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Results of Limb-Sparing Surgery of Soft Tissue Sarcoma of the Lower Extremity with Sciatic Nerve Involvement.

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To my beloved family

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LIST OF ABBREVIATIONS

AIB	Carbon-11 aminoisobutyric acid
AJCC	American Joint Committee on Cancer
CAM	Cerium-ammonium-molybdate
CK	Cytokeratin
cm	centimeter
CR	Complete tumor resection
CT	Computer tomography
FDG	Fludeoxyglucose [18F]
FNCLCC	Fédération Nationale des Centres de Lutte Contre le Cancer
FUS/CHOP	Fused in Sarcoma/ C/EBP Homologous Protein
HE Stain	Hematoxylin and Eosin stain
IQR	Interquartile range
MRI	Magnetic resonance imaging
MSTS	Musculoskeletal Tumor Society
NCI	National Cancer Institute
O15-water	Oxygen-15-labeled water
PET	Positron emission tomography
PNET	Primitive neuroectodermal tumor
STS	Soft tissue sarcoma
SUV	Standardized uptake value
UICC	International Union Against Cancer
UPS	Undifferentiated pleomorphic sarcoma

1. INTRODUCTION

1.1 Epidemiology

Soft tissue sarcomas (STS) are a rare and heterogeneous group of mesenchymal tumors, representing only 1% of all adult malignancies [1, 2]. The incidence in Europe is increasing and has been recently reported as 4 per 100,000 people per year [3]. These tumors are highly heterogeneous in their histopathology and tendency for aggressive behavior and they can occur in all age groups and in a variety of anatomic sites [4]. The lower extremity appears to be the most commonly affected site, with approximately 28% of all STS arising there [5]. Mortality rates of up to 50% for patients with STS have been previously reported [6]. The overall survival of patients with STS has recently been reported as 75% at 5 years following treatment [7].

1.2 Diagnosis

The diagnosis of STS can be clinically challenging as these tumors are commonly painless, difficult to palpate and are often located deeply in proximal parts of the body [8]. In addition, STS do not commonly cause symptoms such as fever or night sweats and are not associated with weight loss or cachexia [9]. Any soft tissue mass should be assessed with the awareness that it may represent a sarcoma [9]. Features of a soft tissue mass that are suggestive of malignancy include pain or tenderness, a rapid increase in size, lesions larger than 5 cm in diameter and a location that is intramuscular or extending towards the deep fascia [9].

Further imaging of a suspicious lesion is often helpful in establishing the diagnosis [10]. The size of the lesion and its relationship to the fascia can initially be assessed by an ultrasound examination [9]. However, magnetic resonance imaging (MRI) is considered the standard imaging modality for diagnosing soft tissue lesions and provides useful information and anatomical detail necessary for the surgical planning process [9]. Gadolinium enhancement helps demonstrate the vascularity of the lesion and its anatomical relation to blood vessels and nerves [10]. Computed tomography (CT) imaging can be used as an alternative when an MRI examination is not feasible. A chest CT scan should be carried out as part of the screening process for metastatic

disease [8]. Positron emission tomography (PET) scanning is developing an increasing role in the investigation of STS as it provides information on the biological activity of tissue, particularly when screening for metastatic disease and involvement of lymph nodes, as well as assessing the response to neoadjuvant therapy [8, 9]. A correlation between tumor grade and FDG uptake has been shown, allowing the potential future use of FDG PET scans as both a diagnostic and prognostic tool in patients with STS [11, 12]. Furthermore, different radiotracers in addition to FDG, such as AIB and O15-water, have been used to identify viable tumor tissue [13, 14].

Obtaining a biopsy is essential in identifying the histopathological subtype of the tumor. Although needle biopsies are associated with fewer complications, open or trucut biopsies are often preferred due to their superior diagnostic accuracy regarding the histologic cell type and grade [8]. This procedure should be carried out after MRI imaging has taken place, as the biopsy may cause local trauma to the surrounding tissues and compromise the interpretation of the MRI images [9]. Furthermore, the biopsy incision should be made in line with future incisions for resections [9]. The exposure of neurovascular structures should be avoided in the extremities [15, 16]. If the placement of drains is necessary, they should be brought out in an imaginary line extending from the incision [15]. The biopsy should ideally be performed by the surgeon who will be carrying out the definitive resection of the tumor to ensure its correct placement [7].

1.3 Staging

The preoperative planning of the tumor resection, particularly regarding the surgical margins, relies heavily on local staging of the tumor [7]. MRI is the imaging modality of choice for local staging [9]. Systemic staging involves screening for metastatic disease. Radiographic or CT imaging of the lungs is essential as STS metastasize predominantly to the lungs [9]. The main staging systems in current use are the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) system [17] and the Musculoskeletal Tumor Society (MSTS) staging system [18]. Both systems require the tumor grade (G1/G2/G3 for the AJCC/UICC system and high vs. low grade, G1/G2, for the MSTS system) and the absence or presence of metastases, M0 or M1 respectively. The location of the tumor, confined to an anatomic compartment (T1) or extracompartmental (T2), is incorporated into

the MSTS system. The AJCC/UICC system also includes the tumor size (T1: maximum diameter < 5 cm, T2: maximum diameter > 5 cm) and the absence or presence of regional lymph node involvement, N0 and N1 respectively. Both staging systems are summarized in tables 1 and 2.

Table 1. AJCC/UICC staging system for STS [17]

Stage	4 Tumor Components
IA	G1, T1, N0, M0
IB	G1, T2, N0, M0
IIA	G2, T1, N0, M0
IIB	G2, T2, N0, M0
IIIA	G3, T1, N0, M0
IIIB	G3, T2, N0, M0
IVA	any G, any T, N1, M0
IVB	any G, any T, any N, M1

Table 2. MSTS staging system for STS [18]

Stage	3 Tumor Components
IA	G1, T1, M0
IB	G1, T2, M0
IIA	G2, T1, M0
IIB	G2, T2, M0
III	any G, any T, M1

1.4 Histopathology

Accurate diagnosis and identification of the histopathologic subtype of STS is essential in planning the correct treatment regime, particularly when deciding whether neoadjuvant or adjuvant radiation therapy or which chemotherapy agents are appropriate [7]. At least 50 histologic subtypes have been identified, with undifferentiated pleomorphic sarcoma (UPS) and liposarcoma being the most common subtypes in adult patients [19]. The most common subtypes of STS are

summarized in table 3 [20]. Most STS metastasize hematogenously; some subtypes, such as synovial sarcoma, are however also capable of spreading through the lymphatic system [19]. A reference pathological examination to confirm the tumor histopathology is recommended due to the high rate of pathological misdiagnoses, reported as high as up to 30%, particularly in community pathology [21]. Stable chromosomal translocations found exclusively in tumor cells have been demonstrated in a subset of STS. These translocations provide a unique marker for tumor detection, such as the FUS/CHOP fusion gene in myxoid and round cell liposarcomas, which appear to have strong oncogenic properties [22].

Table 3. Most common soft tissue tumors based on WHO Classification [20]

Tissue of origin	**Tumor Type**	**Subtypes**
Adipocytic	Liposarcoma	6: dedifferentiated, myxoid, round cell, pleomorphic, mixed-type, not otherwise specified
Fibroblastic/ Myofibroblastic	Fibrosarcoma	4: adult fibrosarcoma, myxofibrosarcoma, low grade fibromyxoid (spindle cell tumor), sclerosing epithelioid
So-called fibrohistiocytic	Undifferentiatiated pleomorphic 'MFH' sarcoma (UPS)	3: UPS, UPS with giant cells, UPS with prominent inflammation
Skeletal muscle	Rhabdomyosarcoma	3: embryonal, alveolar, pleomorphic
Smooth muscle	Leiomyosarcoma (excluding skin)	None
Vascular	Epithelioid hemangioendothelioma, Angiosarcoma	None
Uncertain	Synovial sarcoma, Epithelioid sarcoma, Alveolar soft part, Clear cell sarcoma, Extraskeletal Ewing	None

	tumor	

1.5 Prognosis

There are many factors which have been shown to play an important role in determining the prognosis of STS. Tumor grade, in particular, has been shown to be an important prognostic factor in several studies [4, 23, 24]. However, Pisters et al. have suggested that the prognostic significance of tumor grade for distant metastasis decreases with time [24]. Most studies differentiated between prognostic factors for local disease recurrence and those for distant metastasis.

The independent risk factors for the development of a local recurrence in a study with a large cohort of 1,041 patients carried out by Pisters et al. in 1996 were reported as presentation with local recurrent disease, positive surgical margins, patients older than 50 years of age and the histologic subtypes of fibrosarcoma and malignant peripheral nerve sheath tumor [24]. The significant prognostic factors for the development of distant metastases in this study were presentation with local recurrent disease, large tumors [> 5 cm], deep tumor location, high grade tumors and the histologic subtype of leiomyosarcoma [24]. The authors of this study also emphasized the role of histologic subtype as an independent prognostic factor, which was previously considered to be of secondary importance [25]. Liposarcoma was found to be of favorable prognostic significance in the development of metastatic disease [24] and has also been associated with a reduced risk of local recurrence in previous studies [23, 26].

Negative surgical margins have been identified as a significant predictor of local disease control in many studies [23, 24, 26, 27] and are widely accepted in clinical practice as essential in reducing the risk of local recurrence. The surgical margins were, however, not found to be predictive of local disease control in a review of 211 patients with high grade STS of the extremities carried out by Potter et al. [28]. Oncological reresection in patients with STS of the extremities and positive margins has been associated with favorable clinical outcomes [29]. Tumor localization and the involvement of important neighboring structures, amongst other factors, appear to play a key role in achieving negative margins. The rate of microscopically positive margins is, for example, higher in retroperitoneal STS with a rate of approximately

30% in primary tumors and up to 70% in resections of recurrent tumors, when compared to STS of the extremities [30]. On the other hand, certain cases of STS with vascular or neural involvement require well-planned vascular resections and replacement strategies to achieve negative microscopic margins [31, 32].

An additional prognostic factor reported by Elias et al. was the primary tumor site [4]. Intraperitoneal and retroperitoneal sarcomas are associated with a poorer prognosis, possibly due to the increased difficulty in obtaining microscopically negative margins in these anatomical locations, which are often in close proximity to many vital structures [4]. Radiation-induced sarcomas have also been associated with a poor prognosis despite radical resections [33].

The development of a local recurrence has been associated with a poor prognosis regarding local and distant disease control in addition to overall survival [34, 35]. Metastatic STS is associated with a poor overall survival, with 5-year survival rates of 10% or less being reported in patients with pulmonary metastases not treated with a metastasectomy [19]. Factors which improve the prognosis of these patients include a single pulmonary metastatic lesion, negative resection margins after metastasectomy and a disease-free interval of at least 12 months prior to the development of metastatic disease [36]. In addition, the standardized uptake value (SUV) measured in FDG PET studies has demonstrated a prognostic relevance regarding the further course of the disease in patients with STS [12].

1.6 Treatment of STS with sciatic nerve involvement

The treatment of STS of the lower limb with sciatic nerve involvement presents a unique surgical and oncological challenge. In the past, sciatic nerve involvement was an indication for limb amputation [37, 38]. The increased use of multimodality treatment, particularly adjuvant radiation therapy, has however led to less radical surgery with better functional outcomes [39]. More aggressive local treatment is usually indicated with unplanned or intralesional positive margins, such as high dose radiation therapy followed by a wide excision or amputation. Patient outcomes are still inferior despite aggressive treatment, highlighting importance of appropriate diagnosis and management in the initial treatment [9]. A multidisciplinary approach in a specialist center has been shown to significantly improve patient outcome [40].

Inferior outcomes have been demonstrated in patients receiving surgical interventions, including biopsies, prior to referral to a multidisciplinary center [15, 16, 41, 42].

1.6.1 Surgical treatment

Surgery remains the most important factor in achieving a local disease-free state and maximizing function [43]. There has been a continuous shift towards preservation of the limb and multimodality treatment since the results of the National Cancer Institute's (NCI) randomized prospective study were published in 1982 [23]. This study found no significant difference in the survival rates of patients with STS of the extremities when comparing amputation with limb sparing surgery in combination with radiation therapy [27]. The first report of sciatic nerve resection in a STS of the lower extremity in 1984 [44] was based on the hypothesis that the use of ankle-foot orthoses leads to a superior function of the leg when compared to hip disarticulation. Limb preserving surgery is currently considered the standard surgical treatment for STS of the lower extremity [31].

Local disease control is essential in the management of STS, with surgical resection being the only treatment modality capable of achieving a local disease-free state [43]. Surgical resection of STS with negative microscopic margins has been shown to significantly reduce the risk of local recurrence [45]. The ability to obtain wide margins may however be particularly challenging if the tumor is adjacent to important neurovascular structures. The tumor size greatly influences the ability to obtain negative microscopic margins, with larger tumors leading to smaller resection margins [43]. A resection margin of 1 to 2 mm, for example, is generally accepted when trying to preserve functional tissue, such as when dissecting a major nerve [43].

Regarding the tumor resection, it is more important to achieve wider margins with the longitudinal tumor excision compared to the transverse excision due to the growth pattern of STS [43]. Drains should be placed in line with the skin incision and exit distally in case a future secondary amputation is necessary [19]. In addition, any

previous incisions or tracts from biopsies or drain placements must also be excised in the definitive tumor resection [43].

For STS with vascular involvement, reasonable oncological outcomes have been reported with vessel reconstruction in limb salvage surgery [31, 46, 47]. Nerve reconstruction, on the other hand, does not guarantee preservation of function [48]. Tumor infiltration of the sciatic nerve has previously been an indication for limb amputation [37], but more recent studies have shown limb sparing surgery with partial or complete sciatic nerve resection to be an excellent alternative [49-52].

The most commonly reported complications following limb sparing surgery are related to delayed wound healing and infection. A wound morbidity rate of 34.4% has been reported in en bloc resections alone without adjuvant treatment modalities [53]. Risk factors for developing wound complications include prolonged duration of surgery and adjuvant therapy, particularly neoadjuvant radiation or chemotherapy [7]. Postoperative delayed wound healing may also lead to a delay in commencing adjuvant radiation or chemotherapy. Other complications specific to limb sparing surgery include unplanned neurovascular injury, particularly in confined anatomical spaces such as the popliteal fossa, devascularization of soft tissue flaps, joint dislocations and fractures [7].

Proposed contraindications for limb sparing surgery include an expected survival of less than 3 months which would not justify complex surgery, significant tumor contamination of adjacent tissues through poorly performed biopsies or excisions or a pathological fracture, as well as severe local infection or systemic sepsis [7].

1.6.2 Radiation therapy

When used as a single treatment modality, local surgical resection and marginal excisions of high-grade STS have been associated with high local failure rates of 70-90% [54]. In addition, a 25% recurrence rate has been reported in patients undergoing radical limb sparing surgery as a single treatment modality [54]. Surgical resection alone has however been demonstrated to be sufficient in low grade subcutaneous STS of the extremities [55]. Baldini et al. also reported good local control rates in a cohort of 74 patients with STS of the trunk or extremities with low or intermediate grade small tumors when managed with surgical resection alone [56].

The standard goal of surgery has always been to achieve wide margins upon tumor resection. The development of neoadjuvant and adjuvant radiation therapy has led to equivalent local control rates with focally positive marginal resections [57]. The beneficial effects of adjuvant radiation therapy in treating STS are generally well documented in the literature, with reported local control rates of 90% or greater [19]. Several studies found no significant difference when comparing the effects of neoadjuvant and postoperative radiation therapy on local and distant disease control or disease-free survival [58, 59]. Many authors, however, recommend neoadjuvant radiation therapy as it has been associated with better long term functional outcomes, especially in lower limbs, despite higher rates of wound complications [9, 19, 58]. Flugstad et al. reported major wound complications in 18% of patients treated with adjuvant radiation therapy compared to an incidence of up to 37% in patients treated with neoadjuvant radiation therapy as reported by Bujko et al. [43, 60]. An increased incidence of skin fibrosis, edema, joint stiffness and fracture has been shown in adjuvant radiation therapy [58]. Some authors argue, however, that radiation therapy is most effective when delivered to a low tumor load and therefore recommend adjuvant radiation therapy, particularly in bulky tumors [4]. The dose of radiation has not been found to significantly influence local disease control [23].

Brachytherapy refers to the implantation of a sealed radiation source, usually administered through the insertion of a catheter over a 3-day period, and has been shown to decrease local recurrence rates in some studies [61, 62].

1.6.3 Chemotherapy

The use of adjuvant chemotherapy in non-metastatic disease is still controversial and is usually an individual and interdisciplinary decision, even in patients at an increased risk of developing metastatic disease [63]. Commonly accepted factors which favor the administration of adjuvant chemotherapy include local or distant disease recurrence, or a histologically confirmed synovial sarcoma or pediatric rhabdomyosarcoma [19]. High grade deeply located tumors larger than 5 cm in size or intermediate grade deeply located tumors larger than 10 cm in size, especially in younger patients, are considered a relative indication for chemotherapy [64].

The standard first-line chemotherapeutic agent used for metastatic STS is doxorubicin. Tap et al. compared a combination of doxorubicin and olaratumab with doxorubicin alone an demonstrated a significant improvement of 11.8 months in the median overall survival was in the group of patients receiving both doxorubicin and olaratumab [65]. These results could lead to the addition of olaratumab in the first-line chemotherapeutic treatment of metastatic STS. Gronchi et al. investigated the effects of histology-tailored neoadjuvant chemotherapy versus the standard chemotherapy regime of doxorubicin and ifosfamide in a randomized phase 3 multicenter trial consisting of 287 patients with STS [66]. Interestingly, the group of patients receiving the standard chemotherapy regime demonstrated superior outcomes, particularly regarding the projected disease-free survival, when compared to the group receiving histology-tailored chemotherapy [66].

Several studies have demonstrated the beneficial short-term effects of chemotherapy which were, however, not maintained over time [67-69]. When histologic subtypes of STS were studied separately, synovial sarcoma and pediatric rhabdomyosarcoma were found to have the most favorable response to chemotherapy [70]. This is possibly due to the potential of developing specific treatment which targets gene products, as these histologic subtypes of STS have known chromosomal translocations [70].

1.7 Postoperative follow up

Early detection of recurrent local or metastatic disease is important and can lead to a prolongation of the long-term survival of these patients [43]. The surveillance of patients following the definitive treatment of the STS consists of monitoring the primary tumor site for signs of a local recurrence. This is principally carried out through the conduction of regular follow up appointments and physical examinations of the primary tumor site in addition to serial MRI scans of the site with and without gadolinium enhancement [19].

Regular follow-up appointments and physical examinations of the surgical site are essential particularly in the early postoperative period to screen for postoperative complications such as wound dehiscence or devascularization of soft tissue flaps.

CT scans of the chest are also warranted as part of the surveillance process for metastatic disease as the most common site of metastases is the lung. CT scans are usually performed every 3 months for the first 2 years postoperatively, every 4 months for the third year and every 6 months for the fourth and five years in patients with high-grade STS [19]. Such frequent CT scans of the chest are not necessary in patients with low-grade STS and should be selectively carried out in patients considered to be at high risk of developing metastatic disease, as the surveillance of patients at low risk of metastatic disease with regular radiographs of the chest is otherwise sufficient [71].

1.8 Aim

Only a few reports on the outcomes of limb preserving surgery in patients with STS with nerve involvement have been published to date [49-52], with most studies limited to a small number of patients (≤20) [49-51]. The size and results of these studies have been summarized in table 4. In addition, no treatment guidelines exist on how to manage STS with major neural involvement. The aim of this study is to analyze the oncological and functional outcomes of limb sparing surgery in STS with sciatic nerve involvement. In addition, we aim to classify the degree of nerve involvement and suggest a treatment algorithm.

Table 4 Summary of studies examining patients with STS with sciatic nerve involvement to date [49-52]

Author	Year of publication	Number of patients	Summary of findings
Bickels et al.	2002	15	The sciatic nerve was resected in all patients. Overall function good in 11, moderate in 3 and poor in 1 patient. *Conclusion: sciatic nerve resection is not an indication for amputation.*
Brooks et al.	2002	18	One secondary amputation was carried out due to disease recurrence. The functional deficits were acceptable in surviving patients both objectively and subjectively. *Conclusion: limb sparing surgery with sciatic nerve resection is an excellent alternative to limb amputation.*
Fuchs et al.	2001	20	Patients rated their level of impairment after sciatic nerve resection as mild to moderate. *Conclusion: the acceptable functional outcomes in patients with STS with sciatic nerve involvement highlights that these patients can be treated with limb sparing*

			surgery is an alternative to hip disarticulation or hindquarter amputation.
Clarkson et al.	2005	50	43 patients treated with epineural dissection were compared to 7 patients who were treated with complete resection of the sciatic nerve. Epineural dissection was not attempted in patients with tumor encasement of the nerve. Functional benefit of preserving the nerve by epineural dissection was demonstrated. *Conclusion: resection of the sciatic nerve should be reserved for patients with complete macroscopic tumor encasement of the nerve.*

2. MATERIALS AND METHODS

2.1 Study design and patient selection

The data of all adult patients with STS of the extremities, truncal STS and retroperitoneal STS undergoing surgical treatment at the Clinical Center Frankfurt Höchst from January 1st 2010 until January 31st 2017 was collected in a computerized database on an ongoing basis and retrospectively analyzed. Patients with STS of the lower limb with sciatic nerve involvement who underwent limb-sparing surgery were selected from the database and included in this study. All patients were consented on the use of their clinical data for research purposes. The study was approved by the ethics committee of the Medical Council of the State of Hesse, Germany.

Involvement of the sciatic nerve was confirmed preoperatively when CT or MRI scans showed no layer of normal tissue between the tumor and the sciatic nerve. For the purpose of this analysis, sarcomas affecting other anatomic sites or other nerves were excluded.

2.2 Classification of nerve involvement

The extent of neural involvement was assessed using high-resolution CT and MRI scans. Intraoperative reassessment of sciatic nerve involvement was also carried out by visually analyzing and palpating the relationship of the nerve to the tumor when possible. Intraoperative ultrasound visualizing the extent of the contact between the tumor and the nerve was additionally carried out in selected cases.

STS with encasement of the nerve were classified as type A tumors. Encasement was defined as ≥ 180° of nerve contact with the tumor. These tumors were reassessed intraoperatively and were treated with en-bloc compartmental resection together with the nerve if the classification was confirmed. STS with direct nerve contact (< 180°) without encasement or disruption of its continuity were classified as type B and underwent compartmental resection of the tumor with epineural nerve dissection. STS without nerve involvement were classified as type C and were resected without nerve dissection or resection. The proposed classification of STS with sciatic nerve involvement and the suggested treatment approach has been summarized in Figure 1. Figures 2, 3, 4, 5, 6 and 7 are examples of MRI scans from six of our patients to illustrate radiological type A and type B sciatic nerve involvement.

Figure 1. Classification of sciatic nerve involvement and suggested surgical treatment algorithm for patients with STS of the lower extremity

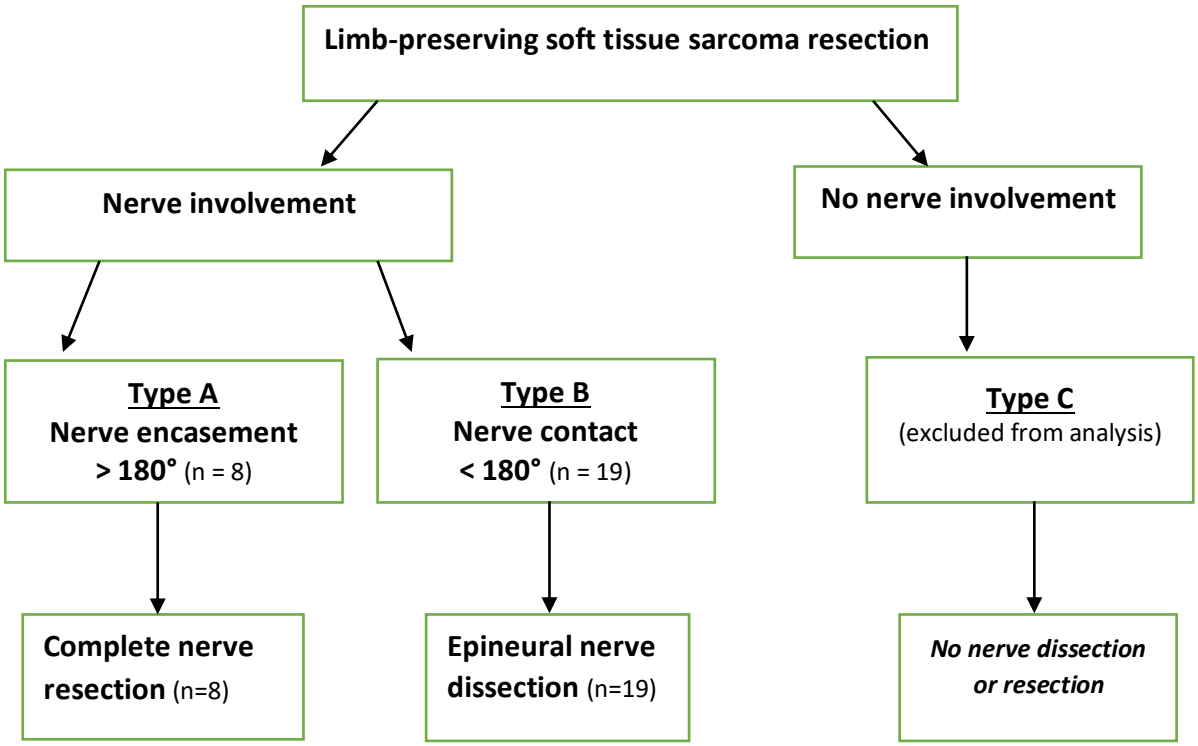


Figure 2. Preoperative MRI scan (T2-weighted, 1.5 Tesla) of a patient with a G3 pleomorphic sarcoma and type A sciatic nerve involvement *(source: Radiological Institute, Clinical Center Frankfurt Höchst)*

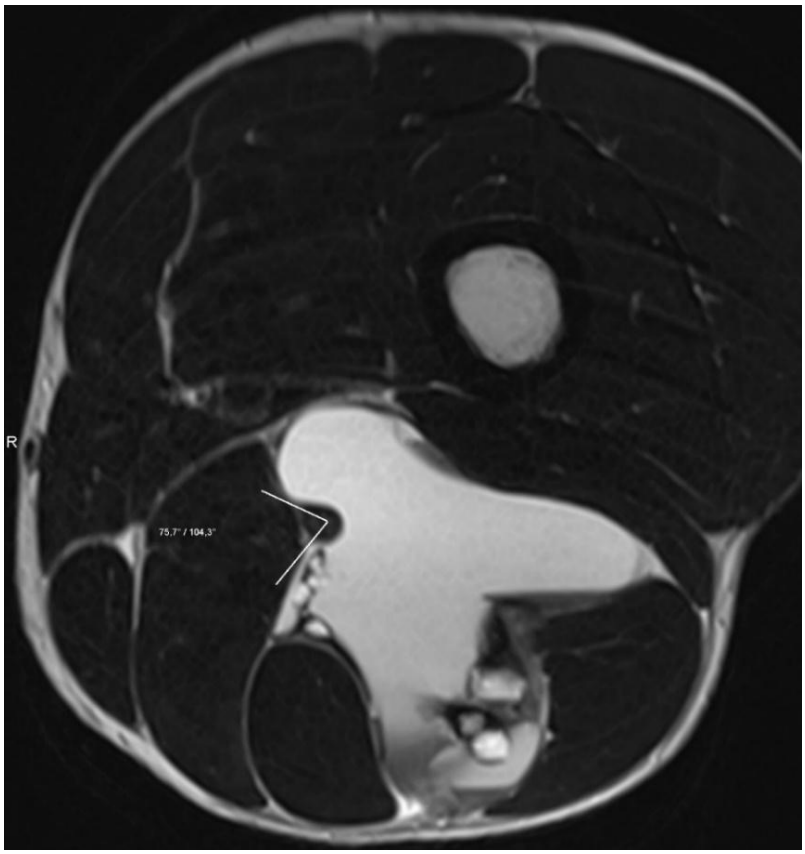


Figure 3. Preoperative (left) and postoperative (right) MRI scans of a patient with G3 myxoid liposarcoma and type A sciatic nerve involvement *(source: Radiological Institute, Clinical Center Frankfurt Höchst)*

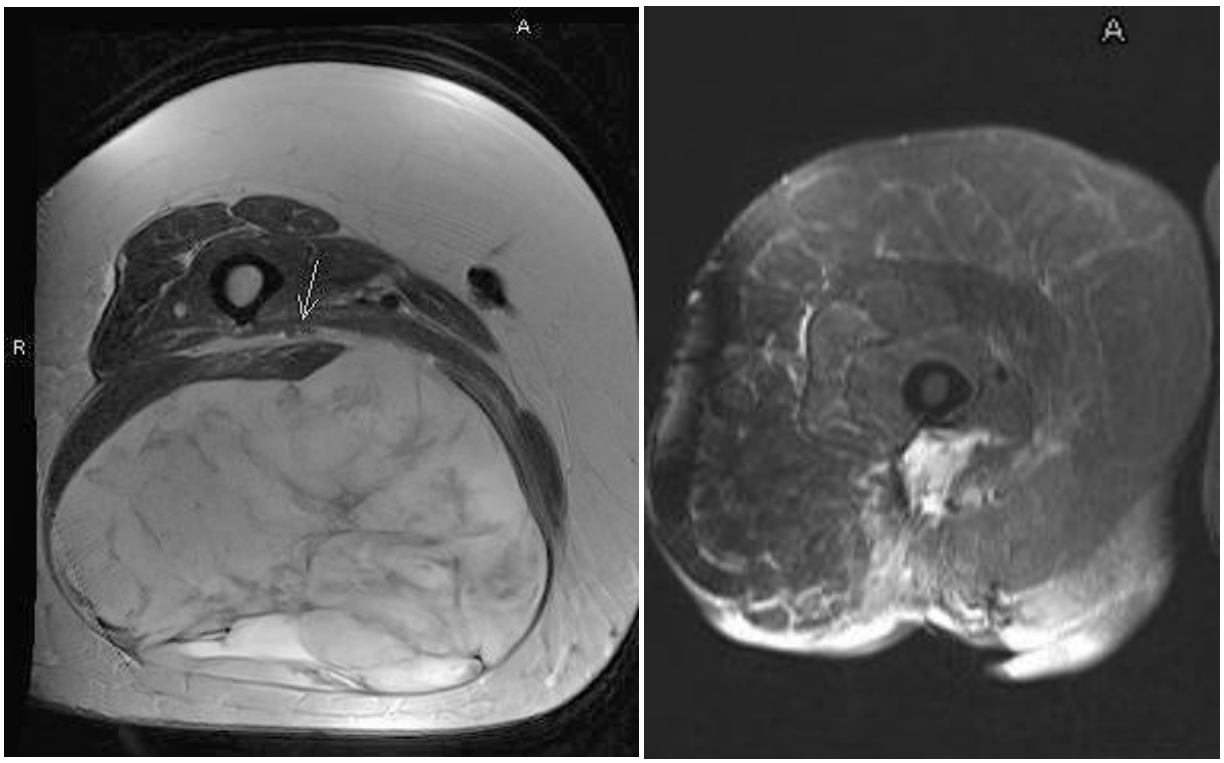


Figure 4. Preoperative MRI scan (T2 weighted, 1.5 Tesla) of a patient with a G2 pleomorphic sarcoma and type A sciatic nerve involvement *(source: Radiological Institute, Clinical Center Frankfurt Höchst)*

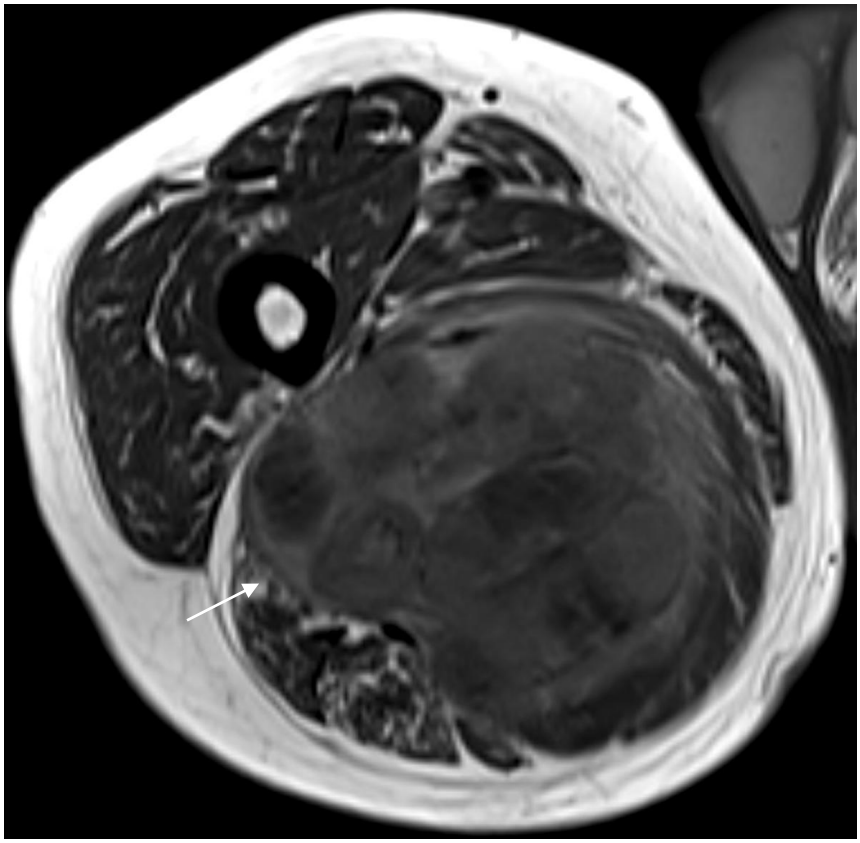


Figure 5. Preoperative MRI scan (T2 weighted fat saturated sequence, 1.5 Tesla) of a patient with a G2 myxoid liposarcoma and type B sciatic nerve involvement *(source: Radiological Institute, Clinical Center Frankfurt Höchst)*

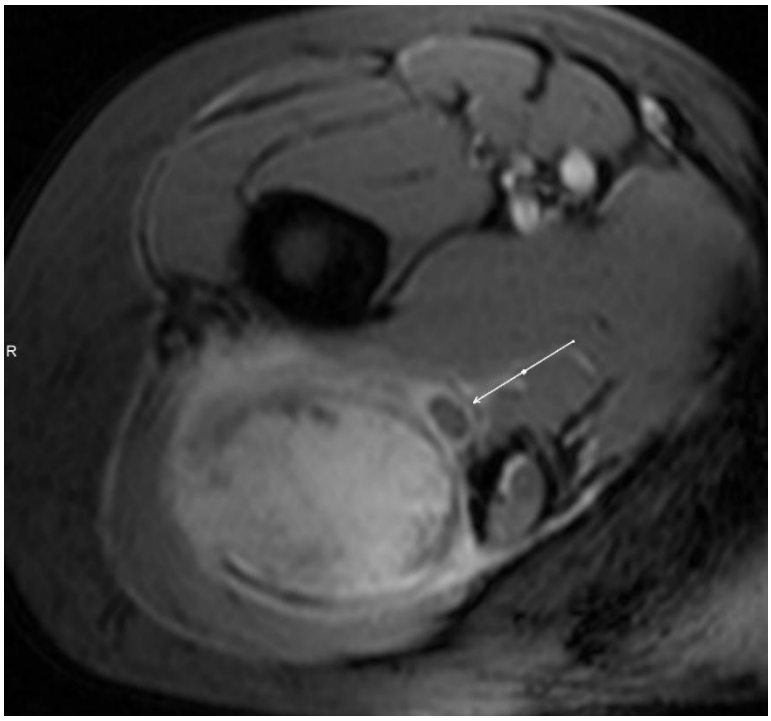


Figure 6. Preoperative MRI scan (T2 weighted fat saturated sequence, 1.5 Tesla) of a patient with a G2 pleomorphic sarcoma and type B sciatic nerve involvement *(source: Radiological Institute, Clinical Center Frankfurt Höchst)*

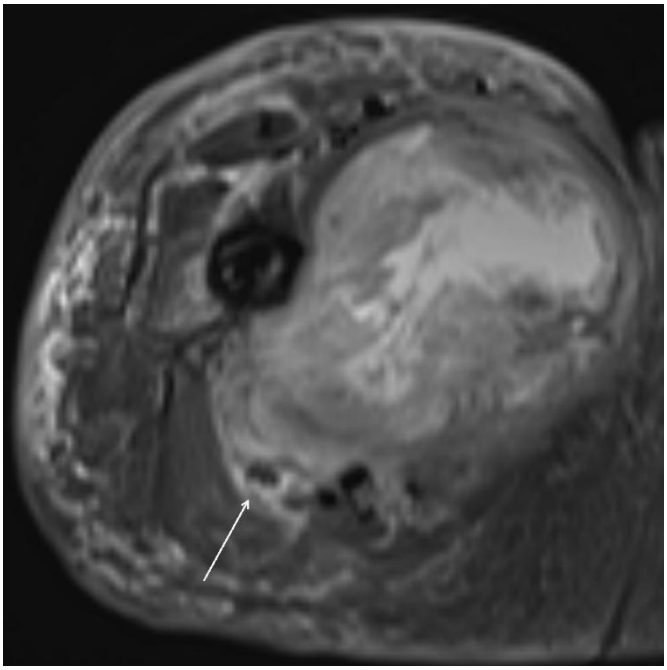
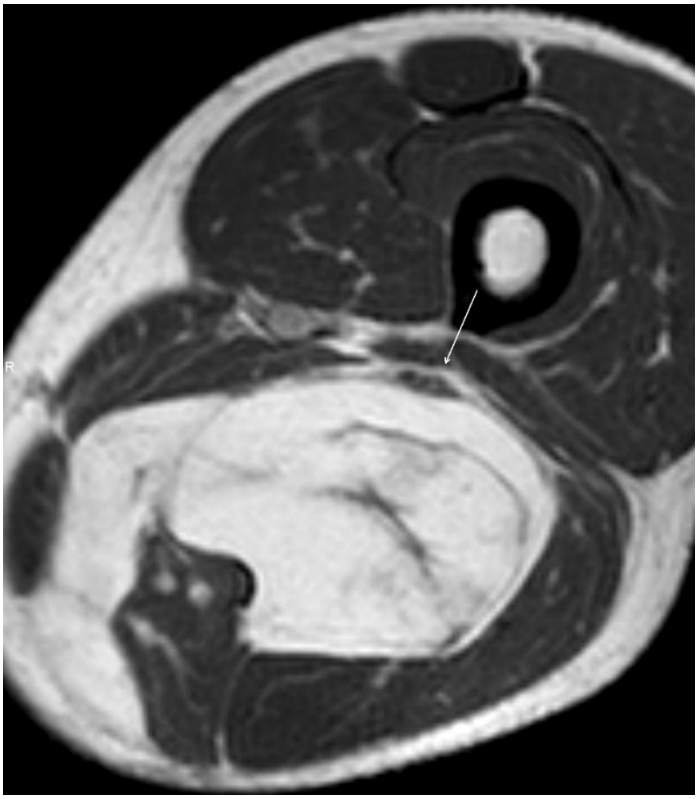


Figure 7. Preoperative MRI scan (T1 weighted, 3 Tesla) of a patient with a G1 liposarcoma and type B sciatic nerve involvement *(source: Radiological Institute, Clinical Center Frankfurt Höchst)*



2.3 General and perioperative variables

The presentation status of each patient (primary tumor, local recurrence or presence of metastatic disease) in addition to basic patient demographic data such as age, gender and side of the affected limb were documented. All therapeutic measures such as neoadjuvant or adjuvant external radiation therapy, neoadjuvant or adjuvant chemotherapy, isolated limb perfusion or surgical resection were carried out upon recommendation by a multidisciplinary tumor board and were also recorded in our database. En-bloc compartmental resections were carried out in accordance with the surgical standards described by Enneking et al. [18, 72]. Involved thigh compartments as well as any concurrent vascular reconstruction, plastic reconstruction or bone stripping were documented. An example of an en-bloc resection of the medial thigh compartment with partial resections of the posterior and anterior thigh compartment in a patient with a liposarcoma of the lower extremity with type B sciatic nerve involvement is displayed in figures 8 and 9.

Figure 8. Intraoperative photo documentation of liposarcoma of right lower extremity with type B sciatic nerve involvement prior to en-bloc resection

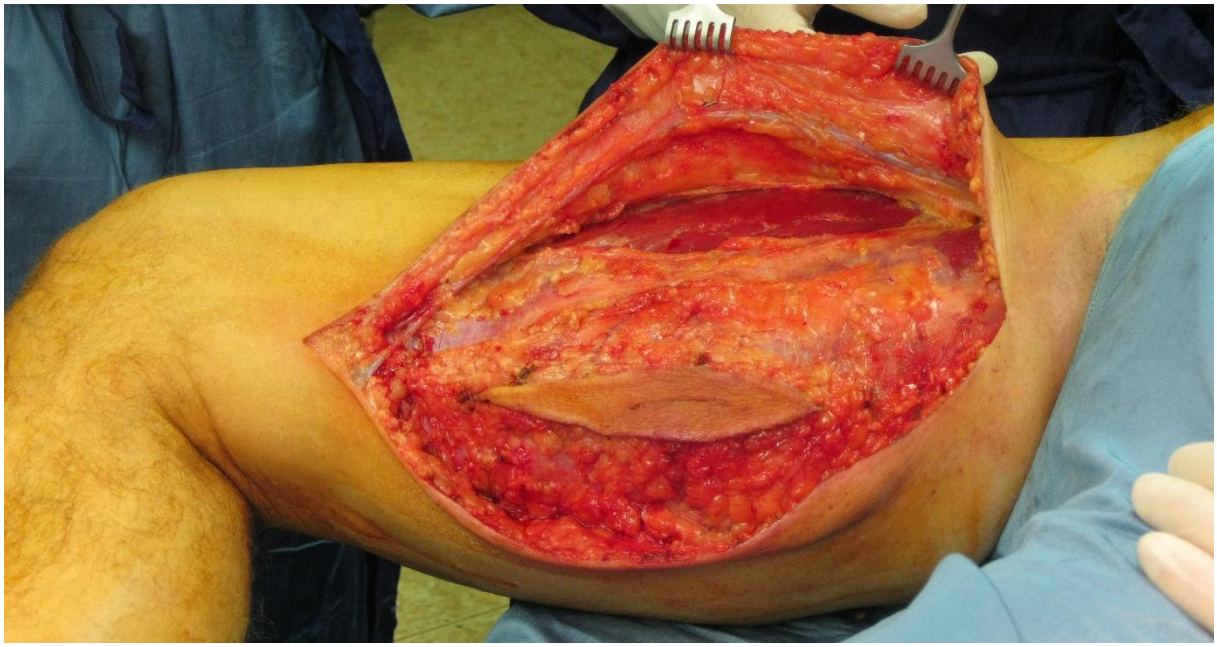
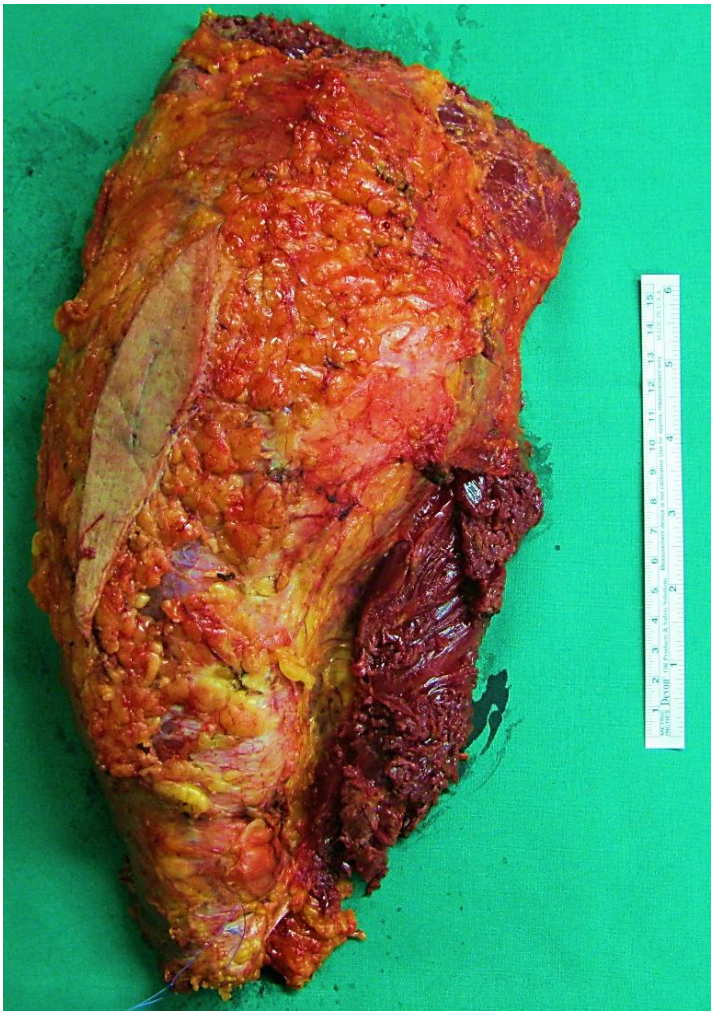


Figure 9. Postoperative photo documentation following en-bloc resection of liposarcoma of right lower extremity with type B sciatic nerve involvement



Assessment of tumor specimens was carried out by the in-house pathologists and confirmed by the reference pathological department of Heidelberg University Hospital. The resected tissue was assessed for histological entity, tumor size (maximum diameter), grade and microscopic margins. All samples were explicitly examined for the occurrence of histopathologic infiltration of sciatic nerve tissue by tumor cells. Tumor grading was based on the criteria of the “Fédération Nationale des Centres de Lutte Contre le Cancer” (FNCLCC), which takes cell differentiation, mitotic activity and necrosis into consideration [73]. The FNCLCC grading system is summarized in table 5. The duration of surgery, incidence of surgical and medical complications, reoperations and the duration of hospital stay were also recorded.

Table 5. FNCLCC grading system [73]

Dedifferentiation Score	Mitosis Score	Necrosis Score	Total Score	Grade
1: resembling normal	1: 0-9 / 10 HPF	0: None	2 – 3	1
2: definitive	2: 10-19 / 10 HPF	1: < 50%	4 – 5	2
3: undifferentiated	3: > 20 / 10 HPF	2: > 50%	6 – 8	3

2.4 Survival, disease progression and functional outcome

Patients were seen at regular intervals as part of their cancer follow-up care following discharge. The follow-up care plan for these patients has been summarized in table 6. Data regarding progression of disease (local recurrence or metastasis) as well as overall survival were also collected. In cases of disease progression, the site of metastasis as well as secondary amputations due to local recurrence were recorded.

Table 6. Follow-up care plan following hospital discharge for our patients at Frankfurt Höchst Clinical Center

Tumor grade	Frequency of postoperative clinical examinations	Frequency of postoperative radiological examinations
High/ intermediate	Years 1 and 2: Three monthly Year 3: Six monthly Years 4 and 5: Annually	MRI of primary site with every clinical examination. Chest CT scans: Six monthly
Low	Years 1 and 2: Six monthly Years 3, 4 and 5: Annually	MRI of primary site with every clinical examination. Chest CT scan / radiograph of chest: Annually

The functional outcome of our patients was assessed by examining the lower limb for function and range of motion. The results of the clinical examination were then categorized as either normal, limited or severely limited. Limited function was defined as a reduced active knee flexion of between 90° and 110° and / or weakness of the intrinsic foot muscles; movement of the foot was possible but reduced. Patients with

severely limited function of the leg had a severely reduced knee flexion of less than 90° and minimal or no movements of the foot were possible. Patients were also asked about the presence of chronic swelling, paresthesia or chronic pain as well as their walking range and the use of walking aids. Finally, the musculoskeletal tumor society [MSTS] rating score modified by Enneking was calculated in the 20 surviving patients at approximately one year postoperatively during the outpatient follow up examination [74]. This scoring system is summarized in table 7 and consists of six main categories: pain, limb function, walking aids, walking distance, gait and emotional acceptance. A score of 0 – 5 is assigned to each category; higher scores are associated with a greater level of function. The scores out of a total of 30 were then converted to percentages. Finally, as part of their most recent follow-up visit, patients were asked about their satisfaction with limb preservation and whether they would make the same choice again. The answers, either a “yes” or “no”, were then recorded in our database.

Table 7. Musculoskeletal Tumor Society [MSTS] Rating Score modified by Enneking [74]

Pain	Function	Walking aids	Walking distance	Emotional	Score
Severely disabling	Complete restriction	Two crutches or wheelchair	Unable to walk independently	Dislikes	0
Moderately disabling	Partial restriction	One crutch/ walking stick	Only mobile indoors	Accepts	1
Intermediate	Intermediate	Occasional use of crutch	Severely limited outdoors	Intermediate	2
Modest	Recreational restriction	Brace	Limited	Satisfied	3
Mild	Mildly restricted	Orthotics	Mildly limited	Content	4
No pain	No restriction	None	No limitation	Enthused	5

2.5 Statistical methods:

Statistical analyses were performed with IBM SPSS Statistics 24. Continuous variables were expressed as median and range and correlations between continuous variables were explored using the Pearson correlation test [75].

The X^2 test and Fisher exact test were used when comparing categorical variables. When comparing continuous variables, the Kolmogorov-Smirnov-Lilliefors-Test was implemented in determining whether data followed a normal distribution. The independent t-Test was used with normally distributed data and the Wilcoxon-Mann-Whitney-U-Test with non-normally distributed data [75].

The Kaplan-Meier method was used to calculate the survival and disease progression curves and the log-rank test was used to calculate differences between groups. Within the exploratory nature of this work, we considered a p value of ≤0.05 significant [75].

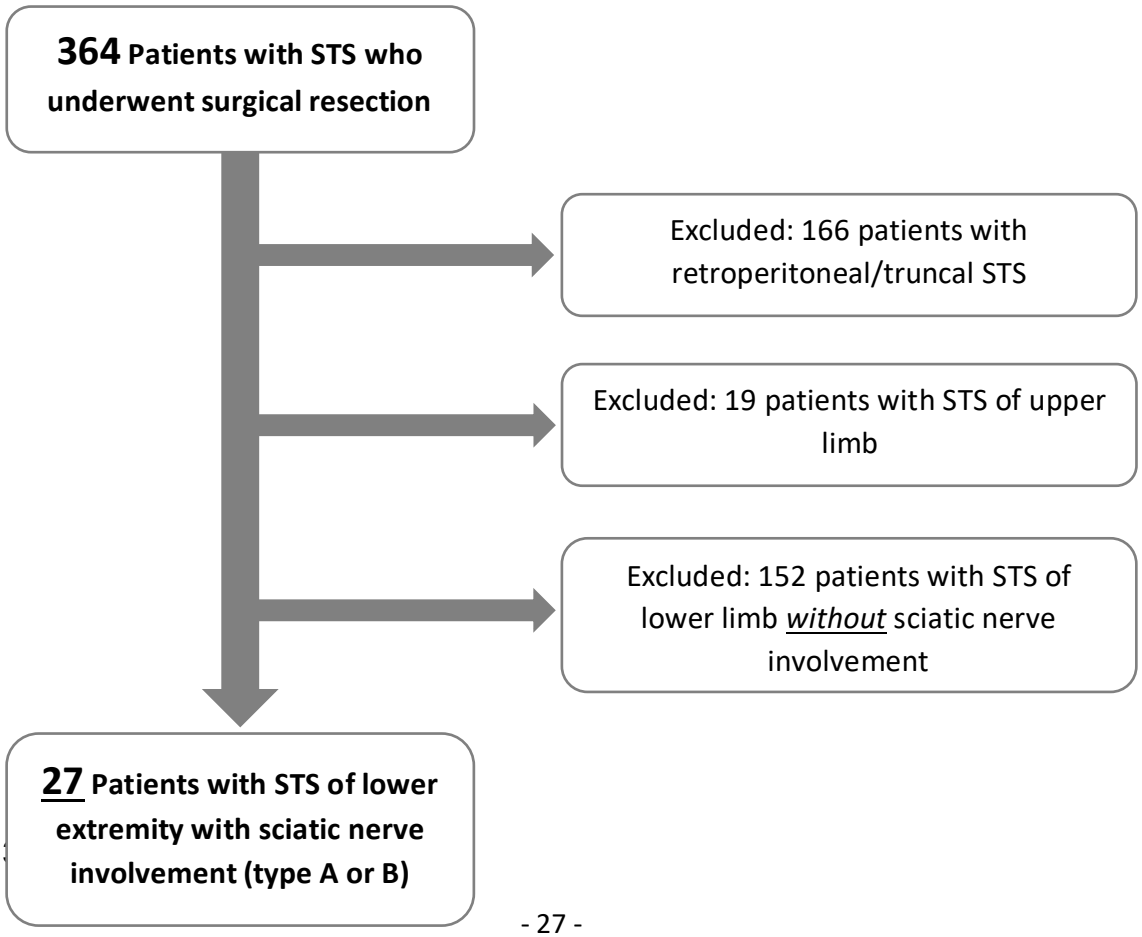
3. RESULTS

3.1 General and preoperative characteristics

A total of 364 patients with STS underwent surgical resection between January 1st 2010 and January 31st 2017. Truncal and retroperitoneal STS was recorded in 166 patients (45.6%), and 19 patients (5.2%) were diagnosed with upper extremity STS. These patients were excluded from our analysis.

A total of 179 patients (49.2%) were found to have lower limb STS, of which 27 patients (15.1% of all patients with lower limb STS) had sciatic nerve involvement (type A or B) and were included for further analysis (n = 27). Figure 10 summarizes the results of the patient selection process.

Figure 10. Patient selection



The median age of these 27 patients was 57 years (Interquartile Range [IQR] 46 – 74 years). Six out of 27 patients (22.2%) presented with a local recurrence while the remaining 21 patients (77.8%) presented with primary tumors. None of the patients presented with metastatic disease. The tumor entity was confirmed in all cases via biopsy or prior excision. Based on our proposed classification system, radiological tumor encasement of the sciatic nerve greater than 180° (type A) was demonstrated in 8 patients (29.6 %) and direct contact with the sciatic nerve less than 180° (type B) was displayed in the remaining 19 patients (70.4 %). Concurrent vascular involvement was confirmed in 6 cases (22.2%). Additional general and preoperative characteristics are summarized in table 8.

Table 8. General and preoperative characteristics

Characteristic	**Number of patients** *(n = 27)*	**%**
Gender		
Male	12	44.4
Female	15	55.6
Side		
Right	16	59.3
Left	11	40.7
Presentation status		
Primary tumor	21	77.8
Local Recurrence	6	22.2
Sciatic Nerve Involvement		
Type A	8	29.6
Type B	19	70.4
Neoadjuvant therapy		
External radiation therapy	10	37.0
Chemotherapy	6	22.2
Isolated limb perfusion	5	18.5
Adjuvant therapy		
External radiation therapy	8	29.6

Chemotherapy	6	22.2

3.2 Perioperative variables

All tumor resections were carried out by one experienced surgeon (MS). A macroscopically complete resection without amputation was achieved in all patients. The median duration of surgery was 5.17 hours (IQR: 3.92 – 6.54 hours). The preoperative radiological categorization of type A and type B nerve involvement was confirmed intraoperatively in all 27 cases. Eight patients (29.6%) with type A sciatic nerve involvement underwent complete resection of the sciatic nerve and the remaining 19 patients with type B nerve involvement underwent epineural nerve dissection. Liposarcoma was the most common histopathologic entity (48.1%), with 9 out of 13 liposarcomas diagnosed as low-grade (G1), 3 intermediate-grade (G2) liposarcomas and one high-grade (G3) liposarcoma. The median maximum tumor diameter measured by the pathologist following resection was 15 cm (IQR: 8.5 – 26.5 cm). The microscopically negative margin rate in our series was 92.6% with a median margin size of 5 mm (IQR: 3 – 10 mm). Two patients with positive margins (R1), both with type B neural involvement, were disease-free at the latest follow-up appointments (22 and 17 months postoperatively). One of these patients was also treated with neoadjuvant radiotherapy and the other patient received adjuvant radiation therapy. Adjuvant radiation therapy (60-66 Gy total dose) was administered to 7 patients (25.9%) and one patient (3.7%) received adjuvant radiochemotherapy. Five other patients (18.5%) were subject to adjuvant chemotherapy. Table 9 summarizes additional operative and histopathologic findings.

Table 9. Operative and histopathologic findings

Characteristic	**Number of patients** *(n = 27)*	**%**
Thigh compartment involvement *(involvement of multiple compartments possible)*		
Posterior	27	100
Medial	19	70.4
Anterior	14	51.9
Bone stripping	21	77.8
Plastic Reconstruction		
Local skin flap	4	14.8
Local musculocutaneous flap	21	77.8
Pedicled flap	2	7.4
Histologic Entity		
Liposarcoma *(all subtypes)*	13	48.1
Pleomorphic Sarcoma *(all subtypes)*	11	40.7
Malignant giant cell tumor	1	3.7
Myxofibrosarcoma	1	3.7
Primitive neuroectodermal tumor	1	3.7
Grade		
Low Grade (G1)	10	37.0
Intermediate Grade (G2)	5	18.5
High Grade (G3)	12	44.4
Margin		
CR with negative margins (R0)	25	92.6
CR with positive margin (R1)	2	7.4

3.3 Postoperative morbidity

A total of 20 patients (74.1%) developed a surgical morbidity and 6 patients (22.2%) experienced medical complications postoperatively. Wound related morbidity, such as skin necrosis, wound dehiscence or infection, was the most common complication affecting 10 patients (37.0%), followed by hematoma or seroma which affected 6 patients (22.2%). Two patients (7.4%) also suffered a pathological fracture of the

operated extremity following discharge; two months postoperatively for one patient and almost two years postoperatively for the other patient. Both patients had also undergone adjuvant radiation therapy. Hospital mortality was zero and the median duration of postoperative hospital stay was 30 days (IQR: 22 – 48 days). Table 10 provides a list of all postoperative complications.

Table 10. Postoperative Morbidity

Complication	**Number of patients** *(n = 27)*	**%**
Surgical Complications		
Wound necrosis / dehiscence	10	37.0
Hematoma / seroma	6	22.2
Fracture	2	7.4
Bleeding	1	3.7
Reoperations	13	48.1
Medical Complications		
Pneumonia	2	7.4
Urinary tract infection	2	7.4
Sepsis	1	3.7
Deep venous thrombosis	1	3.7
Hospital Mortality	0	0

3.4 Oncological outcome

Patients were followed up for a maximum of 5 years postoperatively. The median postoperative follow-up duration of our patients was 23 months (IQR 15.5 – 50 months). Eight patients (29.6%) were found to have recurrence of disease (local recurrence or metastasis). All of these 8 patients had metastatic disease, 3 of which (11.1%) also developed a local recurrence. The most common site of metastasis was the lung, with 5 patients developing pulmonary metastases. The type of disease progression, postoperative disease-free duration and survival in these 8 patients has been summarized in table 11. A secondary limb amputation was carried out in one patient with a high grade (G3) pleomorphic sarcoma due to a local recurrence.

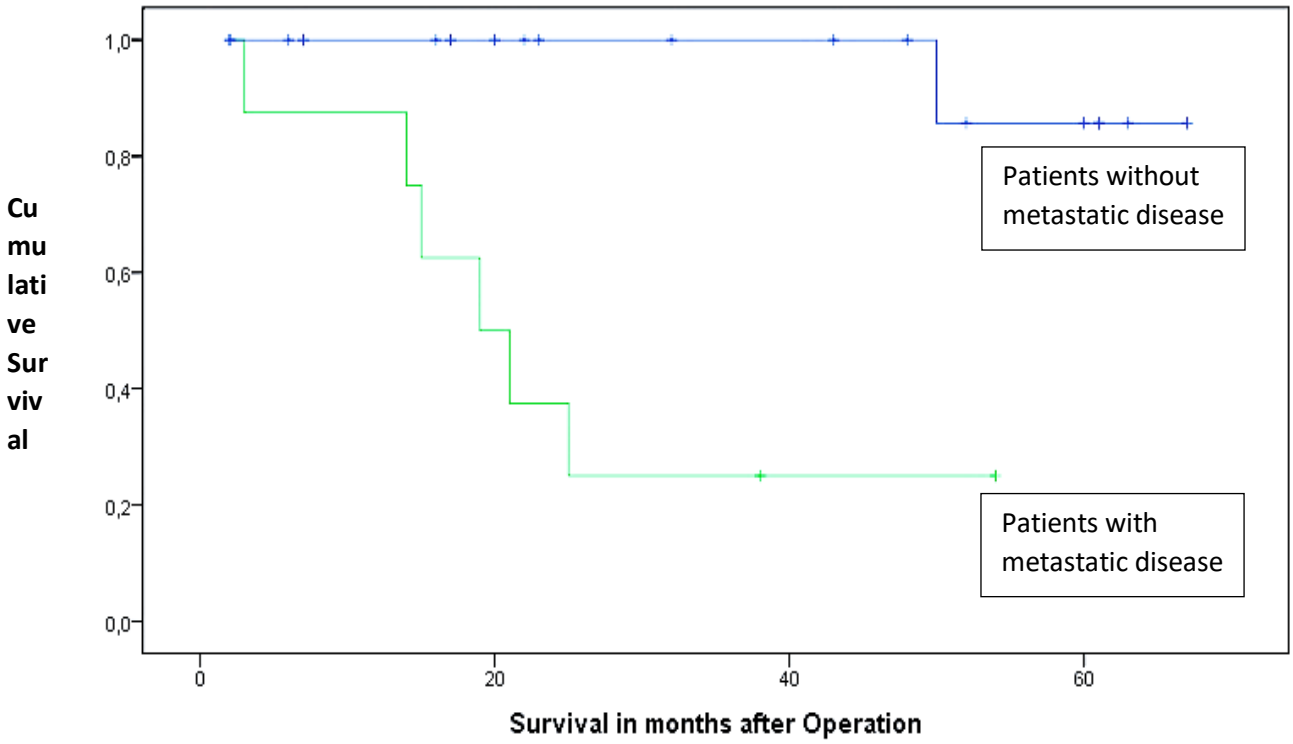
Table 11. Progression of disease

Site of metastases	Local recurrence	Postoperative disease-free duration (months)	Postoperative survival (months)
Pulmonary	No	2	3
Hepatic and bone	Yes	4	29
Pulmonary and hepatic	No	12	54*
Pulmonary	Yes	13	15
Pulmonary	No	9	14
Pulmonary	Yes	6	38*
Bone	No	10	25
Retroperitoneal	No	7	19

**patients are still alive*

The overall mortality rate in our series was 25.9% (n = 7), with a tumor related mortality rate of 22.2% (n = 6). The median survival was not reached in our cohort. For the 8 patients who developed progression of disease, the median survival was 21 months. A significant association between the development of metastasis and mortality was demonstrated by the Kaplan-Meier survival analysis ***(p < 0.001)***, as shown in Graph 1.

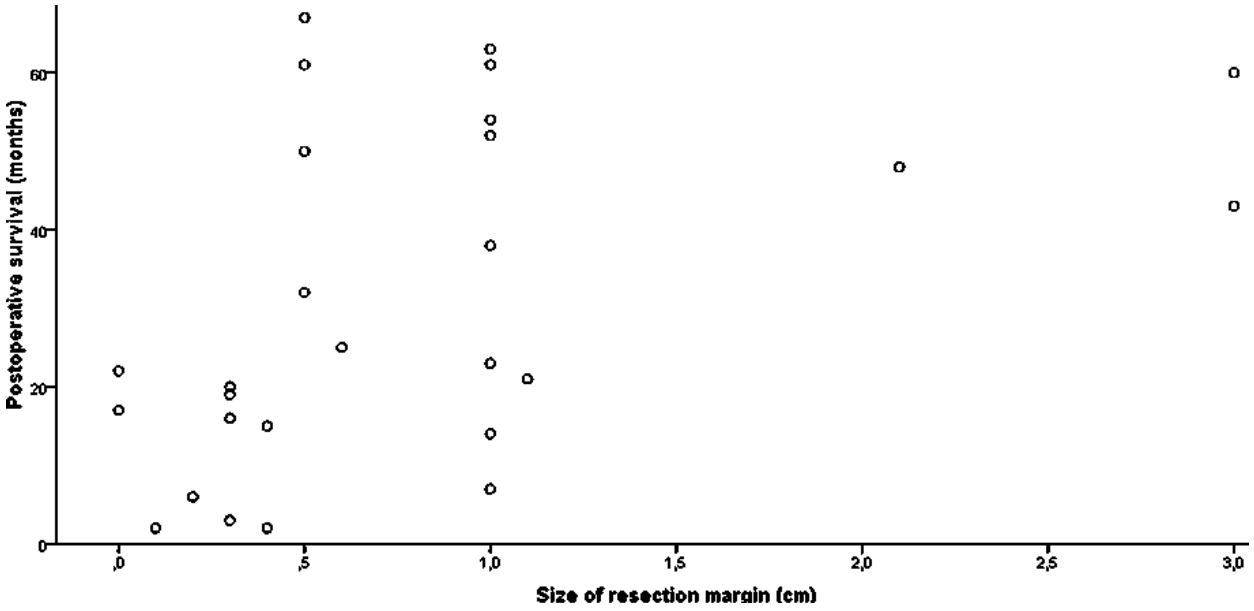
Graph 1. Development of metastatic disease and overall survival



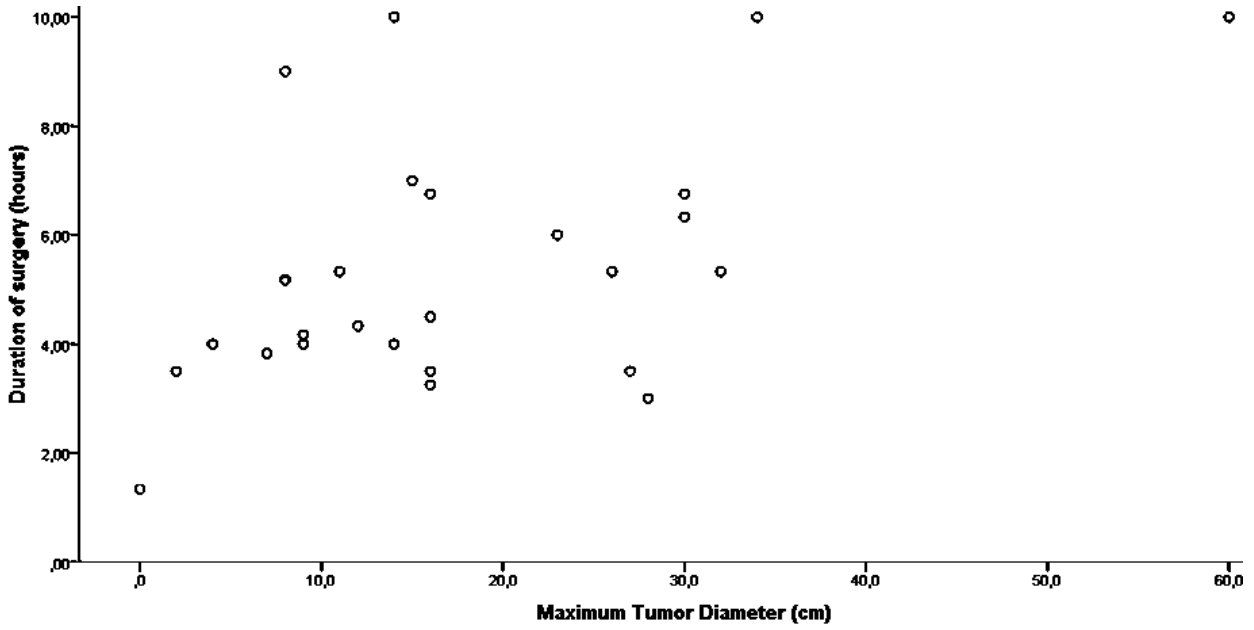
Various general, perioperative and histopathologic parameters were investigated for their association with disease progression or mortality. Patient age, initial presentation with recurrent disease, tumor size, tumor histology, type of nerve resection, duration of surgery and duration of hospital stay were not found to have a statistically significant impact on the development of postoperative complications, disease progression or overall survival.

The resection margin positively correlated with postoperative survival ***(p = 0.014)***. A simple scatterplot of the relationship between the size of the resection margins and postoperative survival is depicted in Graph 2. There was also a significant correlation between the size of the tumor and the duration of surgery ***(p = 0.007)***. The relationship between these two variables has also been displayed in a simple scatterplot (Graph 3). There was, however, no significant association between the duration of surgery and the development of postoperative surgical complications (p = 0.858).

Graph 2. Scatterplot representing relationship between resection margin size and postoperative survival *(p = 0.014)*

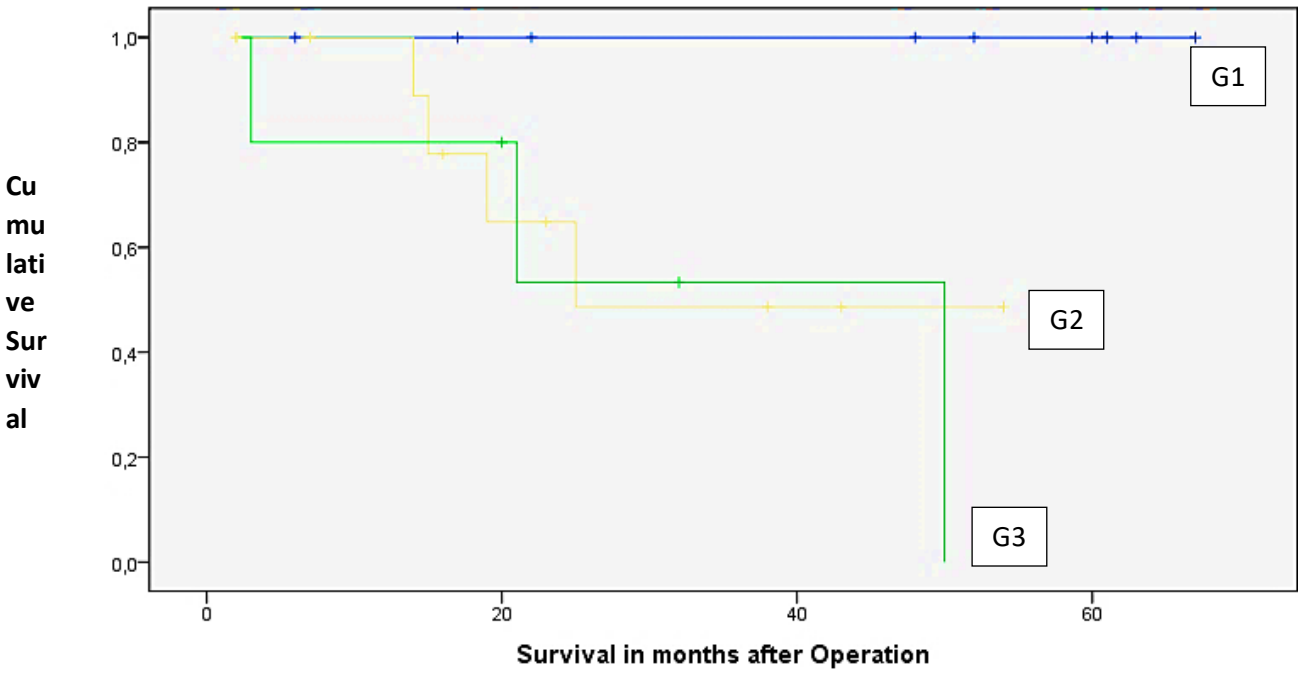


Graph 3. Scatterplot representing relationship between size of tumor and duration of surgery *(p = 0.007)*



Intermediate and high-grade tumors (G2 and G3) were significantly associated with the development of distant metastatic disease ***(p = 0.010)*** as well as mortality ***(p = 0.020)***, compared to low grade tumors (G1). The Kaplan-Meier survival curve for different tumor grades ***(p = 0.023)*** is displayed in Graph 4.

Graph 4. Tumor grade (G1/G2/G3) and overall survival *(p = 0.023)*



Tumor infiltration of the sciatic nerve was histopathologically confirmed in only one patient (3.7%) with a G3 primitive neuroectodermal tumor (PNET), as displayed in figures 11, 12, 13 and 14. The preoperative radiographic imaging of this tumor demonstrated nerve encasement. Figures 15 and 16 demonstrate histopathological nerve encasement without nerve infiltration in a patient with a G3 UPS. An example of histopathological nerve contact without encasement is shown in figure 17.

Figure 11. Hematoxylin and eosin (H&E) stain of nerve infiltration in a patient with a G3 PNET (under x 100 magnification)

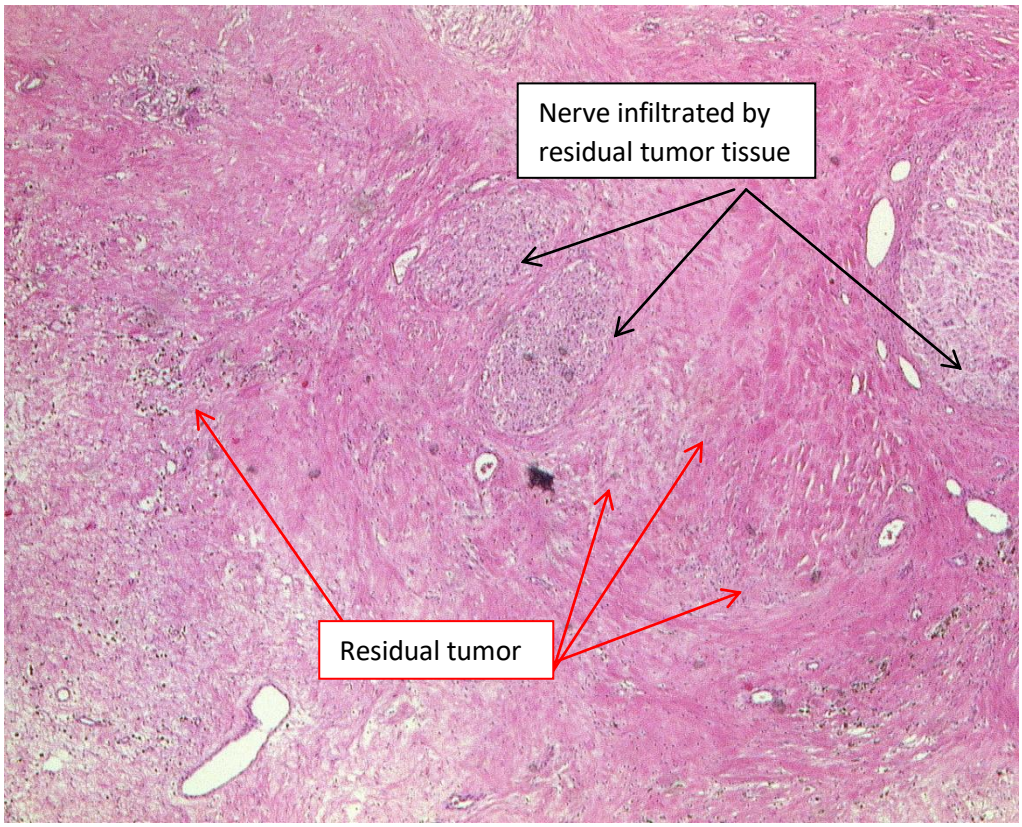


Figure 12. H&E stain of nerve infiltration in a patient with a G3 PNET (under x 400 magnification)

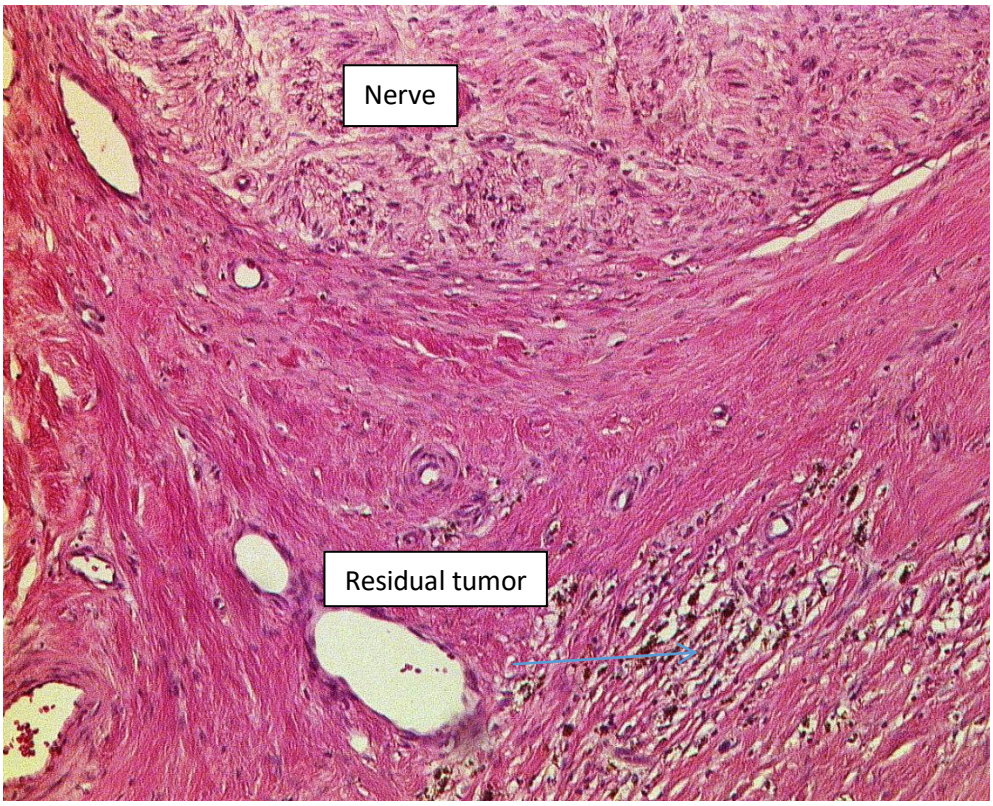


Figure 13. Elastica van Gieson (EvG) stain of nerve infiltration in a patient with a G3 PNET (under x 400 magnification)

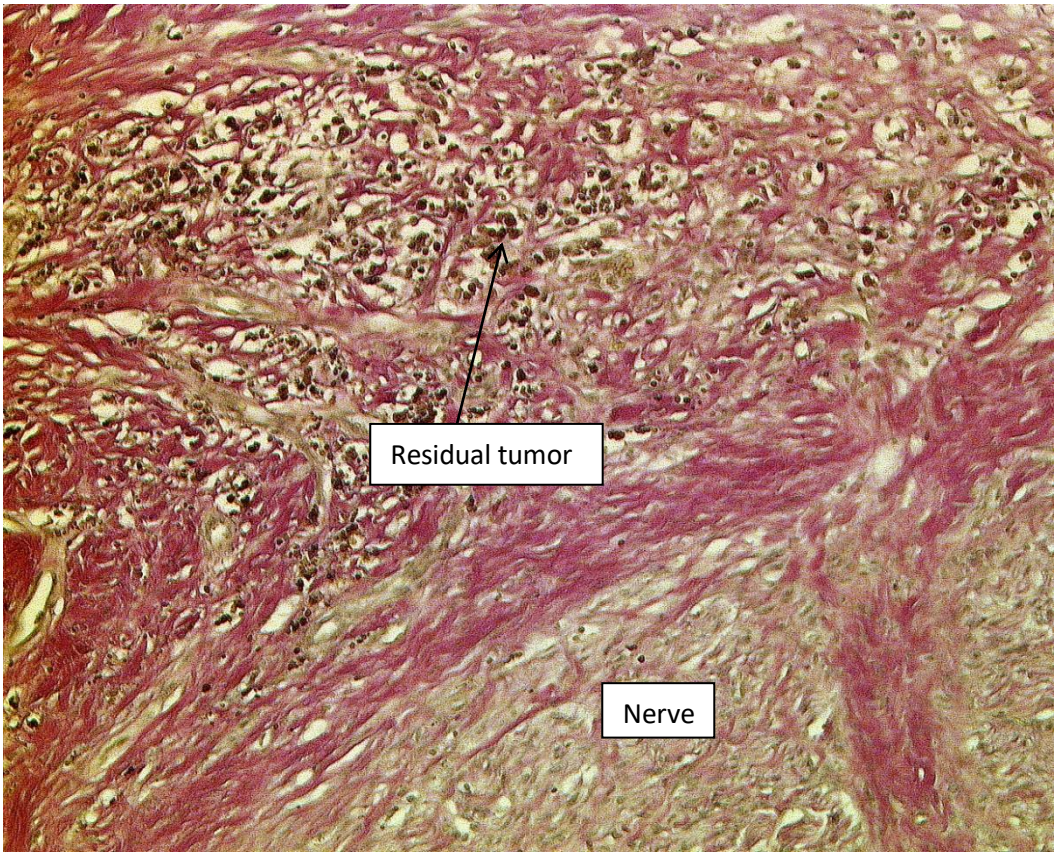


Figure 14. Immunohistochemical Cytokeratin (CK) CAM 5.2 stain (under x 400 magnification) of residual tumor cells after neoadjuvant chemotherapy in a patient with a G3 PNET

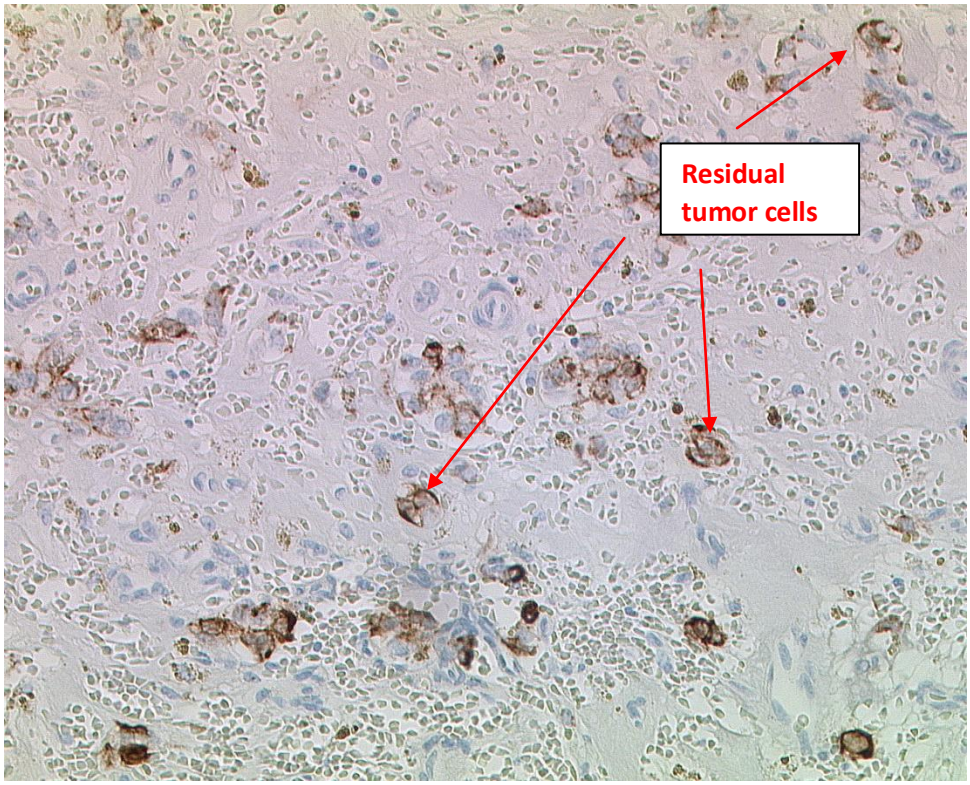


Figure 15. H&E stain of nerve encasement without infiltration in a patient with a G3 UPS (under x 100 magnification)

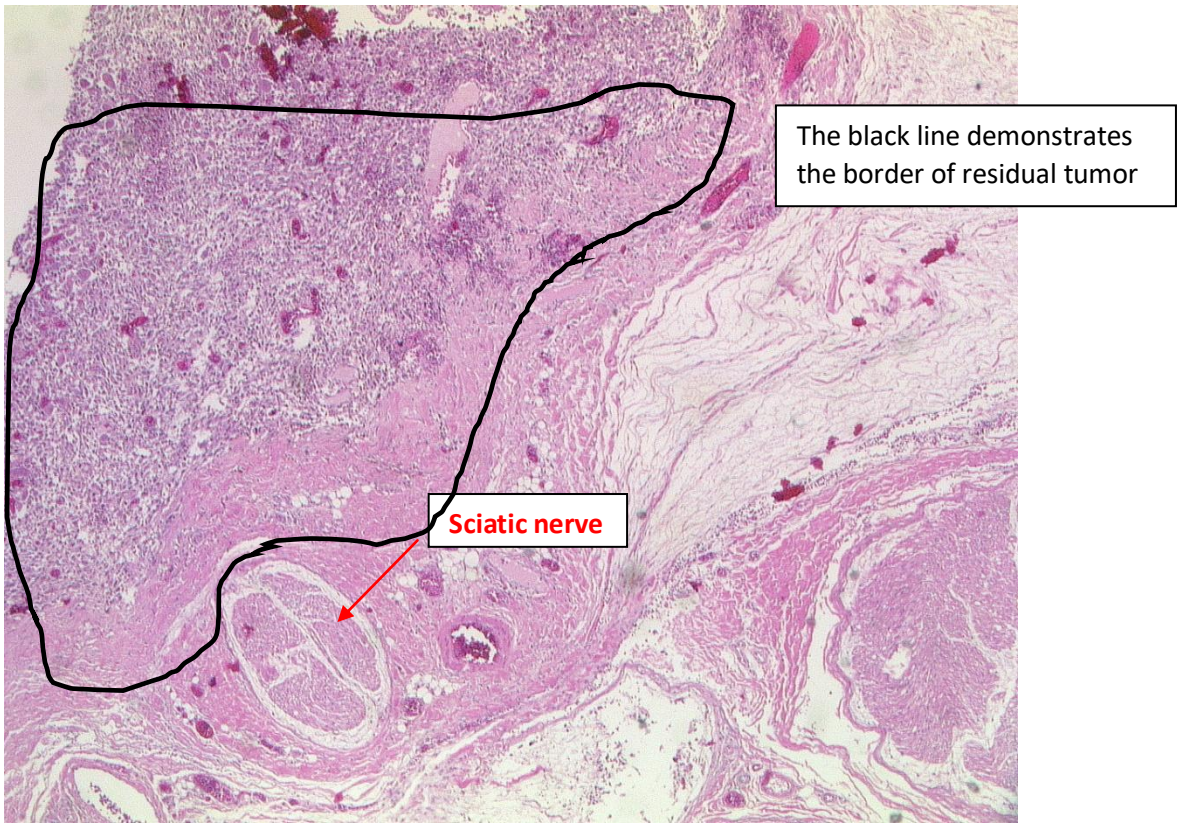


Figure 16. H&E stain of nerve encasement without infiltration in a patient with a G3 UPS (under x 400 magnification)

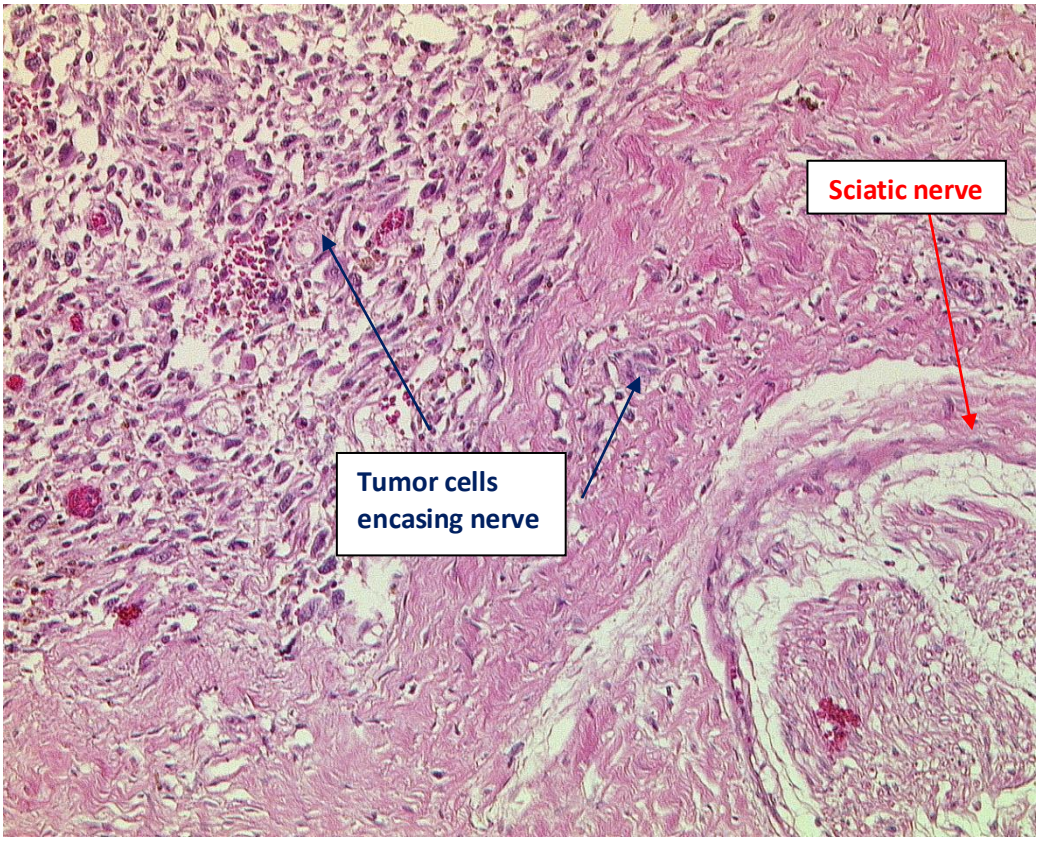
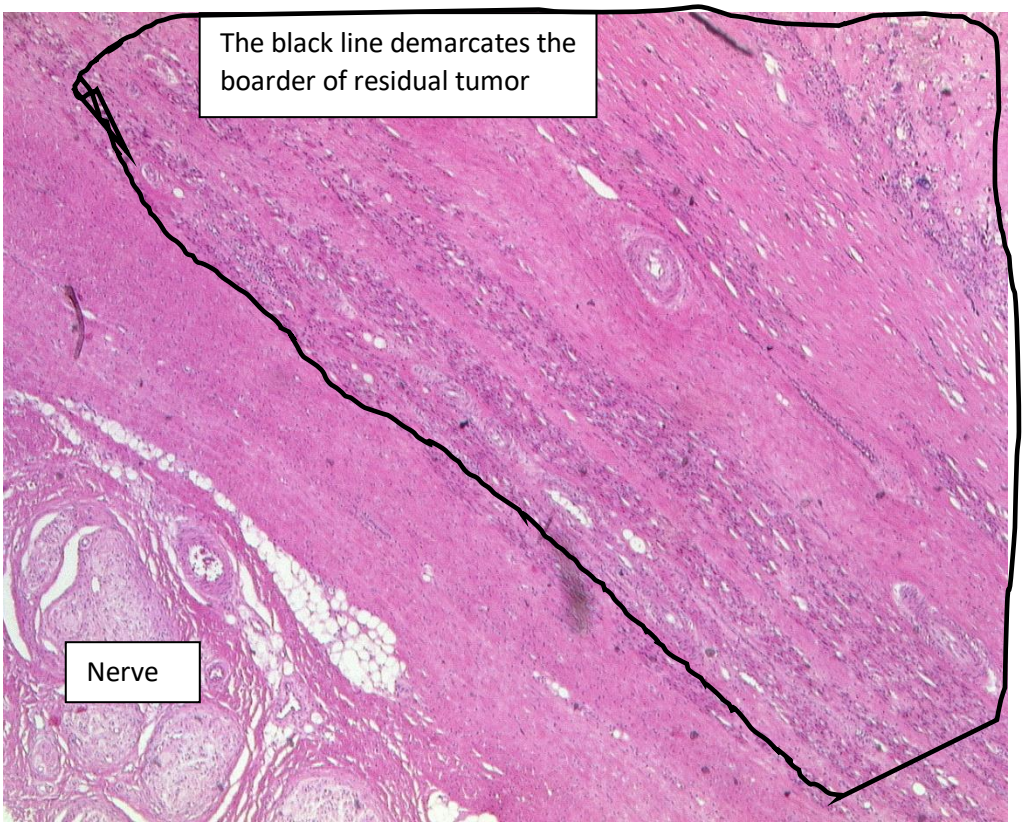


Figure 17. H&E stain of nerve contact without encasement or infiltration in a patient with a G3 UPS (under x 100 magnification)



3.5 Functional outcome

In addition to carrying out the necessary follow-up screening diagnostics, patients were also clinically examined and were asked questions regarding their functional status and limitations in carrying out their activities of daily living. The main functional outcomes which were measured are summarized in Table 12.

Complete sciatic nerve resection was found to be significantly associated with the development of leg edema ***(p = 0.017)***, chronic pain ***(p = 0.003)***, reduced leg function ***(p < 0.001)*** and lower MSTS scores ***(p = 0.001)*** when compared to epineural nerve dissection.

Table 12. Functional outcome

Functional component	**Number of patients** *(n = 27)*	**%**
Chronic leg edema	15	55.6
Paresthesia	18	66.7
Chronic pain	12	44.4
Walking aids/braces	17	63.0
Leg function/range of motion		
Severely limited/no function	9	33.3
Limited	12	44.4
Normal	6	22.2
Walking distance		
Normal	15	55.6
100-500m	9	33.3
<100m	3	11.1

The MSTS scores of the 20 surviving patients was calculated at their latest follow-up appointments, with a median follow-up duration of 35 months postoperatively. 50% of surviving patients had an MSTS score of 83% or greater. Five patients (25%) scored between 67% and 80% and the remaining 5 patients received a score of less than 67%. The MSTS scores have been summarized in table 13.

Table 13. MSTS scores

MSTS score	**Number of patients** *(n = 27)*	**%**
25-30 (≥ 83%)	10	50
20-24 (67 - 80%)	5	25
< 24 (< 67%)	5	25

The use of walking aids and/or orthoses is summarized in table 14. All 8 patients (100%) with type A sciatic nerve involvement wore a peroneal splint compared to two patients (11%) from the type B nerve involvement group. Three out of 8 patients (38%) with type A nerve involvement were only adequately mobile in a wheelchair compared to 2 patients (11%) with type B involvement. Apart from one patients, all other patients who required a wheelchair for their mobilization were over 70 years old. A total of 15 patients (56%) did not require any walking aids at their latest follow up appointment, 3 of which were patients with type A nerve involvement.

Patients were asked how they felt about undergoing limb sparing surgery and whether they had any regrets during their follow up appointments. All patients, including those with complications or recurrence of disease, were satisfied with their decision in opting for limb sparing surgery as opposed to amputation of the affected extremity.

Table 14. Use of walking aids and orthoses

Type of Neural Involvement	Walking Aids	Orthoses
A	None	Peroneal splint
A	None	Peroneal splint
A	Wheelchair	Peroneal splint
A	Walking stick	Peroneal splint
A	Wheelchair	Peroneal splint
A	Wheelchair	Peroneal splint
A	None	Peroneal splint
A	Walking stick	Peroneal splint
B	None	None
B	None	None
B	None	Peroneal splint
B	None	None
B	Wheelchair	None
B	None	None
B	None	None
B	Walking stick	None
B	Walking stick	None
B	None	None
B	Zimmerframe	None
B	None	None
B	None	None
B	None	None
B	None	None
B	Walking stick	None
B	Zimmerframe	None
B	None	Peroneal splint
B	Wheelchair	None

4. DISCUSSION

4.1 Proposed classification system

Our proposed classification system provides a simple and clinically applicable algorithm to facilitate the choice between nerve resection or epineural dissection in patients undergoing limb sparing surgery due to STS with sciatic nerve involvement. The significance of this classification lies in its potential to encourage a limited epineural dissection in eligible patients (type B neural involvement) without compromising the oncological outcome or unnecessarily sacrificing the leg function. In addition, this classification may help establish limb sparing surgery as the procedure of choice in patients with type A sciatic nerve involvement. The initial assessment of nerve involvement is radiological followed by an intraoperative confirmation. Hence, this classification may be used in the preoperative setting to inform and consent the patient on the expected procedure and its' alternatives.

In addition, the already established classification system for vascular involvement in STS by Schwarzbach et al. [31, 32] could also be combined with our proposed classification system for nerve involvement, enabling STS with neurovascular involvement to be more accurately classified. Tumors with arterial involvement, no vein involvement and nerve encasement > 180° would, for example, be classified as a type IIA STS. This could be used to generate an individualized plan for the surgical procedure and thus improve the resection strategy within a multimodal treatment concept. A precise surgical concept based on the proposed classification system of neural and vascular involvement could allow the planning of additional radiotherapy. For example, the preoperative identification of regions with minimal safety margins and thus neoadjuvant external beam radiotherapy could lead to function-sparing surgery without compromising the oncological outcome.

4.2 Discussion of oncological results and review of current literature

Our study assessed the functional and oncological outcomes in a carefully selected cohort of 27 patients with STS and sciatic nerve involvement treated in a specialist

center. To our knowledge, it is the second largest series of patients (following the cohort of 94 patients examined by Clarkson et al.) with this diagnosis published to date. Reasonable oncological outcomes were demonstrated in our patient series following limb sparing surgery. The frequency of local recurrence (11.1%) and distant metastasis (29.6%) compare well with a large prospective study of 1,041 patients with STS of the extremities, which reported rates of 17% and 22% respectively [24]. More recent studies, however, demonstrated local recurrence rates of 10% or less [19, 34, 57, 58, 76]. Our local control rate of 88.9% is also comparable to most modern series, which report local control rates of approximately 90% [19]. Pisters et al. found that high-grade lesions were a significant prognostic factor in the development of metastatic disease, which was also confirmed in our patient cohort [24].

Liposarcoma and pleomorphic sarcoma were the two most common histopathologic entities in our study population, which is analogous to the current literature [19]. However, the histopathologic subtype was not found to be of prognostic significance in our study, despite being shown to be an independent prognostic factor in other studies [23, 24]. This may be due to the small number of patients and the resulting low statistical power in our series.

Resection margins have also been shown to be an independent prognostic factor in local and distant disease control [23, 77, 78]. Stojadinovic et al. found that positive margins double the risk of local recurrence in a large cohort of 2084 patients [79]. The importance of the surgical resection margins was confirmed in our study, as the size of the negative margins significantly correlated with survival after surgery. However, negative margins are not always achievable, particularly when the tumors are located near vital neurovascular structures. O'Donnell et al. found that sparing adjacent critical structures did not increase the risk of a local recurrence or reduce survival rates and led to superior functional outcomes in 169 patients with STS and positive margins following surgical tumor resection [80]. This study, however, involved a heterogeneous group of patients with STS in diverse anatomic locations with varying neurovascular involvement. The results should therefore be interpreted with caution, particularly when discussing positive margins in our specific cohort of patients with sciatic nerve involvement.

Aggressive local treatment such as higher radiation doses followed by a wide excision or even amputation is usually recommended when the surgical resection margins are positive, particularly when the positive margins are unplanned or macroscopically visible [9]. Patient outcomes have however been shown to be inferior despite aggressive treatment, highlighting the importance of accurate diagnosis and management of these lesions in the initial treatment phase [9].

Presentation with local recurrent disease and positive margins following tumor resection have been shown to be prognostic factors for the development of a local recurrence in several studies [24, 81]. Presentation with locally recurrent disease has even been shown to be a significant independent risk factor for the development of a further local recurrence following resection of recurrent disease [82]. This was not observed in our study, probably due to the small number of postoperative local recurrences, occurring in only 3 of our patients.

The 5-year overall survival of patients with metastatic STS has been shown to be poor [19]. Our study confirmed the correlation between the development of metastatic disease and mortality, which has been shown in previous studies [24]. This highlights the importance of improving systemic control of disease. Williard et al. reported a tumor related mortality rate of greater than 50% despite local tumor control, independent of whether patients were treated with limb amputation or limb sparing surgery, further emphasizing the need to improve systemic disease control [83].

Pisters et al. analyzed numerous prognostic factors for STS of the extremities in their large patient cohort and found that the adverse prognostic factors for developing a local recurrence differ from those predicting metastatic disease and tumor related mortality [24]. The authors therefore proposed two separate staging systems for patients with STS, identifying patients at risk of developing a local recurrence and another system for those at risk of distant metastatic disease and tumor related mortality. These distinctive staging systems would allow an early classification of patients at high risk of local or distant disease recurrence and thus the prompt initiation of local or systemic adjuvant therapy, respectively [24]. These two distinct staging systems and their potential therapeutic consequences could be further validated in future research.

Our series consists of primarily large, deep and in 7 cases recurrent STS with sciatic nerve involvement undergoing compartmental tumor resections in a multimodal

therapeutic approach. The most common postoperative complications in our study were wound complications, arising in 37% of our patients, followed by hematomas and seromas, occurring in 22.2% of cases. These factors contributed to a high reoperation rate of 48.1% as well as a median hospital stay of 30 days. A wound complication rate of 34.4% has been reported in en bloc resections without intraoperative adjuvant treatment modalities [53]. A long duration of surgery, patients over 40 years of age and adjuvant intraoperative treatment modalities such as radiotherapy, brachytherapy or regional chemotherapy have been identified as risk factors for developing wound complications [53, 84]. Duration of surgery, patient age and adjuvant treatments were not found to be associated with the development of wound complications in our study. These results should however be interpreted with caution due to the limited number of patients in our series.

4.3 Discussion of functional results and review of current literature

Some authors have previously recommended hip disarticulation or hindquarter amputation when complete resection of the sciatic nerve is necessary as a limb without tactile sensations was not considered worth saving from a functional perspective [37, 38, 40, 81, 85]. Several authors have, however, reported acceptable functional outcomes after complete resection of the sciatic nerve [44, 50-52, 86] with some studies demonstrating superior function when comparing sciatic nerve resection with amputation of the leg [87, 88]. The function of the leg is also dependent on the level of the sciatic nerve resection as distal resections have been shown to lead to a superior function of the salvaged leg [49].

In our study, all patients were satisfied with their decision to undergo limb-sparing surgery, despite functional limitations which were particularly apparent in the sciatic nerve resection group. Patients should be informed about requiring walking aids and orthoses for the rest of their life after resection of the sciatic nerve due to the partial muscle paralysis, especially in muscles controlling the foot. It is also important that patients are properly instructed preoperatively regarding adequate foot care of their postoperative insensate feet to minimize skin complications, particularly the development of foot ulcers, which can ultimately lead to a secondary amputation of the limb [51]. The foot care and treatment are analogous to patients with diabetic foot

syndrome or polyneuropathy of other causes and can be carried out in an outpatient center for diabetic foot syndrome.

All of our patients with type A sciatic nerve involvement wore a peroneal splint compared to just 11% of patients from the type B nerve involvement group. With regards to mobility aids, 38% of patients with type A nerve involvement were only adequately mobile in a wheelchair compared to just 11% with type B involvement. The use of a wheelchair also appears to be strongly associated with age, as four out of five patients requiring a wheelchair were over the age of 70. These results have important implications when consenting patients preoperatively. For example, patients with type A nerve involvement will be informed that they require a peroneal splint postoperatively and that they will most likely require walking aids particularly if they are over the age of 70. Preoperative physiotherapy and simulation of peroneal nerve injury could also be considered as a form of prophylaxis from falls.

The extent of nerve resection was not found to affect the local or distant recurrence rate or have an impact on survival in our study. Similar local recurrence rates were also reported by Clarkson et al. in their cohort of 94 patients when comparing sciatic nerve resection with epineural nerve dissection [52]. Their study also demonstrated superior functional outcomes with patients receiving epineural nerve dissection compared to complete nerve resection. Our study further confirms these findings, as there was a significant association in the development of chronic leg edema, chronic pain, poor leg function as well as lower MSTS scores in the group of patients who underwent complete sciatic nerve resection when compared to the patients treated with an epineural nerve dissection.

None of the patients in our study underwent reconstruction of the sciatic nerve after its resection. Whether such reconstruction is truly indicated remains controversial. Some authors do not believe that it is justified as preservation of leg function cannot be guaranteed and the reconstruction prolongs the duration of surgery, increasing the risk of postoperative complications such as delayed wound healing and infections [48, 51]. The gold standard for nerve reconstruction is grafting of autogenic nerve [48]. Melendez et al. demonstrated positive functional outcomes in 5 patients with STS of the thigh with sciatic nerve involvement who underwent autogenic common peroneal nerve reconstruction. The sural nerve was also used in 2 of these patients. All 5 patients recovered metatarsal sensation and could walk with the aid of an ankle

joint brace [89]. Further research regarding the regeneration potential of reconstructed sciatic nerves under the influence of chemotherapy and radiation therapy is warranted [51].

4.4 Limitations

The present study is one of the largest published series of patients with STS and sciatic nerve involvement to date, as most prior studies were limited to a cohort of less than 20 patients [23, 49-51]. Nevertheless, the small absolute number of patients limit the statistical power of our analysis. In addition, the median follow-up duration in our study was 23 months and patients were followed up to a maximum duration of 5 years postoperatively. As the follow up duration in some patients was short, a repeat analysis of this cohort could be carried out in 5 and in 10 years to further assess the long term functional and oncological outcomes, with particular focus on patient survival.

It is essential to validate our proposed classification and to assess the potential role of prognostic parameters, such as tumor grade, in further optimizing patient and procedure selection. The tumor grade may influence the extent of surgical resection and could potentially be incorporated into the treatment algorithm. For example, a nerve-sparing surgical resection may be considered in a young patient with a low grade liposarcoma and type A sciatic nerve involvement to minimize the loss of function. This is because these tumors rarely metastasize and the risk of local recurrence may be reduced by incorporating adjuvant or neoadjuvant radiotherapy. It is also necessary to assess the applicability of this classification for different nerves separately due to the variations in their sensorimotoric functions and in the degree of compensation following nerve resection.

It is also important to note only 1 patient (3.7%) in our study with a G3 primitive neuroectodermal tumor and sciatic nerve encasement greater than 180° revealed histopathologic nerve infiltration. This low rate of histopathologic infiltration may encourage a more nerve-preserving approach whenever technically possible.

The functional evaluation of our patients was largely centered on the musculoskeletal tumor society rating score modified by Enneking [74]. There are several established scores and systems available for assessing the function of patients after undergoing

limb sparing operations. Davis et al. compared the Toronto extremity salvage score with the musculoskeletal tumor society scores [74, 90] and the short form 36 [91] for the postoperative functional assessment of 97 patients with STS of the lower extremity [92]. The Toronto extremity salvage score was found to be superior regarding the measurement properties and was recommended as an efficient and reliable functional evaluation method in patients receiving limb sparing surgery [92]. Further analyses of our cohort could therefore incorporate the Toronto extremity salvage score as part of the functional outcome assessment.

The effects of neoadjuvant and adjuvant therapy on both functional and oncological outcomes were also not addressed in our current study and could be studied in future analyses. Furthermore, the role of PET scans particularly for the early detection of metastatic disease could be investigated and compared to patients who did not receive PET scans as part of the postoperative surveillance. PET scans have also been shown to play a valuable role in the preoperative prognostic assessment of patients with resectable STS [11]. Postoperative functional data could also be compared to preoperative functional data, as it has been suggested that patients with worse function preoperatively have a higher capacity to improve postoperatively [50].

There was no significant association found between the involved thigh compartments and postoperative morbidity, functional or oncological outcomes in our study. This may also be due to the small size of our study population. Rimner et al. investigated the influence of compartmental involvement on the patterns of morbidity and outcome in a cohort of 255 patients with STS of the thigh [93]. The authors found no significant difference between the three thigh compartments regarding local and distant tumor control. The rates of wound complications requiring reoperations and postoperative edema were however significantly higher in patients with medial-compartment tumors [93]. In addition, nerve damage was more frequent in posterior-compartment tumors [93]. These differences in the involved thigh compartments could be further investigated in future research as the management of patients with STS of the thigh could potentially vary and be adjusted depending on the involved compartments.

4.5 Conclusion

This study describes the multimodal treatment options, functional and oncological results in a carefully selected patient cohort with STS and sciatic nerve involvement. It is the first study to date to propose a classification for the extent of sciatic nerve involvement in STS and to suggest a surgical treatment algorithm. The surgical strategies of choice in patients with sciatic nerve involvement in our study were en bloc tumor resection with either epineural nerve dissection or sciatic nerve dissection in a limb-sparing treatment approach. Both techniques were associated with adequate local tumor control and excellent limb salvage rates.

Patients were satisfied with limb-sparing surgery even when the sciatic nerve was resected and despite the considerable amount of associated short and long-term physical impairment. The perioperative data of our patient cohort including the high rate of perioperative wound morbidity, reoperation rate and increased length of hospital stay associated with limb salvage surgery allows improved understanding of the perioperative course in this subset of sarcoma patients. This knowledge helps inform patients preoperatively about the expected postoperative course including likely physical impairment and need for orthotics and walking aids.

Precise classification of nerve involvement may be useful in selecting the appropriate degree of nerve resection, without compromising the oncological outcome or unnecessarily sacrificing leg function. Additional studies are necessary to validate and optimize this classification.

5. SUMMARY

The surgical resection of lower limb soft tissue sarcomas with sciatic nerve involvement presents a significant surgical and oncological challenge. In the past, sciatic nerve involvement was an indication for limb amputation. However, recent studies have shown acceptable functional outcomes and no significant difference in overall survival rates for limb sparing surgery. Current treatment strategies are therefore more targeted towards limb preservation.

The aim of our study was to evaluate the outcomes of limb sparing surgery of soft tissue sarcomas with sciatic nerve involvement in a cohort of adult patients treated in a specialist center. We also proposed a classification for sciatic nerve involvement and a treatment algorithm for soft tissue sarcomas of the lower extremity.

Demographic, clinical and oncological data of 27 patients with soft tissue sarcomas of the lower extremity with sciatic nerve involvement undergoing limb sparing surgery at the Clinical Center Frankfurt Höchst between January 2010 and January 2017 were collected on an ongoing basis in a computerized database and retrospectively analyzed. Nerve involvement of lower limb soft tissue sarcomas was classified as follows: Type A for nerve encasement greater than 180° and type B for nerve contact. Patients with type A tumors underwent sciatic nerve resections whereas patients with type B tumors were treated with an epineural nerve dissection. Disease progression was observed in 8 patients (29.6%) with a local recurrence rate of 11.1% and distant metastasis in 29.6% of patients. The overall survival rate was 74%. Tumor grade was the single parameter significantly associated with metastatic disease and overall survival. The type of nerve resection significantly influenced the functional outcome but had no significant impact on oncological outcome or overall survival.

To our knowledge, this is the first study to date to classify the extent of nerve involvement in soft tissue sarcomas and to suggest a treatment algorithm based on

the classification. We have demonstrated that acceptable oncological and survival outcomes can be achieved for patients undergoing limb sparing surgery with no significant difference between patients undergoing complete nerve resection or epineural dissection of the sciatic nerve. Hence, precise classification of nerve involvement is essential in selecting the appropriate degree of nerve resection, without compromising oncological outcome or unnecessarily sacrificing the functional outcome.

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7. CURRICULUM VITAE

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RESEARCH

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