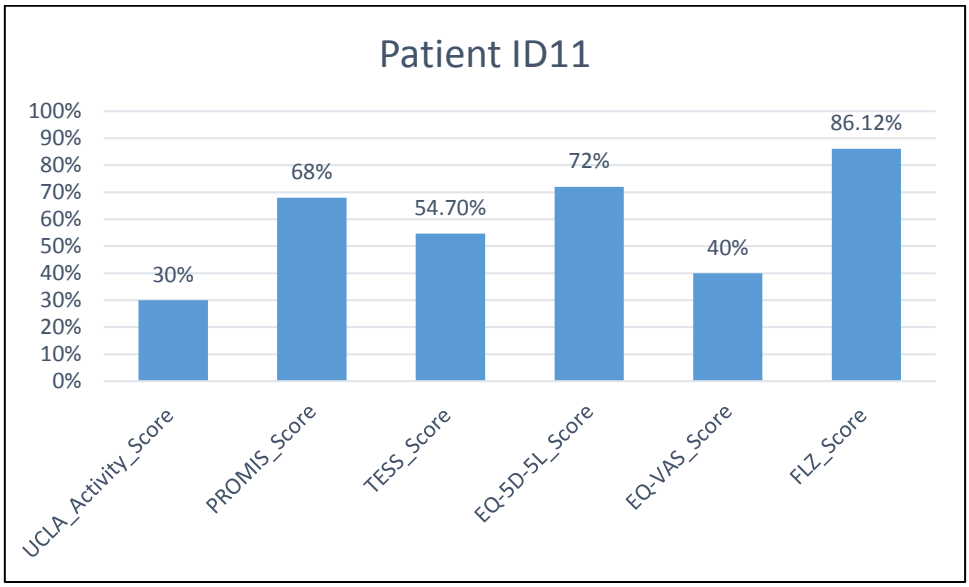


Figure 20: The diagram describes the percentage scored by the patient in reference to the maximum points (100%).

The UCLA Activity Score was 30% (crude value: 3), i.e. “Sometimes participates in mild activities, such as walking, limited housework and limited shopping”. PROMIS Score was 68% (crude value: 34) and TESS Score 54.7%. The overall health status according to the EQ-5D-5L was 72% (crude value: 18), and 40% according to the EQ-VAS (crude value: 40). The

overall FLZ Score was 86.1% (crude value: 42.2), with highest outcome in item “partnership” and lowest outcome in the item “health”. The MWAS was with 0.5 relatively low, since the patient sometimes worked in the garden. In comparison to the other patients of the present study, results below average for UCLA, MWAS, TESS, EQ-5D-5L and EQ-VAS were found. During physical examination, ROM was 10°/0°/35° (extension/neutral/flexion) for the upper ankle joint. Supination and pronation were 35° and 5°, respectively. Knee extension was 0°, and knee flexion 130°. Despite a forefoot-elevation weakness requiring a special orthesis, the patient was fully weight bearing the affected limb at last follow-up.

Patient ID 17

This male patient was aged 14 years at initial surgery. He had been diagnosed with an OS, grade 3, with a size of 6.2 cm, at the right distal tibia (Figure 21). The patient underwent limb-salvage surgery with wide resection and reconstruction with vascularized fibular graft as well as upper ankle joint arthrodesis (Figure 22, A & B). He developed vascular fibular graft failure requiring autograft and plate removal two years after the initial surgery, as well as re-arthrodesis with arthrodesis nail (Figure 22, C & D). At last follow-up five years after primary surgery, the arthrodesis had well healed and the patient was fully weight bearing.

Figure 21: X-Ray of the osteosarcoma (G3) in the right distal tibia (A). Codman triangle and sunburst appearance visible at the posterior aspect of the distal tibia (B). Transversal T2-weighted fat-suppressed MRI scan of the same patient at time of diagnosis showing soft tissue expansion into the posterior compartment (C).

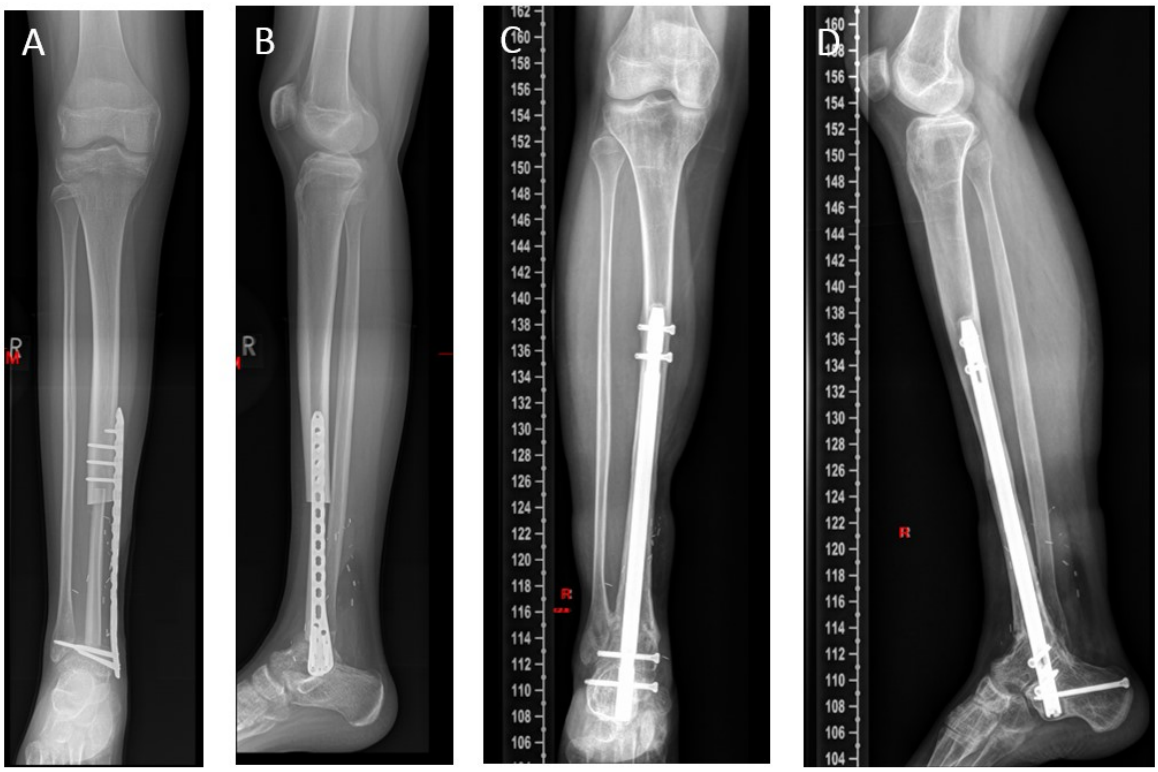


Figure 22: X-Ray of the right lower leg after wide resection of the distal tibia and subsequent reconstruction with vascularized fibular graft and upper ankle joint arthrodesis (A, B). Due to autograft failure and pseudoarthrosis, revision arthrodesis had to be performed after two years (images not shown). X-Ray four years after the initial surgery, showing healed arthrodesis with arthrodesis nail (C, D).

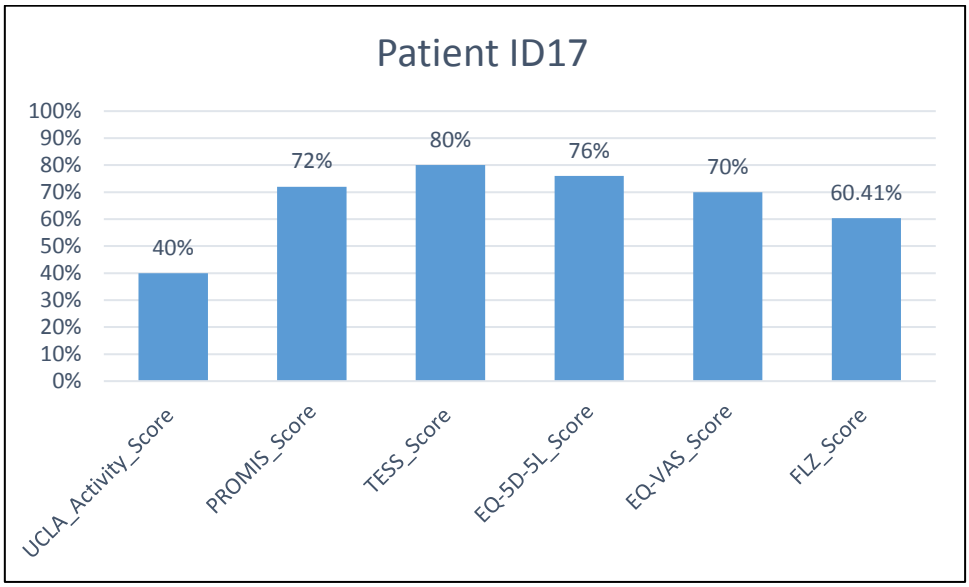


Figure 23: The diagram describes the percentage scored by the patient in reference to the maximum points (100%).

The UCLA Activity Score was 40% (crude value: 4), implying “Regularly Participates in mild activities”. PROMIS Score was 72% (crude value: 36), and TESS Score 80%. The overall health status in the EQ-5D-5L was rated with 76% (crude value: 19), and in EQ-VAS with 70%

(crude value: 70). The FLZ Score was 60.4% (crude value: 29.6), with highest outcomes in the category “health” and lowest outcomes for items “sexuality” and “housing”. Habitual walking exercise resulted in a modified weight activity score of 5. In comparison to the other patients, results below average in EQ-5D-5L and FLZ were observed. During physical examination of this patient, ROM of the ankle joint (i.e. subtalar joint due to arthrodesis) was 0°/0°/10° for extension/neutral/flexion, as well as 0° for pronation and supination. Knee extension and flexion were 0° and 120°, respectively. The local status was inconspicuous. The patient was fully weight bearing the affected limb, with minimal limping, at latest follow-up 3 years after surgery.

5 Discussion

Due to the advances in endoprosthetic devices and surgical procedures, limb-salvage surgery has become the standard procedure for surgical treatment of sarcomas in the upper – and even more – in the lower limb. (89) Nonetheless, wide resection in ankle sarcomas might not always be feasible. Despite the fact that therapeutic principles recommend a wide resection with a free margin of about 1-2 mm, this might not always be possible in ankle sarcomas, due to the complex anatomical structure and the proximity of nerves, muscles and bones in this region. (4) Preservation of essential structures and concurrent marginal or intralesional resection potentially increases the risk of local recurrence. Furthermore, higher risk of wound healing deficit and infections might lead to revision surgery or even secondary amputation, considering the thin soft tissue coverage. (90) The authors of more recent studies about ankle sarcomas have proposed that limb-salvage surgery may be the most favourable option, also pointing out that patients might suffer from emotional distress and reduced mobility after amputation. (91) Patients' reaction on the prospect of amputation is variable, though. (92) Limitations in normal activities after amputation depend on factors as the individuals working status, gender, and age. Notably, patients with amputation might be socially and economically more vulnerable. (93)

According to our results, the most frequent tumours in the ankle region were synovial sarcoma and osteosarcoma (20.8%), followed by the liposarcoma and Ewing´s Sarcoma (16.7%). In comparison to the results obtained by *Toepfer et al.,* lower rates of chondrosarcomas and myxofibrosarcomas were found in the present study. (1) Moreover, there was a female predominance in our study, which is most likely related to the small sample size of 24 patients in the retrospective cohort.

No significant difference in tumour size or grading with regards to the surgical method (limb-salvage vs. amputation) was present in our cohort. The highest average tumour size was found for tumours in the distal fibula with a mean of 9.0 cm, as well as tumours in the ankle region with a mean of 9.3 cm (SD ± 6.5 cm). In contrast, tumours in the calcaneus were the smallest, with an average mean of 4.2 cm (SD ± 1.5 cm). This discrepancy in size can be explained by the fact that tumours of the calcaneus usually cause pain during walking as soon as they penetrate the cortex and lead to visible deformities of the heel's shape, wherefore they may be detected at earlier stages. At last follow-up, all patients were fully weight bearing. Notably, we measured a limited range of joint mobility in some patients.

Additionally, our data showed that 50% of patients experienced postoperative complications out of which soft tissue complications (46%) such as wound healing deficit, venous thrombosis, haematoma, and mechanical complications (27%) were the most common ones. The results of the subsequently performed correlation analysis supports the idea that type of margin and patient gender could be possible risk factors for postoperative complications, albeit only analysed in the univariate setting.

In comparison to *Houdek et. al.* who performed a retrospective study on prognostic factors in 62 patients with STS of the food and ankle, we found a considerably lower 5-year overall survival rate ($67\%_{LSG}$ & $43\%_{AG}$ vs. $79\%_{Houdek}$) and higher complication rate ($50\%_{entire\ cohort}$ vs. $24\%_{Houdek}$). According to *William et. al*., amputation does not significantly improve the survival rate of patients in comparison to limb salvage surgery. (89) In line with this, no significant survival benefit of patients undergoing amputation vs. limb salvage surgery was found in our cohort (p= .160).

Notably, the complication rate observed in the present study was highest in the limb-salvage group (91.7%) and is also higher than the one reported in a similar study by *Ozger et al* (32.6%) including 48 patients with ankle sarcoma *(91).* It is worth mentioning that with 89.6%, the limb-salvage rate in the study by *Ozger et al.* was higher than the 58.3% in the present study and the 53% in the study by *Houdek et al.*. (94) Frequent complications mentioned in the study by *Houdek et al.* included wound drainage, wound infections and skin graft failure. (94) Neither male gender (p = .45) nor wide resection (p = .81) were identified as risk factors for postoperative complications in the study by *Houdek et al*.. (94) In the present study, there was a time-dependent effect of experiencing the first postoperative complication after surgery, with patients undergoing limb-salvage surgery being at significantly higher risk of developing complications (p = .013; Log Rank Test). All complications in the present study necessitated revision surgery. While patients in the LSG required up to 4 further reoperations, none of the patients in the AG necessitated another revision surgery after the first one.

Seven patients out of the entire study cohort could be enrolled in the prospective part. Due to the small sample size and the lack of a control group, the data used in this diploma thesis was analysed as descriptive only. No visible differences between the two groups (LSG vs. AG) were found with regards to functional or quality-of-life-related questionnaires. In order to allow better interpretation of our findings, results of questionnaires were transposed into T-scores.

In general, it may be assumed that patients undergoing surgery for sarcomas of the lower limb could present with poorer functional outcome scores as compared with patients undergoing

surgery for other conditions involving the musculoskeletal system. However, in a study from Zurich, the activity levels in 100 patients undergoing TKA (61 women; mean age, 66.5 years) were equivalent to a median UCLA activity score of 4.9 (SD ±2.0), being comparable to the median UCLA scores of 5.4 and 4.0 for our patients in the AG and LSG, respectively. (95) In a study from the *Orthopaedic Hospital, Oswestry, United Kingdom*, patients that had undergone limb salvage surgery of the lower limb due to STS or BS presented with an average TESS of 70.1 (SD 22.3) (n=209) in males and 63.2 (SD 24.1) (n=190) in females. (96) In comparison, TESS scores observed in the present study were relatively higher, with a median TESS of 82.1 for patients in the LSG and 66.1 for patients in the AG. However, TESS score for amputees in the present study was relatively lower than the one reported by *Davis et al.,* which was 75.6 (93). Similar results – and again better than in the present study – were found by *Nagarajan et al*, with a TESS score of 83.8 to 87.6 (97)

In another study, the adult PROMIS measures centered on the US General Census 2000 was 48.9 (SD 10.0) in women (n=2044) and 51.7 (SD 9.7) in men (n=1363) (98), which is higher than the 39.6 observed in the present study.

Bearing in mind that the individual quality of life is not only based on physical, but also on mental and psychosocial parameters, (99) EQ-5D-5L, EQ-VAS and FLZ scores were also ascertained in the prospective part of this study. In the current study, the EQ-VAS was 66.4 for all patients combined. Altogether, regarding the patients' quality of life, no significant difference was found between limb-salvage and amputation. As a comparison, the e-survey across 30 countries performed by *Mastboom et. al.* (n=337) in patients with tenosynovial giant cell tumour revealed a median EQ-VAS of 75 for localized tumours (100), being slightly better than our findings.

In our study, significant correlations between the questionnaire results of TESS and PROMIS ($r = .91$; $p = .004$) as well as between the TESS and EQ-VAS were found ($r = .85$; $p = .016$). Moreover, we observed strong tendencies between the UCLA and MWAS ($r = .73$; $p = .06$), the MWAS and PROMIS ($r = .685$; $p = .089$), the MWAS and TESS ($r = .69$; $p = .087$), as well as the EQ-5D-5L and EQ-VAS ($r = .73$; $p = .063$). These correlations indicate that questionnaires used for this study were well selected to assess patients' mobility and quality of life.

6 Limitations

Some limitations of the present study have to be mentioned. First, some of the questionnaires used in this study have not been originally designed for or are not yet standardised for the ankle region, or postoperative settings after amputation. Second, only a small patient cohort could be prospectively analysed, as 24 patients had been treated between 2000 and 2017 at the *Department of Orthopaedics and Trauma, Medical University of Graz* for sarcomas of the ankle region, and some of them had already died at time of set-up of the prospective study. Therefore, the data presented in this thesis serves as case series of patients treated at a single tertiary sarcoma centre and have to be interpreted bearing the small sample size as limitation in mind.

7 Conclusion

According to the retrospective part of the present diploma thesis, the majority of postoperative complications occur following limb-salvage surgery. The most frequent complications are wound healing deficits and mechanical complications. Further potential risk factors for complications include male gender and wide margins, although not analysed in a multivariate model. According to the prospective part, no significant differences are present between patients with amputation and those with limb salvage surgery regarding functional outcome and quality of life. Nevertheless, certain tendencies are observed in the PROMIS, TESS and FLZ questionnaires. Our study may aid to better understand the impact of the surgical procedure performed on postoperative complications, function and quality of life in ankle sarcoma patients. Understanding these factors may help to reduce the risk of complications and revision surgeries in the future, therefore ensuring better functional outcomes and improved quality of life.

8 Literature Cited

1. Toepfer A, Harrasser N, Recker M, Lenze U, Pohlig F, Gerdesmeyer L et al. Distribution patterns of foot and ankle tumors: a university tumor institute experience. BMC Cancer 2018; 18(1):735.
2. Antonescu CR. Soft tissue and bone tumours. 5th ed. Lyon: International Agency for Research on Cancer; 2020. (WHO Classification of Tumours. 5th edition. pp. 6, 10-12, 290, 340-344, 400, 403, 404, 410, 414, 417, 419)
3. Thacker MM, Potter BK, Pitcher JD, Temple HT. Soft tissue sarcomas of the foot and ankle: impact of unplanned excision, limb salvage, and multimodality therapy. Foot Ankle Int 2008; 29(7):690–8.
4. Khan Z, Hussain S, Carter SR. Tumours of the foot and ankle. Foot (Edinb) 2015; 25(3):164–72.
5. Özger H, Alpan B, Aycan OE, Valiyev N, Kir MÇ, Ağaoğlu F. Management of primary malignant bone and soft tissue tumors of foot and ankle: Is it worth salvaging? J Surg Oncol 2018; 117(2):307–20.
6. Myhre-Jensen O, Kaae S, Madsen EH, Sneppen O. Histopathological grading in soft-tissue tumours. Relation to survival in 261 surgically treated patients. Acta Pathol Microbiol Immunol Scand A 1983; 91(2):145–50.
7. Casali PG, Blay J-Y. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 Suppl 5:v198-203.
8. Katenkamp K, Katenkamp D. Soft tissue tumors: new perspectives on classification and diagnosis. Dtsch Arztebl Int 2009; 106(39):632–6.
9. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2016/, based on November 2018 SEER data submission, posted to the SEER web site, April 2019.
10. Mukherjee D, Chaichana KL, Gokaslan ZL, Aaronson O, Cheng JS, McGirt MJ. Survival of patients with malignant primary osseous spinal neoplasms: results from the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2003. J Neurosurg Spine 2011; 14(2):143–50.
11. Widhe B, Widhe T. Initial symptoms and clinical features in osteosarcoma and Ewing sarcoma. J Bone Joint Surg Am 2000; 82(5):667–74.
12. Schlag PM, Senn H-J, Tunn P-U. Treatment of Bone and Soft Tissue Sarcomas. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009. (vol 179).
13. Fidler MM, Reulen RC, Winter DL, Allodji RS, Bagnasco F, Bárdi E et al. Risk of Subsequent Bone Cancers Among 69 460 Five-Year Survivors of Childhood and Adolescent Cancer in Europe. J Natl Cancer Inst 2018; 110(2).
14. Ilaslan H, Schils J, Nageotte W, Lietman SA, Sundaram M. Clinical presentation and imaging of bone and soft-tissue sarcomas. Cleve Clin J Med 2010; 77 Suppl 1:S2-7.
15. GRIMER, R. J. 2006. Size matters for sarcomas! Ann R Coll Surg Engl, 88, 519-24.
16. Park K, van Rijn R, McHugh K. The role of radiology in paediatric soft tissue sarcomas. Cancer Imaging 2008; 8:102–15.
17. Berry JD, Cook GJR. Positron emission tomography in oncology. Br Med Bull 2006; 79-80:171–86.
18. Moon L, McHugh K. Advances in paediatric tumour imaging. Arch Dis Child 2005; 90(6):608–11.

19. Pohlig F, Kirchhoff C, Lenze U, Schauwecker J, Burgkart R, Rechl H et al. Percutaneous core needle biopsy versus open biopsy in diagnostics of bone and soft tissue sarcoma: a retrospective study. Eur J Med Res 2012; 17:29.
20. Trojani M, Contesso G, Coindre JM, Rouesse J, Bui NB, Mascarel A de et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984; 33(1):37–42.
21. Oliveira AM, Nascimento AG. Grading in soft tissue tumors: principles and problems. Skeletal Radiol 2001; 30(10):543–59.
22. SALZER-KUNTSCHIK, M., DELLING, G., BERON, G. & SIGMUND, R. 1983. Morphological grades of regression in osteosarcoma after polychemotherapy - study COSS 80. J Cancer Res Clin Oncol, 106 Suppl, 21-4.
23. Tanaka K, Ozaki T. New TNM classification (AJCC eighth edition) of bone and soft tissue sarcomas: JCOG Bone and Soft Tissue Tumor Study Group. Jpn J Clin Oncol 2019; 49(2):103–7.
24. Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop Relat Res 1980; (153):106–20.
25. Jawad MU, Scully SP. In brief: classifications in brief: enneking classification: benign and malignant tumors of the musculoskeletal system. Clin Orthop Relat Res 2010; 468(7):2000–2.
26. Casali PG, Bielack S, Abecassis N, Aro HT, Bauer S, Biagini R et al. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4):iv79-iv95.
27. Isakoff MS, Bielack SS, Meltzer P, Gorlick R. Osteosarcoma: Current Treatment and a Collaborative Pathway to Success. J Clin Oncol 2015; 33(27):3029–35.
28. Anninga JK, Gelderblom H, Fiocco M, Kroep JR, Taminiau AHM, Hogendoorn PCW et al. Chemotherapeutic adjuvant treatment for osteosarcoma: where do we stand? Eur J Cancer 2011; 47(16):2431–45.
29. Valery PC, Laversanne M, Bray F. Bone cancer incidence by morphological subtype: a global assessment. Cancer Causes Control 2015; 26(8):1127–39.
30. Klein MJ, Siegal GP. Osteosarcoma: anatomic and histologic variants. Am J Clin Pathol 2006; 125(4):555–81.
31. Wenaden AET, Szyszko TA, Saifuddin A. Imaging of periosteal reactions associated with focal lesions of bone. Clin Radiol 2005; 60(4):439–56.
32. Marko TA, Diessner BJ, Spector LG. Prevalence of Metastasis at Diagnosis of Osteosarcoma: An International Comparison. Pediatr Blood Cancer 2016; 63(6):1006–11.
33. Scandinavian Sarcoma Group& Oncologic center. Euroboss1: A European treatment protocol for bone sarcomain patients older than 40 years 2003 Feb 1 [cited 2020 Apr 9]. Available from: URL: http://www.ssg-org.net/wp-content/uploads/2011/05/Euroboss1.pdf.
34. Bielack S, Jürgens H, Jundt G, Kevric M, Kühne T, Reichardt P et al. Osteosarcoma: the COSS experience. Cancer Treat Res 2009; 152:289–308.
35. Rajani R, Gibbs CP. Treatment of Bone Tumors. Surg Pathol Clin 2012; 5(1):301–18.
36. Maheshwari AV, Cheng EY. Ewing sarcoma family of tumors. J Am Acad Orthop Surg 2010 Feb;18(2):94-107.
37. Liu H-F, Wang J-X, Zhang D-Q, Lan S-H, Chen Q-X. Clinical Features and Prognostic Factors in Elderly Ewing Sarcoma Patients. Med Sci Monit 2018; 24:9370–5.
38. Mansoor A, White CR. Myxofibrosarcoma presenting in the skin: clinicopathological features and differential diagnosis with cutaneous myxoid neoplasms. Am J Dermatopathol 2003; 25: 281-286.

39. Hambleton C, Noureldine S, Gill F, Moroz K, Kandil E. Myxofibrosarcoma with metastasis to the lungs, pleura, and mediastinum: a case report and review of literature. Int J Clin Exp Med. 2012;5(1):92–95.
40. Roland CL, Wang W-L, Lazar AJ, Torres KE. Myxofibrosarcoma. Surg Oncol Clin N Am 2016; 25(4):775–88.
41. Nishio J, Iwasaki H, Nabeshima K, Naito M. Cytogenetics and molecular genetics of myxoid soft-tissue sarcomas. Genet Res Int 2011; 2011:497148.
42. Dadrass F, Gusho C, Yang F, Culvern C, Bloom J, Fillingham Y et al. A clinicopathologic examination of myxofibrosarcoma. Do surgical margins significantly affect local recurrence rates in this infiltrative sarcoma subtype? J Surg Oncol 2021; 123(2):489–96.
43. Mujtaba B, Wang F, Taher A, Aslam R, Madewell JE, Nassar S. Myxoid Liposarcoma With Skeletal Metastases: Pathophysiology and Imaging Characteristics. Curr Probl Diagn Radiol 2019.
44. Ramu D, Manjunath S, Anuradh G. Recurrent Retroperitoneal Liposarcoma: a Case Report and Literature Review. Indian J Surg Oncol 2018; 9(4):640–3.
45. Coindre J-M, Pédeutour F, Aurias A. Well-differentiated and dedifferentiated liposarcomas. Virchows Arch 2010; 456(2):167–79.
46. Gootee JM, Curtin CE, Aurit SJ, Randhawa SE, Kang BY, Silberstein PT. Treatment Facility: An Important Prognostic Factor for Dedifferentiated Liposarcoma Survival. Fed Pract 2019; 36(Suppl 5):S34-41.
47. Dei Tos AP. Liposarcoma: new entities and evolving concepts. Ann Diagn Pathol 2000; 4(4):252–66.
48. Anderson WJ, Jo VY. Pleomorphic liposarcoma: Updates and current differential diagnosis. Semin Diagn Pathol 2019; 36(2):122–8.
49. Orvieto E, Furlanetto A, Laurino L, Dei Tos AP. Myxoid and round cell liposarcoma: a spectrum of myxoid adipocytic neoplasia. Semin Diagn Pathol 2001; 18(4):267–73.
50. Creytens D. A contemporary review of myxoid adipocytic tumors. Semin Diagn Pathol 2019; 36(2):129–41.
51. Thway K, Fisher C. Synovial sarcoma: defining features and diagnostic evolution. Ann Diagn Pathol 2014; 18(6):369–80.
52. Stacchiotti, S., & Van Tine, B. A. (2018). Synovial Sarcoma: Current Concepts and Future Perspectives. Journal of Clinical Oncology, 36(2), 180–187. doi:10.1200/jco.2017.75.1941.
53. Gao J, Yuan Y-S, Liu T, Lv H-R, Xu H-L. Synovial sarcoma in the plantar region: A case report and literature review. World J Clin Cases 2019; 7(17):2549–55.
54. Andritsch E, Beishon M, Bielack S, Bonvalot S, Casali P, Crul M et al. ECCO Essential Requirements for Quality Cancer Care: Soft Tissue Sarcoma in Adults and Bone Sarcoma. A critical review. Crit Rev Oncol Hematol 2017; 110:94–105.
55. Brownstein JM, DeLaney TF. Malignant Soft-Tissue Sarcomas. Hematol Oncol Clin North Am 2020; 34(1):161–75.
56. T A Alvegård, H Sigurdsson, H Mouridsen, O Solheim, B Unsgaard, U Ringborg et al. Adjuvant chemotherapy with doxorubicin in high-grade soft tissue sarcoma: a randomized trial of the Scandinavian Sarcoma Group.
57. McGee L, Indelicato DJ, Dagan R, Morris CG, Knapik JA, Reith JD et al. Long-term results following postoperative radiotherapy for soft tissue sarcomas of the extremity. Int J Radiat Oncol Biol Phys 2012; 84(4):1003–9.
58. Edge SB. AJCC cancer staging manual. 7th ed. / edited by Stephen B. Edge … [et al.]. New York, London: Springer; 2010.
59. Grimer RJ. Surgical options for children with osteosarcoma. The Lancet Oncology 2005; 6(2):85–92.

60. Racano A, Pazionis T, Farrokhyar F, Deheshi B, Ghert M. High infection rate outcomes in long-bone tumor surgery with endoprosthetic reconstruction in adults: a systematic review. Clin Orthop Relat Res 2013; 471(6):2017–27.
61. Strander H, Turesson I, Cavallin-Ståhl E. A systematic overview of radiation therapy effects in soft tissue sarcomas. Acta Oncol 2003; 42(5-6):516–31.
62. DuBois SG, Krailo MD, Gebhardt MC, Donaldson SS, Marcus KJ, Dormans J et al. Comparative evaluation of local control strategies in localized Ewing sarcoma of bone: a report from the Children's Oncology Group. Cancer 2015; 121(3):467–75.
63. Gronchi A, Ferrari S, Quagliuolo V, Broto JM, Pousa AL, Grignani G et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. The Lancet Oncology 2017; 18(6):812–22.
64. Wesolowski R, Budd GT. Use of chemotherapy for patients with bone and soft-tissue sarcomas. Cleve Clin J Med 2010; 77 Suppl 1:S23-6.
65. Ravi V, Patel S. Adjuvant chemotherapy for soft tissue sarcomas. Surg Oncol Clin N Am 2012; 21(2):243–53.
66. Wood WC. Neoadjuvant chemotherapy. In: Henderson IC, editor. Adjuvant Therapy of Breast Cancer. Boston, MA: Springer US; 1992. p. 279–91 Available from: URL: https://doi.org/10.1007/978-1-4615-3496-9_13.
67. Casali PG, Abecassis N, Aro HT, Bauer S, Biagini R, Bielack S et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018; 29(Suppl 4):iv51-iv67.
68. Pazdur R. Cancer management: A multidisciplinary approach : medical, surgical, & radiation oncology. 11th ed. Lawrence, Ks: CMP Media; 2008.
69. Pollack SM, Ingham M, Spraker MB, Schwartz GK. Emerging Targeted and Immune-Based Therapies in Sarcoma. J Clin Oncol 2018; 36(2):125–35.
70. Hall F, Villalobos V, Wilky B. Future directions in soft tissue sarcoma treatment. Curr Probl Cancer 2019; 43(4):300–7.
71. “Targeted Cancer Therapies was originally published by the National Cancer Institute.”. Targeted Cancer Therapies Fact Sheet - National Cancer Institute [cited 2020 Jan 8]. Available from: URL: https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.
72. Dancsok AR, Asleh-Aburaya K, Nielsen TO. Advances in sarcoma diagnostics and treatment. Oncotarget 2017; 8(4):7068–93.
73. Mohindra N, Agulnik M. Targeted therapy and promising novel agents for the treatment of advanced soft tissue sarcomas. Expert Opin Investig Drugs 2015; 24(11):1409–18.
74. Liu W, Jiang Q, Zhou Y. Advances of systemic treatment for adult soft-tissue sarcoma. Chin Clin Oncol 2018; 7(4):42.
75. Takenori Uehara, Tomohiro Fujiwara, Ken Takeda, Toshiyuki Kunisada, Toshifumi Ozaki, and Heiichiro Udono, “Immunotherapy for Bone and Soft Tissue Sarcomas,” BioMed Research International, vol. 2015, Article ID 820813, 11 pages, 2015.
76. Singer AD, Datir A, Tresley J, Langley T, Clifford PD, Jose J et al. Benign and malignant tumors of the foot and ankle. Skeletal Radiol 2016; 45(3):287–305.
77. Musculoskeletal Key Fastest Musculoskeletal Insight Engine. Applied Surgical Anatomy of the Approaches to the Ankle; 2016 [cited 2020 Feb 25]. Available from: URL: https://musculoskeletalkey.com/applied-surgical-anatomy-of-the-approaches-to-the-ankle/.
78. Boer PG de, Buckley R, Hoppenfeld S. Surgical exposures in foot & ankle surgery: The anatomic approach / by Piet DeBoer, Richard Buckley, Stanley Hoppenfeld. Philadelphia, Pa., London: Lippincott Williams & Wilkins; 2012.

79. Golanó P, Vega J, Leeuw PAJ de, Malagelada F, Manzanares MC, Götzens V et al. Anatomy of the ankle ligaments: a pictorial essay. Knee Surg Sports Traumatol Arthrosc 2010; 18(5):557–69.
80. Röhrig B, Du Prel J-B, Wachtlin D, Blettner M. Types of study in medical research: part 3 of a series on evaluation of scientific publications. Dtsch Arztebl Int 2009; 106(15):262–8.
81. Cassidy RJ, Indelicato DJ, Gibbs CP, Scarborough MT, Morris CG, Zlotecki RA. Function Preservation After Conservative Resection and Radiotherapy for Soft-tissue Sarcoma of the Distal Extremity: Utility and Application of the Toronto Extremity Salvage Score (TESS). Am J Clin Oncol 2016; 39(6):600–3.
82. Ghomrawi HMK, Lee Y-Y, Herrero C, Joseph A, Padgett D, Westrich G et al. A Crosswalk Between UCLA and Lower Extremity Activity Scales. Clin Orthop Relat Res 2017; 475(2):542–8.
83. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013; 22(7):1717–27.
84. Hafner BJ, Gaunaurd IA, Morgan SJ, Amtmann D, Salem R, Gailey RS. Construct Validity of the Prosthetic Limb Users Survey of Mobility (PLUS-M) in Adults With Lower Limb Amputation. Archives of Physical Medicine and Rehabilitation 2017; 98(2):277–85.
85. Hobusch GM, Bollmann J, Puchner SE, Lang NW, Hofstaetter JG, Funovics PT et al. What Sport Activity Levels Are Achieved in Patients After Resection and Endoprosthetic Reconstruction for a Proximal Femur Bone Sarcoma? Clin Orthop Relat Res 2017; 475(3):817–26.
86. Hays RD, Spritzer KL, Schalet BD, Cella D. PROMIS®-29 v2.0 profile physical and mental health summary scores. Qual Life Res 2018; 27(7):1885–91.
87. Fahrenberg J, Myrtek M, Schumacher J, Brähler E (2000) Fragebogen zur Lebenszufriedenheit (FLZ). [FLZ].
88. Pera F, Anderhuber F, Waldeyer AJ, Streicher J. Waldeyer: Anatomie des Menschen: Lehrbuch und Atlas in einem Band (Anatomie des Menschen). De Gruyter.
89. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Ann Surg. 1992;215(3):269-75.
90. Ozdemir HM, Yildiz Y, Yilmaz C, Saglik Y. Tumors of the foot and ankle: analysis of 196 cases. J Foot Ankle Surg. 1997;36(6):403-8.
91. Ozger H, Alpan B, Aycan OE, Valiyev N, Kir MC, Agaoglu F. Management of primary malignant bone and soft tissue tumors of foot and ankle: Is it worth salvaging? J Surg Oncol. 2018;117(2):307-20.
92. Bhuvaneswar ea. Rounds in the General Hospital: Reactions to Amputation: Recognition and Treatment.
93. Davis AM, Devlin M, Griffin AM, Wunder JS, Bell RS. Functional outcome in amputation versus limb sparing of patients with lower extremity sarcoma: a matched case-control study. Arch Phys Med Rehabil. 1999;80(6):615-8.
94. Houdek MT, Beahrs TR, Wyles CC, Rose PS, Sim FH, Turner NS. What Factors Are Predictive of Outcome in the Treatment of Soft Tissue Sarcomas of the Foot and Ankle? Foot Ankle Spec 2017; 10(1):12–9.
95. Naal FD, Impellizzeri FM, Leunig M. Which is the best activity rating scale for patients undergoing total joint arthroplasty? Clin Orthop Relat Res 2009; 467(4):958–65.
96. Heaver C, Isaacson A, Gregory JJ, Cribb G, Cool P. Patient factors affecting the Toronto extremity salvage score following limb salvage surgery for bone and soft tissue tumors. J Surg Oncol 2016; 113(7):804–10.

97. Nagarajan R, Clohisy DR, Neglia JP, Yasui Y, Mitby PA, Sklar C, et al. Function and quality-of-life of survivors of pelvic and lower extremity osteosarcoma and Ewing's sarcoma: the Childhood Cancer Survivor Study. Br J Cancer. 2004;91(11):1858-65.
98. 2020 Northwestern University. PROMIS® Reference Populations: Sub-norms for Interpreting scores [cited 2020 Jan 25]. Available from: URL: http://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/reference-populations.
99. Nagarajan R, Neglia JP, Clohisy DR, Robison LL. Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications? J Clin Oncol. 2002;20(22):4493-501.
100. Mastboom MJ, Planje R, van de Sande MA. The Patient Perspective on the Impact of Tenosynovial Giant Cell Tumors on Daily Living: Crowdsourcing Study on Physical Function and Quality of Life. Interact J Med Res 2018; 7(1):e4.

Appendix – questionnaires

UCLA Activity Score	Hip ID:
	Study Hip: Left Right
	Examination Date (MM/DD/YY): / /
	Subject Initials: |____|____|____|
	Medical Record Number:

Interval: _____

Check one box that best describes current activity level.
1: Wholly Inactive, dependent on others, and can not leave residence
2: Mostly Inactive or restricted to minimum activities of daily living
3: Sometimes participates in mild activities, such as walking, limited housework and limited shopping
4: Regularly Participates in mild activities
5: Sometimes participates in moderate activities such as swimming or could do unlimited housework or shopping
6: Regularly participates in moderate activities
7: Regularly participates in active events such as bicycling
8: Regularly participates in active events, such as golf or bowling
9: Sometimes participates in impact sports such as jogging, tennis, skiing, acrobatics, ballet, heavy labor or backpacking
10: Regularly participates in impact sports

Physical Function – Short Form 10a

Please respond to each question or statement by marking one box per row.

		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFA1	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC36r1	Does your health now limit you in walking more than a mile (1.6 km)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC37	Does your health now limit you in climbing one flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Cannot do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB26	Are you able to shampoo your hair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA55	Are you able to wash and dry your body? ..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFC45r1	Are you able to sit on and get up from the toilet?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Gesundheitsfragebogen

Deutsche Version für Deutschland

(German version for Germany)

Bitte kreuzen Sie unter jeder Überschrift DAS Kästchen an, das Ihre Gesundheit HEUTE am besten beschreibt.

BEWEGLICHKEIT / MOBILITÄT

Ich habe keine Probleme herumzugehen ❑

Ich habe leichte Probleme herumzugehen ❑

Ich habe mäßige Probleme herumzugehen ❑

Ich habe große Probleme herumzugehen ❑

Ich bin nicht in der Lage herumzugehen ❑

FÜR SICH SELBST SORGEN

Ich habe keine Probleme, mich selbst zu waschen oder anzuziehen ❑

Ich habe leichte Probleme, mich selbst zu waschen oder anzuziehen ❑

Ich habe mäßige Probleme, mich selbst zu waschen oder anzuziehen ❑

Ich habe große Probleme, mich selbst zu waschen oder anzuziehen ❑

Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen ❑

ALLTÄGLICHE TÄTIGKEITEN *(z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)*

Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich habe leichte Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich habe mäßige Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich habe große Probleme, meinen alltäglichen Tätigkeiten nachzugehen ❑

Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen ❑

SCHMERZEN / KÖRPERLICHE BESCHWERDEN

Ich habe keine Schmerzen oder Beschwerden ❑

Ich habe leichte Schmerzen oder Beschwerden ❑

Ich habe mäßige Schmerzen oder Beschwerden ❑

Ich habe starke Schmerzen oder Beschwerden ❑

Ich habe extreme Schmerzen oder Beschwerden ❑

ANGST / NIEDERGESCHLAGENHEIT

Ich bin nicht ängstlich oder deprimiert ❑

Ich bin ein wenig ängstlich oder deprimiert ❑

Ich bin mäßig ängstlich oder deprimiert ❑

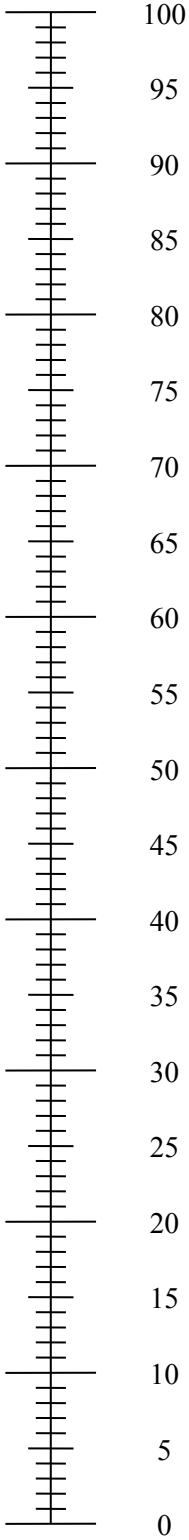
Ich bin sehr ängstlich oder deprimiert ❑

Ich bin extrem ängstlich oder deprimiert ❑

Beste
Gesundheit, die
Sie sich
vorstellen können

- Wir wollen herausfinden, wie gut oder schlecht Ihre Gesundheit HEUTE ist.
- Diese Skala ist mit Zahlen von 0 bis 100 versehen.
- 100 ist die beste Gesundheit, die Sie sich vorstellen können. 0 (Null) ist die schlechteste Gesundheit, die Sie sich vorstellen können.
- Bitte kreuzen Sie den Punkt auf der Skala an, der Ihre Gesundheit HEUTE am besten beschreibt.
- Jetzt tragen Sie bitte die Zahl, die Sie auf der Skala angekreuzt haben, in das Kästchen unten ein.

IHRE GESUNDHEIT HEUTE = ☐



Schlechteste Gesundheit, die sie sich vorstellen können

EuroQol Group EQ-5D

Prosthetic Limb Users Survey of Mobility (PLUS-M)

Version 1.2 – English (US)

12- item Short Form

(v12)

PLUS™ MOBILITY

Name: _____ Date: _____

Instructions: Please respond to all questions as if you were wearing the prosthetic leg(s) you use most days. If you would normally use a cane, crutch, or walker to perform the task, please answer the questions as if you were using that device.

Please choose "unable to do" if you:

- Would need help from another person to complete the task,
- Would need a wheelchair or scooter to complete the task, or
- Feel the task may be unsafe for you

Please mark one box per row.

Question	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1. Are you able to walk a short distance in your home?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
2. Are you able to step up and down curbs?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
3. Are you able to walk across a parking lot?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
4. Are you able to walk over gravel surfaces?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
5. Are you able to move a chair from one room to another?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
6. Are you able to walk while carrying a shopping basket in one hand?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
7. Are you able to keep walking when people bump into you?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
8. Are you able to walk on an unlit street or sidewalk?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
9. Are you able to keep up with others when walking?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
10. Are you able to walk across a slippery floor?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
11. Are you able to walk down a steep gravel driveway?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)
12. Are you able to hike about 2 miles on uneven surfaces, including hills?	☐ (5)	☐ (4)	☐ (3)	☐ (2)	☐ (1)

FLZ

Kreuzen Sie bitte bei jeder der Feststellungen auf den folgenden Seiten jeweils jenes Kästchen an, das am ehesten Ihrer Zufriedenheit in Bezug auf die betreffende Feststellung entspricht.

Beispiel	Sehr unzu - frieden	Unzu - frieden	Eher unzu - frieden	Wed er/ noch	Eher zu - frieden	Zu- frieden	Sehr zu - frieden
Mit dem Wetter bin ich …	☐	☐	☐	☒	☐	☐	☐

Wenn Sie - in diesem Beispiel - mit dem Wetter also weder zufrieden noch unzufrieden sind, dann kreuzen Sie bitte das Kästchen „weder/noch“ an.

Gesundheit	Sehr unzufrieden	Unzu- frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit meinem körperlichen Gesundheitszustand bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner seelischen Verfassung bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner körperlichen Verfassung bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner geistigen Leistungsfähigkeit bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner Widerstandskraft gegen Krankheit bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie häufig ich Schmerzen habe, dann bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie oft ich bisher krank gewesen bin, dann bin ich …	☐	☐	☐	☐	☐	☐	☐

Arbeit und Beruf (Personen im Ruhestand. bitte ehemaligen Beruf bewerten)	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit meiner Position an meiner Arbeitsstelle bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie sicher mir meine berufliche Zukunft ist, dann bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit den Erfolgen, die ich in meinem Beruf habe, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit den Aufstiegsmöglichkeiten, die ich an meinem Arbeitsplatz habe, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Betriebsklima an meinem Arbeitsplatz bin ich …	☐	☐	☐	☐	☐	☐	☐
Was das Ausmaß meiner beruflichen Anforderungen und Belastungen betrifft, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Abwechslung, die mir mein Beruf bietet, bin ich …	☐	☐	☐	☐	☐	☐	☐

Finanzielle Lage	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit meinem Einkommen/Lohn bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem, was ich besitze bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meinem Lebensstandard bin ich …	☐	☐	☐	☐	☐	☐	☐

Mit der Sicherung meiner wirtschaftlichen Existenz bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meinen zukünftigen Verdienstmöglichkeiten bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit den Möglichkeiten, die ich meiner Familie aufgrund meiner finanziellen Lage bieten kann, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner voraussichtlichen (finanziellen) Alterssicherung bin ich …	☐	☐	☐	☐	☐	☐	☐

Freizeit	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit der Länge meines Jahresurlaubes bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Länge meines Feierabends und meiner Wochenenden bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Erholungswert meines Jahresurlaubs bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Erholungswert meiner Feierabende und meiner Wochenenden bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Menge der Zeit, die ich für meine Hobbies zur Verfügung habe, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Zeit, die ich den mir nahe stehenden Personen widmen kann, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Abwechslung in meiner Freizeit bin ich …	☐	☐	☐	☐	☐	☐	☐

Ehe und Partnerschaft (Bitte nur ausfüllen, wenn Sie eine(n) feste(n) Partner(in) haben)	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit den Anforderungen, die meine Ehe/Partnerschaft an mich stellt, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit unseren gemeinsamen Unternehmungen bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Ehrlichkeit und Offenheit meines/meiner (Ehe-) Partners/Partnerin bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Verständnis, das mir mein(e) (Ehe-)Partner(in) entgegenbringt bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Zärtlichkeit und Zuwendung, die mir mein(e) (Ehe-)Partner(in) entgegenbringt, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Geborgenheit, die mir mein(e) (Ehe-)Partner(in) gibt, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Hilfsbereitschaft, die mir mein(e) (Ehe-)Partner(in) entgegenbringt, bin ich …	☐	☐	☐	☐	☐	☐	☐

Beziehung zu den eigenen Kindern (Nur dann ausfüllen, wenn Sie eigene Kinder haben)	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden

Wenn ich daran denke, wie meine Kinder und ich miteinander auskommen, bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich an das schulische und berufliche Fortkommen meiner Kinder denke, bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie viel Freude ich mit meinen Kindern habe, bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich an die Mühen und Kosten denke, die mich meine Kinder gekostet haben, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Einfluss, den ich auf meine Kinder habe bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Anerkennung, die mir meine Kinder entgegenbringen, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit unseren gemeinsamen Unternehmungen bin ich …	☐	☐	☐	☐	☐	☐	☐

Eigene Person	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit meinen Fähigkeiten und Fertigkeiten bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Art, wie ich mein Leben bisher gelebt habe, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner äußeren Erscheinung bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meinem Selbstvertrauen und meiner Selbstsicherheit bin ich …	☐	☐	☐	☐	☐	☐	☐

Mit meiner charakterlichen Eigenart/meinem Wesen bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner Vitalität (d.h. Lebensfreude und Lebenskraft) bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie ich mit anderen Menschen auskomme, bin ich …	☐	☐	☐	☐	☐	☐	☐

Sexualität	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit meiner körperlichen Attraktivität bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meiner sexuellen Leistungsfähigkeit bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Häufigkeit meiner sexuellen Kontakte bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der Häufigkeit, mit der mein(e) (Ehe-)Partner sich mir körperlich zuwendet (streichelt, berührt) bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meinen sexuellen Reaktionen bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie unbefangen ich über den sexuellen Bereich sprechen kann, bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, inwiefern mein Partner und ich in der Sexualität harmonieren, bin ich …	☐	☐	☐	☐	☐	☐	☐

Freunde, Bekannte Verwandte	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Wenn ich an meinen Freundes- und Bekanntenkreis denke, bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Kontakt zu meinen Verwandten bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Kontakt zu meinen Nachbarn bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der der Hilfe und Unterstützung durch Freunde und Bekannte bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meinen Außen- und gemeinschaftlichen Aktivitäten (Verein, Kirche, etc.) bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit meinem gesellschaftlichen Engagement bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich daran denke, wie oft ich unter Leute komme, bin ich …	☐	☐	☐	☐	☐	☐	☐

Wohnung	Sehr unzufrieden	Unzu-frieden	Eher unzufrieden	Weder/ noch	Eher zufrieden	Zufrieden	Sehr zufrieden
Mit der Größe meiner Wohnung bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit dem Zustand meiner Wohnung bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit den Ausgaben (Miete bzw. Abzahlung) für meine Wohnung bin ich …	☐	☐	☐	☐	☐	☐	☐
Mit der der Lage meiner Wohnung bin ich …	☐	☐	☐	☐	☐	☐	☐

Mit der Anbindung an Verkehrsmittel bin ich …	☐	☐	☐	☐	☐	☐	☐
Wenn ich an den Grad der Lärmbelästigung denke, bin ich mit meiner Wohnung …	☐	☐	☐	☐	☐	☐	☐
Mit dem Standard meiner Wohnung bin ich …	☐	☐	☐	☐	☐	☐	☐

Modified weight activity score: (sports/hours per week)

DOES FUNCTIONAL IMPROVEMENT FOLLOWING TKA CORRELATE TO INCREASED SPORTS ACTIVITY?

David R. Marker, B.S.;* Michael A. Mont, M.D.;* Thorsten M. Seyler, M.D.;*
Michael S. McGrath, M.D.;* Frank R. Kolisek, M.D.;** and Peter M. Bonutti, M.D.***

ABSTRACT

Improved TKA designs and surgical techniques have allowed surgeons to not only treat the pain associated with osteoarthritis but also to restore function. The present study analyzed whether the increase in physical activity of patients following surgery is associated with their level of functional and objective improvement. An activity questionnaire was utilized to collect pre- and post-operative information from 355 patients (417 knees). Corresponding functional and objective assessments were collected using the Knee Society rating system. Overall, a mean 48 point (range, -44 to 97 points) improvement in Knee Society function score showed moderate correlation to a 2.5 point (range, -40 to 57 points) increase in weighted activity score (R = 0.362). There was less of a correlation between the mean objective score increase of 49 points (-32 to 84 points) and change in activity level (R = 0.194). There were 29% of the patients who showed no change in activity level. These results suggest that change in activity level is more closely associated with improved function than changes in objective measures. With more than 52% of TKA patients reporting increased activity scores, further studies are needed to assess longer-term effects of activity levels on the durability of these prostheses.

*The Center for Joint Preservation and Reconstruction, Rubin Institute for Advanced Orthopedics, Sinai Hospital of Baltimore, Baltimore, Maryland

**OrthoIndy, Orthopaedics, Indianapolis, Indiana

***The Bonutti Clinic, Effingham, Illinois

None of the authors has signed agreements with a commercial interest related to this study.

Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

Correspondence to:
Michael A. Mont, M.D.
Director, Center for Joint Preservation and Reconstruction
Rubin Institute for Advanced Orthopedics
Sinai Hospital of Baltimore
2401 West Belvedere Avenue
Baltimore, MD 21215
Phone: 410-601-8500
Fax: 410-601-8501
Email: Rhondamont@aol.com and Mmont@lifebridgehealth.org

INTRODUCTION

Total knee arthroplasty (TKA) has been shown to provide excellent short- and long-term outcomes in individuals who are largely sedentary.[1-4] Recently, there has been more attention to patients achieving more functional outcomes and participating in various sporting activities after total knee arthroplasty. This is still an ill-defined area with some orthopaedic surgeons recommending only sedentary activities and other surgeons allowing certain low impact sports.[5-7] Typically, higher impact sports have not been recommended after TKA. However, it is generally accepted that some level of exercise is beneficial and ideally, the return of function and relief of pain provided by TKA will lead to increased exercise and an overall healthier lifestyle. It remains unclear whether improved functional and objective outcomes correlate with an increase in activity level.

Part of the difficulty of analyzing the effects of differing activity levels on knee replacement outcomes is that there is no validated method to analyze these activity levels. The Knee Society functional score describes basic activities such as use of a cane and walking up and down steps.[8] There have been a few recent studies that have described functional results of patients with total knee arthroplasty. For example, Noble et al. reported on the functional results of 257 knee patients.[9] They found that 48% of the patients did not report a functional limitation while participating in activities. In another recent report, 72 high activity knee replacement patients were compared to sedentary TKA patients and found similar clinical and radiographic outcomes at a mean follow-up of 7 years.[10] The authors analyzed patients with an activity scale which was made up of two components; patient activities and impact of activity levels based on Knee Society and American Association of Hip and Knee Surgeons (AAKHS) recommendations. This activity score lacked any information on the duration of sports participation. There are a few other activity scores that have been utilized, but most are qualitative and have not been validated. For example, the UCLA score is a 10-point scoring system based on a general question about activity participation. It has been recommended

TABLE 1
Impact scores for each activity listed on the sports activity questionnaire

Impact Score = 1	Impact Score = 2	Impact Score = 3
Aerobics	Ice Skating	Baseball/Softball
Badminton	Roller/Inline Skating	Basketball
Bicycling (road)	Skiing (cross country)	Football
Bicycling (stationary)	Skiing (downhill)	Gymnastics
Bowling	Tennis (singles)	Handball
Croquet	Weight lifting/machines	Hockey
Dancing		Jogging
Farming		Lacrosse
Fencing		Martial Arts
Gardening		Racquetball
Golf		Rock Climbing
Hiking		Soccer
Horseback Riding		Squash
Horseshoes		Volleyball
Rowing/Canoeing		
Shooting/Hunting		
Shuffleboard		
Speed Walking		
Swimming		
Tennis (doubles)		

that this score can be adjusted based on a visual analog scale and the surgeons assessment of the frequency and intensity of activity.[11]

This study evaluated changes in activity levels following TKA by asking a number of questions: 1) Can a weighted activity score (adding temporal and duration components, and other new recommendations) be easily utilized for TKA patients?; 2) Does functional improvement correlate to an increase in this weighted activity score?; 3) Does objective improvement predict changes in weighted activity score?; 4) What are the activity levels of patients relative to functional and/or objective outcome?; and 5) Do various clinical or demographic factors influence the weighted activity score and objective functional outcomes?

MATERIALS AND METHODS

A group of 417 total knee arthroplasties were assessed for clinical and radiographic follow-up at three institutions between August 1, 2006 and August 1, 2007. The primary purpose of this study was to analyze the weighted activity score for these patients and correlate these to objective and functional outcomes. The activity survey was utilized a cross-sectional assessment of patients who were returning for follow-up for a minimum of 12 months following TKA. All patients who enrolled in this study had Institutional Review Board approval from each center.

There were 162 men and 255 women who had a mean age of 69 years (range, 35 to 95 years). The group consisted of only patients with primary osteoarthritis and excluded any patients with osteonecrosis or post-traumatic arthritis, rheumatoid arthritis or other diagnoses. Patients had a mean body mass index of 31 (range, 17 to 51). Patients were followed for a mean of 36 months (range, 12 to 116 months).

Patients were evaluated with a new weighted activity questionnaire which can be found in Appendix I. A previously reported questionnaire included a listing of activities, frequencies of the activity participation per week, month, and years, and a series of patient-related questions that had to do with activity level, competitiveness, and satisfaction.[10] The activities were then given scores of 1 to 3 points based on a previous Knee Society survey. Activity scores were calculated using frequency times weighted points. The new weighted activity score utilizes all of these questions with some small modifications, but added further information concerning time of involvement per day. In addition, changes were made for the stratification of the sports on the 3-point scale to reflect recent recommendations based on impact level.[12] Table 1 provides the weighted score for each of the sports. Sports listed by the patient on their survey in the "Other" category were assigned a weighted score based on the surgeon assessment of impact level and

SS Radiation Therapy Oncology Group
Phase II Soft Tissue Sarcoma
Toronto Extremity Salvage Score (TESS)

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

AMENDED DATA ☐ YES

INSTRUCTIONS: This sheet is the cover page used for submission of the (SAQ*-F) questionnaire. This page must be completed by the medical staff (nurse, data manager, physician, etc.) See detailed instructions for TESS questionnaire.

1 ☐ TIME POINT(1)

1 Baseline
2 12 months from start of treatment
3 18 months from start of treatment
4 24 months from start of treatment

2 ☐ WAS PATIENT QUESTIONNAIRE COMPLETED?(2)

1 No (Skip to question 3)
2 Yes

2A DATE PATIENT QUESTIONNAIRE COMPLETED

_____-_____-_____(3)

3 ☐ REASON QUESTIONNAIRE WAS NOT COMPLETED(4)

0 Not applicable, questionnaire was completed
1 Patient refused due to illness
2 Patient refused for other reason, specify_____(5)
3 Patient unable to be contacted
4 Institutional error
5 Tool not available in patient's language
6 Other reason, specify _____(6)
9 Unknown

4 ☐ SPECIFY METHOD OF COMPLETION(7)

0 Not applicable (not completed)
1 At appointment
2 By mail
3 By telephone
9 Unknown

5 ☐ DID THE PATIENT REQUIRE ANY ASSISTANCE IN COMPLETING THE QUESTIONNAIRE?(8)

0 Not applicable (not completed)
1 No
2 Yes
9 Unknown if assistance was given

6 ☐ SPECIFY THE PERSON WHO ASSISTED THE PATIENT(9)

0 Not applicable (not completed, no assistance)
1 Staff member
2 Family
3 Other, specify _____(10)
9 Unknown

7 ☐ EXTENT OF ASSISTANCE GIVEN(11)

0 Not applicable (not completed, no assistance)
1 Read items to patient
2 Interpreted items for patient
3 Marked items per patient's response
4 Combination of above, specify _____(12)
5 Other, specify _____(13)
9 Unknown

_____ _____-_____-_____

Signature of person completing this form(14) **Date form completed(15)**

Toronto Extremity Salvage Score (TESS)
Administration of the Questionnaire

General Guidelines

This questionnaire is designed as a measure of physical disability for patients undergoing limb salvage surgery for musculoskeletal tumours. It is a self-administered questionnaire.

There is an upper extremity and lower extremity version of the questionnaire. It is recommended that study personel complete the general information and review the instructions and sample questions with the subjects. The subjects can independently answer the remaining questions. Total completion time of the questionnaire averages 10 minutes.

Scoring

Each question is a measure of the difficulty that the individual has performing the task. The total potential score for an item is a perfect performance score (ie. 5).

The scale has been designed to allow individuals to respond to a non-applicable category on an item if it is not something they perform in their everyday life. Consequently, a total questionnaire score, if desired, would be a standardized score ranging from 0 to 100 calculated by:

$$\frac{\text{sum of the item scores - \# items}}{\text{possible score range}} \times 100\%,$$

where, sum of the item scores = sum of difficulty responses
items = items completed excluding the NA repsonse items
possible score range = (5 x #items) - (1 x #items)

Mail Administration

The TESS questionnaires have been administered by mail and, although formal testing of measurement properties has not been undertaken, patients are able and willing to complete the forms and the scores fall within anticipated ranges.

SS Radiation Therapy Oncology Group
Phase II Soft Tissue Sarcoma
Toronto Extremity Salvage Score (TESS)

RTOG Study 0630 Case #

PLACE LABEL HERE

Institution Institution No.

Participant's Initials Participant's I.D. No.

TESS - LOWER EXTREMITY

Patient Study ID#: _____ Patient Initials: _____
(first/middle/last)

Date of birth: _____ Form Completion Date: _____
(day/month/year) (day/month/year)

Months from start of treatment
- 0 Baseline
- 0 12 months
- 0 18 months
- 0 24 months

Site: 1____ Bone
2____ Soft Tissue

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week.** Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE

Riding a bicycle is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

You should choose the response "impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "888" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

The following questions ask about your ability to perform activities that are common to every day life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your leg, please answer the questions by choosing the answer that best describes your ability to do the activity **over the past week.**

1) Putting on a pair of pants is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

2) Putting on shoes is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

3) Putting on socks or stockings is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

4) Showering is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.
888____This task is not applicable for me.

5) Light household chores such as tidying and dusting are:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

6) Gardening and yard work are:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

7) Preparing and serving meals is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

8) Going shopping is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

9) Heavy household chores such as vacuuming and moving furniture is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

10) Getting in and out of the bath tub is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

11) Getting out of bed is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

12) Rising from a chair is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

13) Kneeling is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

14) Bending to pick something up off the floor is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

15) Walking upstairs is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

16) Walking downstairs is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

17) Driving is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

18) Walking within the house is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

9) Walking outdoors is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

20) Sitting is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

21) Walking up or down hills or a ramp is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

22) Standing upright is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

23) Getting up from kneeling is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

24) Getting in and out of a car is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

25) Participating in sexual activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

26) Completing my usual duties at work is: (Work includes both a job outside the home and as a homemaker.)

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

27) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker.)

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

28) Participating in my usual leisure activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

29) Socializing with friends and family is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

30) Participating in my usual sporting activities is:

1____impossible to do.
2____extremely difficult.
3____moderately difficult.
4____a little bit difficult.
5____not at all difficult.

888____This task is not applicable for me.

1) Considering all the activities in which I participate in daily life, I would rate the ability to perform these activities during the past week as:

1_____impossible to do.
2_____extremely difficult.
3_____moderately difficult.
4_____a little bit difficult.
5_____not at all difficult.

2) I would rate myself as being :

1_____completely disabled
2_____severely disabled.
3_____moderately disabled.
4_____mildly disabled.
5_____not at all disabled.

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your leg that you feel are important and have not been asked about in this questionnaire.

_____
_____
_____

Please check to make sure that you have answered all the questions.

Thank you for taking the time to answer these questions.

Auenbruggerplatz 2, A-8036 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928, Fax: -14348

VOTUM

gültig bis 20.02.2020

EK-Nummer:	31-054 ex 18/19
Studientitel:	Sarcomas of the ankle region: QOL and functional outcome of limb-salvage vs. amputation.
Prüfer:	Univ.-Prof. Dr. Andreas Leithner Univ.-Klinik für Orthopädie und Traumatologie, Medizinische Universität Graz
Sponsor:	Univ.-Klinik für Orthopädie und Traumatologie, Medizinische Universität Graz
Ansprechpartner:	Univ.-Prof. Dr. Andreas Leithner, 8036 Graz, Auenbruggerplatz 5
CRO:	-
Antragsteller:	Univ.-Klinik für Orthopädie und Traumatologie, Medizinische Universität Graz
Ansprechpartner:	Maria Anna Smolle

Die o.a. Studie wurde von der Ethikkommission erstmals in der Sitzung 02-18/19 am 12.11.2018 behandelt.
Die Ethikkommission ist zu folgendem Schluss gekommen:

Es besteht kein Einwand gegen die Durchführung der Studie in der vorliegenden Form.

Stimmberechtigte bzw. anwesende Mitglieder bei der Behandlung waren: Siehe beiliegende Liste vom 12.11.2018.

Kommissionsmitglieder, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher gemäß Geschäftsordnung an der Entscheidungsfindung und Abstimmung nicht teilgenommen haben: keine

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 13.10.2018, begutachtet in der Sitzung 02-18/19 am 12.11.2018

✓	Antragsformular ECS	13.10.2018
✓	Originalprotokoll Study Protocol 1.0	13.10.2018
	Informed Consent Form IC Youths 1.0	06.10.2018
	Informed Consent Form IC Parents 1.0	06.10.2018
	Informed Consent Form IC Adults 1.0	06.10.2018
✓	CV CV_Smolle 1.0	13.10.2018
✓	CV CV_Trost 1.0	11.04.2018
✓	CV CV_Hobusch 1.0	04.04.2018
✓	Sonstiges: Antrag auf Erlass der Bearbeitungsgebühren 1.0	13.10.2018

Dokumente eingegangen am 12.01.2019 (in der nächsten Begutachtung mitbegutachtet)		
✓	Antragsformular ECS Teil A unterschrieben	15.10.2018
	Informed Consent Form Jugendliche 2	09.12.2018
	Informed Consent Form Eltern 2	09.12.2018
	Informed Consent Form Kinder (10-14J) 2	09.12.2018
✓	Fragebögen PROMIS, Ankle S engl. 2	10.03.2017
✓	Fragebögen Plus-M, Ankle S engl. 1.2/2014	
✓	Fragebögen EQ-5D-5L 2009	
✓	Sonstiges: Stellungnahme zur Bearbeitungsmitteilung	12.01.2019
✓	Antrag Teil B Unterschrift Pkt. 14 undatiert	
Dokumente eingegangen am 17.02.2019, begutachtet im 'expedited Review' am 20.02.2019		
✓	Cover Letter	17.02.2019
✓	Informed Consent Form Jugendliche 3	17.02.2019
✓	Informed Consent Form Eltern 3	17.02.2019
✓	Informed Consent Form Kinder (10-14 Jahre) 3	17.02.2019
✓	Informed Consent Form Erwachsene 3	17.02.2019
✓	Letter of Authorization	17.01.2019

Die Ethikkommission geht - rechtlich unverbindlich - davon aus, dass es sich um keine klinische Prüfung nach AMG bzw. MPG handelt.

Das Votum der Ethikkommission berührt in keiner Weise die alleinige Verantwortung der Prüferin / des Prüfers / der Prüfer für die ordnungsgemäße Durchführung der Studie unter Einhaltung aller einschlägiger gesetzlicher Bestimmungen und Richtlinien.

Weiters machen wir darauf aufmerksam, dass der Kommission unverzüglich zu melden sind:

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

- Änderungen, die das Risiko der Teilnehmer/-innen erhöhen oder die Durchführung der Studie wesentlich beeinflussen

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

- Jegliche Information über sonstige Umstände, die die Sicherheit der Teilnehmer/-innen oder die Durchführung der Studie beeinträchtigen können

Dieses Votum gilt für ein Jahr ab dem Datum der Ausstellung. Bei längerer Studiendauer ist rechtzeitig vor Ablauf der Gültigkeit des Votums ein Zwischenbericht vorzulegen (Berichtsformular), um eine etwaige Verlängerung zu erlangen.

Graz, 20. Februar 2019

Univ.Prof.DI Dr.Josef Haas Vorsitzender	iv. Univ.Prof.Dr.Hans Dimai Stv. Vorsitzender

Achtung: Bitte bei allen das Projekt betreffende Schreiben oder telefonischen Anfragen die EK-Nummer angeben!