Diplomarbeit

Metastasectomy in patients with advanced soft tissue sarcoma: Quantifying the benefit

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Eidesstattliche Erklärung

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Graz, am 20. August 2019 *Ronald Josef Heregger eh*

Preface

My enthusiasm for oncology already began early on in my medical studies. Most of my friends found it frustrating to learn the features of so many tumours for the pathology exams, but I found it interesting. I was fascinated by the fact that there are diseases whose pathogenesis is still not fully understood at the present time.

Thus, I focused my attention on oncologic topics while searching for potential themes for my thesis. Soft tissue sarcomas are a rare group of tumours, which were only mentioned in passing through the study. I found it was a great opportunity to learn more about this tumour entities while writing my diploma thesis.

Acknowledgements

My special thanks belong to my two supervisors of my diploma thesis, Priv.-Doz. Dr.med.univ. Joanna Szkandera from the Division of Clinical Oncology at the Medical University of Graz and Univ.-Prof. Dr.med.univ. Andreas Leithner, head of the Department for Orthopaedic Surgery. Both offered helpful advice and gave me prompt reply to all my questions.

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My special thanks go to my girlfriend Lisa, who supported me through my whole studies in Graz.

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Finally, I want to thank my friends and colleagues, in particular Christoph and Simon, for the unforgettable time that we spent together in Graz.

Kurzfassung

Einführung: Die Entfernung von Metastasen ist eine bewährte Therapieoption bei PatientInnen mit Weichteilsarkomen (WTS). Die Evidenz für diese Methode basiert auf nicht kontrollierten Beobachtungsstudien, welche nicht frei von Fehlern (e.g. Selektions-Bias) sind. Diese Diplomarbeit hatte das Ziel, den Einfluss von Metastasektomie auf das Gesamtüberleben zu quantifizieren.

PatientInnen und Methoden: Diese Studie analysierte die Daten von 87 WTS-PatientInnen, welche an unserem Institut im Zeitraum von 1998 bis 2017 behandelt worden sind. Wir verglichen PatientInnen-, Tumor- und Behandlungsparameter zwischen chirurgisch (i.e. Metastasektomie) und konservativ behandelten PatientInnen. Das Gesamtüberleben war der primäre Endpunkt der Studie, welcher mithilfe von Kaplan-Meier Kurven berechnet wurde. Wir verwendeten eine Propensity-Score-Methode, um unterschiedliche Patientenmerkmale zwischen den beiden Gruppen zu berücksichtigen. Faktoren mit Einfluss auf das Gesamtüberleben wurden mit uni- und multivariater Cox-Regressions-Analyse ermittelt.

Resultate: Siebenundvierzig PatientInnen unterzogen sich einer Metastasektomie. Von den verbliebenen 40 PatientInnen erhielten 27 bestmögliche unterstützende Behandlungsmöglichkeiten und 13 Chemotherapie ± Strahlentherapie. Die uni- ($p<0.004$) und multivariate ($p=0.050$) Cox-Regressions-Analyse zeigte ein verlängertes Gesamtüberleben für PatientInnen in der interventionellen Gruppe. In der univariaten Analyse nahmen höhere Albumin- ($p=0.031$, HR 0.484, 95% CI 0.250–0.937) und Hämoglobinspiegel ($p=0.047$, HR 0.554, 95% CI 0.309–0.992) Einfluss auf das Gesamtüberleben. Die multivariate Cox-Regressions-Analyse identifizierte Primärtumore ausgehend von den Extremitäten ($p=0.011$, HR 0.259, 95% CI 0.091–0.737) und einen niedrigeren Eastern Co-operative of Oncology Group Performancetest als positive prognostische Faktoren hinsichtlich dem Gesamtüberleben. Die unterschiedlichen PatientInnencharakteristika wurden mit dem „Inverse Propensity of Treatment Weighting" (IPTW) score gleichmäßig gewichtet, wobei die Werte für Metastasektomie auch nach Neuberechnung signifikant blieben.

Schlussfolgerung: Unsere Daten zeigen, dass die Entfernung von Metastasen bei WTS-PatientInnen mit einer signifikanten Besserung des Gesamtüberlebens einhergeht. Trotz fehlender kontrollierter randomisierter Studien könnte die Metastasektomie eine wertvolle Therapieoption für ausgewählte PatientInnen darstellen.

Abstract

Introduction: Metastasectomy is an approved therapy option in patients with soft tissue sarcoma (STS). However, the results refer only to a handful of non-controlled observational studies, which are not without limitation (e.g. selection bias). This diploma thesis aimed to quantify the benefit of metastasectomy on overall survival (OS).

Patients and Methods: This study included 87 STS patients treated at our institution in the time from 1998 to 2017. Baseline characteristics such as patient-, tumour-, and treatment-parameters were compared between surgically intervened (i.e. metastasectomy) and conservatively treated patients. The primary endpoint of the study was OS, estimated with the Kaplan-Meier method. We used a propensity score approach to consider differences in patient characteristics between the two comparing groups. Factors with impact on OS were identified via the use of uni- and multivariate Cox proportional hazard models.

Results: Forty-seven patients underwent metastasectomy. Of the remaining 40 patients, 27 received best supportive care (BSC) and 13 chemotherapy (CTX) ± radiotherapy (RTX). According to univariate ($p<0.004$) and multivariate ($p=0.050$) Cox regression-analysis, patients who underwent metastasectomy had a prolonged OS. In the univariate setting, favourable prognostic factors for OS turned out to be higher albumin- ($p=0.031$, Hazard Ratio (HR) 0.484, 95% confidence interval (95% CI) 0.250–0.937) and haemoglobin-level ($p=0.047$, HR 0.554, 95% CI 0.309–0.992). Multivariate analysis identified that primary tumours situated in the extremities ($p=0.011$, HR 0.259, 95% CI 0.091–0.737) and a low score in the Eastern Co-operative of Oncology Group Scale of Performance Status (ECOG-PS) ($p=0.046$, HR 3.848, 95%CI 1.022–14.487) were associated with a better OS. After weighting all patients for the inverse propensity of treatment weighting (IPTW) score and recalculating the data, metastasectomy still remained a positive prognostic factor.

Conclusion: Our data indicate that in STS patients metastasectomy is associated with a significant benefit on OS. Despite the lack of prospective randomised trials, metastasectomy may offer a valuable treatment strategy for selected patients.

Contents

Glossary and Abbreviations

95% CI	95% Confidence Interval
AJCC	American Joint Committee on Cancer
BSC	Best Supportive Care
CT	Computed Tomography
CTX	Chemotherapy
DSF	Disease-Free Survival
ECOG-PS	Eastern Co-operative of Oncology Group Scale of Performance Status
FDG	Fluorodeoxyglucose
FNA	Fine Needle Aspiration
FNCLCC	French Fédéderation Nationale des Centres de Lutte Contre le Cancer
GIST	Gastrointestinal Stromal Tumours
GP	General Practitioner
HR	Hazard Ratio
IHC	Immunohistochemical Staining
IPTW	Inverse Propensity of Treatment Weighting
LR	Local Recurrence
MFH	Malignant Fibrous Histiocytoma
MFI	Metastasis-Free Interval
MPNST	Malignant Peripheral Nerve Sheath Tumour
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
OS	Overall Survival
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PET	Positron Emissions Tomography
PFS	Progression-Free Survival
PMS	Post-Metastasis Survival
RTX	Radiotherapy
STS	Soft Tissue Sarcoma
TNM	Tumour, Node, and Metastasis
UICC	Union for International Cancer Control
UPS	Undifferentiated Pleomorphic Sarcoma
VATS	Video-Assisted Thoracoscopy
WHO	World Health Organisation
WTS	Weichteilsarkomen

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1. Introduction

Definition

Soft tissue sarcomas (STSs) represent a heterogenous group of rare malignancies arising from mesenchymal and neuroectodermal tissue. The name sarcoma is composed of the two Greek words *sárka* = flesh and *om* = tumour. Like other neoplasms, they are capable of destructive growth, recurrence, and distant metastases. Mesenchymal cells differentiate in several other tissues subsumed under the term connective tissue. Thus, there are more than 100 subtypes of STSs, which are categorised by their histological origin.

Epidemiology

The annual incidence of STSs in Europe is around 5.6 per 100 000, with about 28 000 new cases in the EU countries per year [1]. Values for Austria are slightly lower compared to the European average, about 4.4 men per 100 000 and 2.7 women per 100 000 develop STSs [2]. The ratio benign to malign is about 100:1, but exact numbers are missing because tumour registers do not collect data of benign entities. Referring to all malignant tumours, the part of STSs is less than 1% [3]. **Table 1** shows incidence rates of common STSs in Austria [4].

Sarcoma	**2000**	**2008**	**2016**
Sarcoma, not otherwise specified	57	35	64
Vascular tumours			
Kaposi sarcoma	3	4	9
Angiosarcoma of soft tissue	15	18	22
Fibroblastic tumours			
Fibrosarcoma, not otherwise specified	15	17	12
Myxofibrosarcoma	10	14	48
So-called fibrohistiocytic tumours			
Undifferentiated pleomorphic sarcoma	38	24	24
Smooth muscle tumours			
Leiomyosarcoma	101	83	70
Adipocytic tumours			
Liposarcoma	45	64	92
Nerve sheath tumour			
Malignant peripheral nerve sheath tumour	8	10	6
Skeletal muscle tumours			
Rhabdomyosarcoma	19	19	14

Sarcoma	2000	2008	2016
Tumours of uncertain differentiations			
Synovial sarcoma	10	15	14
Clear-cell sarcoma of soft tissue	1	1	0
Epithelioid sarcoma	2	4	3
Malignant mesenchymoma	2	3	1
Undifferentiated embryonal sarcoma	1	2	0
Peripheral neuroectodermal tumour	2	2	3
Alveolar soft part sarcoma	3	0	1
Gastrointestinal stromal tumour	3	66	49
Dermatofibrosarcoma protuberans	16	10	14
Undifferentiated sarcoma, not otherwise specified	3	2	2

Table 1 *Trends in incidence of different STS types in Austria.*

Aetiology and Pathology

The aetiology of STSs is often unknown. Predisposing factors such as genetics (e.g. Neurofibromatosis type I), exposure to radiotherapy (RTX) (e.g. angiosarcoma after RTX of breast cancer), viral infections, and immunodeficiency (e.g. Kaposi Sarcoma) may play a minor role for the development of STSs [3]. The pathogenesis is seldom known, and most STSs arise de novo/sporadic from connective tissue because of genetic mutations of this cell row without apparent reason.

Clinical Characteristics

The histological spectrum of sarcomas is quite different because mesenchymal cells possess the ability to mature into striated skeletal and smooth muscle, bone, cartilage, adipose, vascular, and fibrous tissue. Tumours of peripheral nerves are also part of STS subtypes despite their neuroectodermal origin. All subtypes are classified based on their behaviour: benign, malignant, and borderline malignant. Borderline tumours are locally aggressive but have a low potential of metastasis [5]. Most STSs displace neighbouring tissues during their growth and are surrounded by a pseudocapsule, which might be infiltrated by tumour cells. STS can infiltrate other tissue, but it is not as common as in carcinoma. Local recurrence (LR) and early haematogenous spread to the lungs are more common features of STSs [3].

2. Clinical Presentation

Early detection and referral to a specialist unit are essential for an adequate treatment of STSs. However, presenting symptoms are sometimes only a gradually enlarging lump or nodule and might get overlooked by a general practitioner (GP) [6, 7].

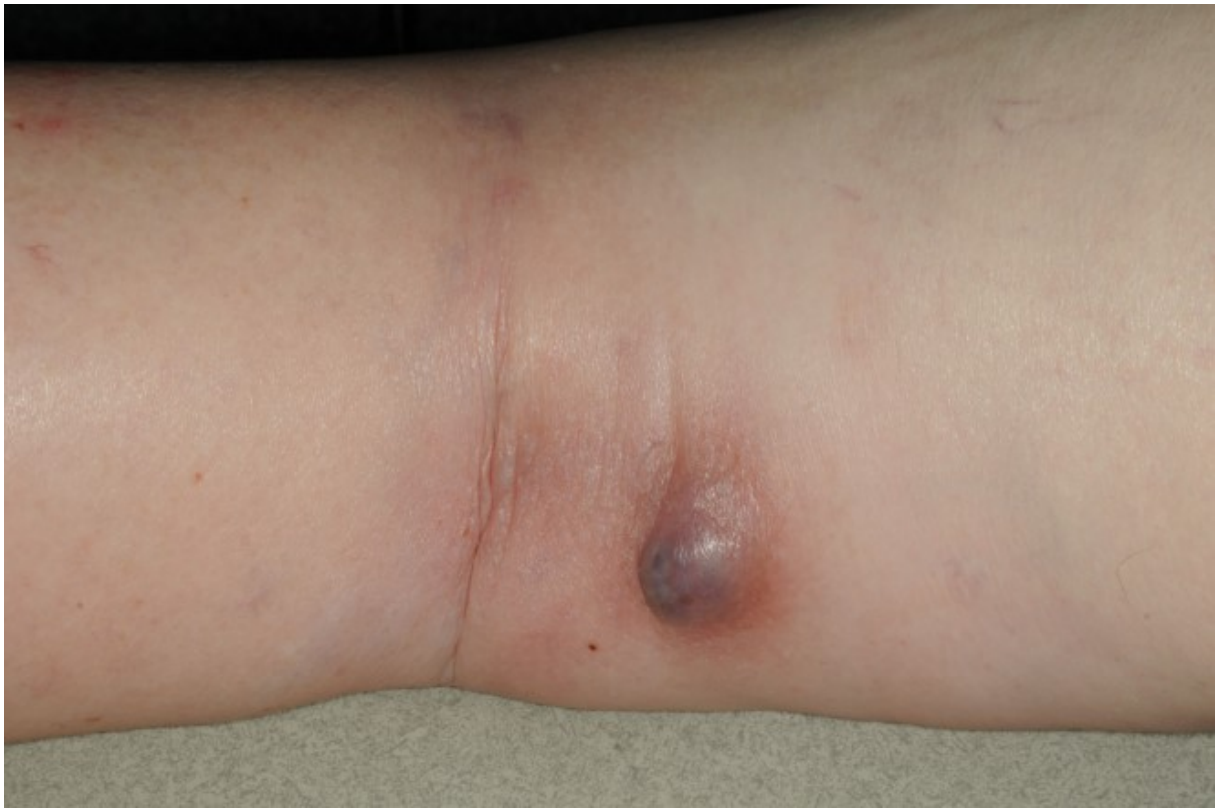

Figure 1 *Lump arising in the popliteal fossa.*

Diagnosis is often challenging and delayed because of STSs' potential to arise in any age group, their rarity, morphological diversity, and unspecific symptoms that are not immediately associated with malignancies. Moreover, STSs may occur in any part of the body though the lower limbs, followed by the upper limbs are the main affected sites. On average, the period between initial symptoms to the final diagnosis takes about 4 months [8]. At the time of diagnosis, 11.6% of the patients have already metastatic lesions [9].
There are several criteria listed to differentiate whether the lesion is benign or malignant. According to the United Kingdom Department of Health, there are five relevant criteria for patients with a suspected soft tissue mass which need a quick referral to a medical centre: a lump with a diameter over 4cm (e.g. golf ball size), a painful lump, a recurrence after an excision, an increase in size, and finally when situated deep to the deep fascia [10, 11].

In a prospective study, more than 50% of the patients did not have pain. Therefore, it is an insecure feature to differentiate between malignant and benign tumours. The size of the lump is more reliable though it has more importance for prognosis than diagnostics. Fast growing tumours situated deep to the fascia are likely to have a malignant background [11]. Clinical examination can help to differentiate between a superficial and a deep tumour. Deep tumours fixed to the fascia do not move simply against the surrounding tissue, whereas superficial ones are easy to touch and move within the subcutis [12]. **Figure 1** and **Figure 2** show variable clinical presentations and sites of STSs.

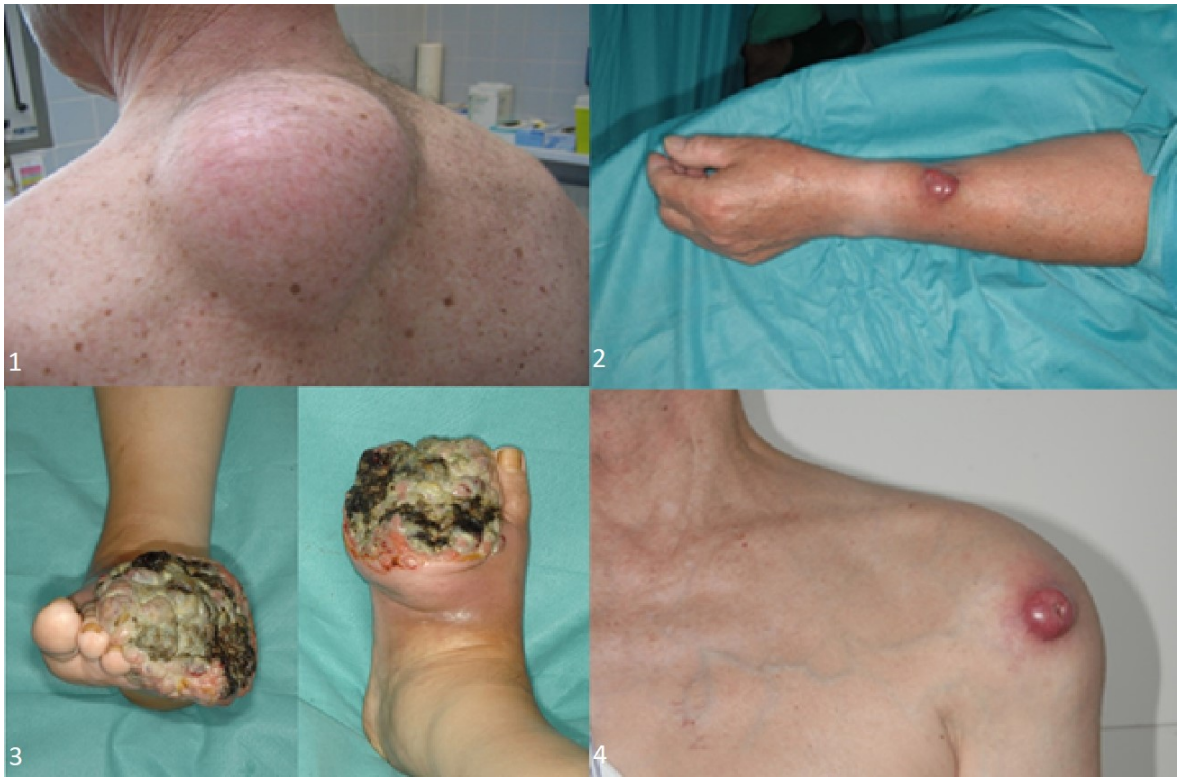

Figure 2 *Several pictures showing clinical presentations of STSs: Massive tumour arising from the back (1). A lump on the forearm (2). Ulcerated STS on the left forefoot (3). Lump arising from the left shoulder (4).*

3. Imaging

A lot of different imaging modalities are available to determine the exact site and extent of STSs and to detect existing metastases. In some cases, the technology may figure out the exact aetiology of a soft tissue mass though it cannot replace a histological diagnosis. Modern imaging is indispensable for staging sarcomas and planning the therapy regime. Magnetic Resonance imaging (MRI) is well-recognised as the gold standard for evaluating

sarcomas of the extremities, trunk, head and neck. Its high contrast tissue resolution makes it the perfect tool to evaluate the extent of the tumorous mass compared to the surrounding structures, especially for muscular tissue. Sarcomas situated visceral or retroperitoneal are more often examined by computed tomography (CT)-scans. Additionally, chest CT-scans are the preferred imaging technique for lung metastases [13-15], as shown in **Figure 3**.

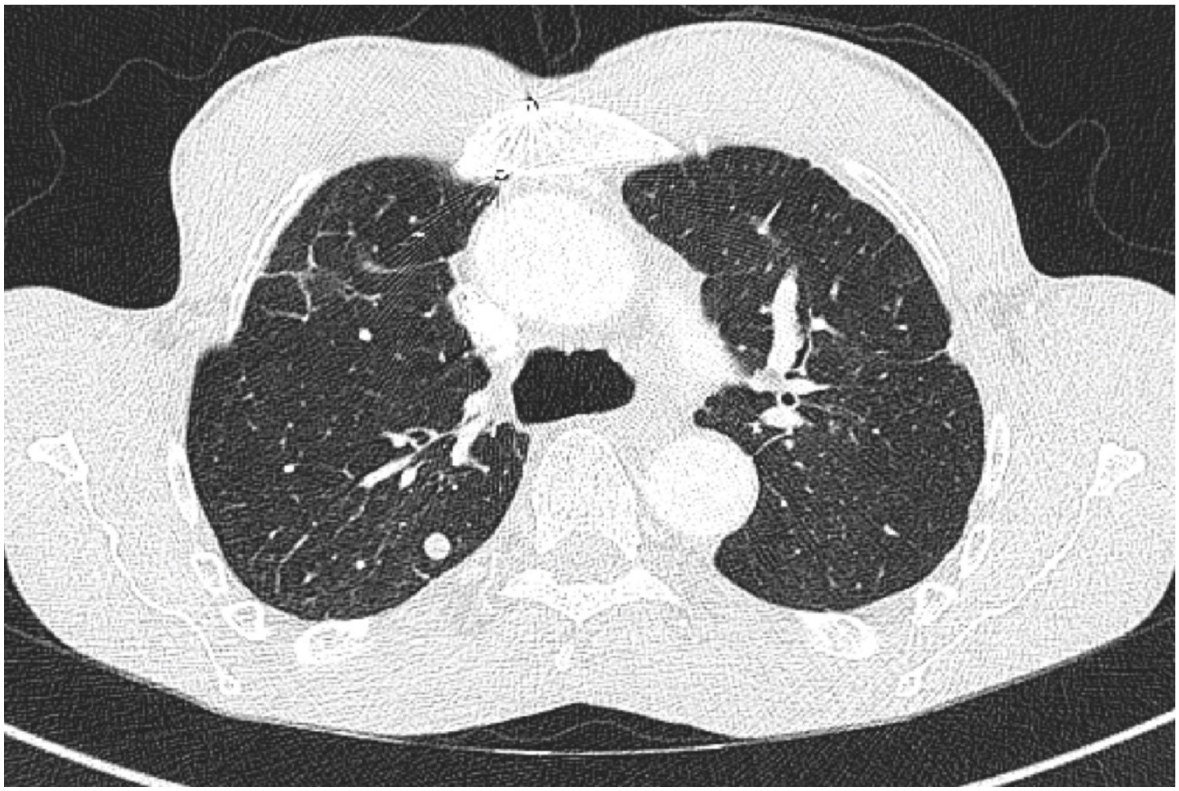

Figure 3 *Chest-CT showing pulmonary metastases of a sarcoma.*

A favourite method to distinguish benign from malign lesions is the positron emissions tomography (PET) with administration of fluorodeoxyglucose (FDG). It has a high sensitivity regarding high-grade sarcomas, but the tracer uptake can be worse in low/intermediate-grade sarcomas. Therefore, the differentiation between low-grade and benign STS is sometimes difficult [16]. Some histologic subtypes might even be unable to uptake the FDG tracer at all.

It can also be used to stage patients suffering from STS. A PET-scan, however, unlikely alters the therapeutic plan and is not superior to chest CT, except for detecting rare occult extrapulmonary metastases. Thus, PET is not recommended as a routine staging method for patients with STS but may answer further issues during disease progression [17, 18].

4. Biopsy

Imaging can be helpful to limit possible differential diagnosis, but only a tissue sample informs about the exact diagnosis, at best, from a soft tissue experienced pathologist. Several studies proved a significant disagreement rate between specialist assessment and non-specialised pathological results. Therefore, only specialised, experienced pathologists should do the final histological review [19, 20].

The sample is histologically examined and usually reveals malignancy, histological grade, and subtype of the tumour entity. This information has an impact on prognosis, outcome, and treatment options. For example, trabectedin is active in myxoid liposarcomas and leiomyosarcomas, whereas undifferentiated high-grade sarcomas respond to gemcitabine [21, 22]. Histology driven therapy is becoming more vital in the treatment of STS.

A core needle biopsy, if possible, should be used because of its low complication rate [23]. Incisional biopsy has better accuracy and delivers a higher amount of sample, which is useful for further planned examinations, such as cytogenetics and molecular analysis. Understanding the molecular background of STSs can help to improve the process of new therapy aspects, like targeted therapy of sarcomas. Imatinib, for example, is successfully used for gastrointestinal stromal tumours (GIST), and further studies showed efficacy in the therapy of dermatofibrosarcoma protuberans [24].

Immunohistochemistry plays an essential role in the differential diagnosis of STSs. Proteins such as actin, desmin, and h-caldesmon are common myogenic markers. Positive S-100 markers represent tumours of neural differentiation, but malignant melanomas can exhibit this protein, too. Epithelial markers include cytokeratin and epithelial membrane antigen, both expressed by synovial sarcomas, epithelioid sarcomas, and epithelioid angiosarcomas. CD99 indicates the presence of Ewing`s sarcomas and other small round-cell sarcomas (e.g. synovial sarcomas, Merkel cell carcinomas, mesenchymal chondrosarcomas) [25, 26].
Biopsies, particularly open-biopsy incisions, should be carefully planned and performed by a surgeon who will later do the definitive surgical resection. The correct placement for each biopsy of a suspect mass is necessary to ensure that the potential tumour-cell contaminated biopsy area itself can be removed en bloc with the primary tumour [27]. This measurement helps to decrease LRs. Ultrasound or CT is advantageous whenever a biopsy of deep lesions

or lesions surrounded by necrosis is needed [28]. Fine needle aspiration (FNA) is not a standard method for making an initial diagnosis of STSs. For examination of metastasis or LR, however, FNA is preferred [29].

5. Staging

The tumour, node, and metastasis (TNM) classification of malignant tumours was created by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). It is the most used staging system for tumours including bonus criteria such as histological grade, depth, and site. TNM stands for size (T), lymph node infiltration (N), and existing distant metastasis (M) and describes the extent of cancer after staging [30]. Visceral sarcomas, Kaposi sarcoma, dermatofibrosarcoma, and desmoid tumours have individual criteria [31].

The following tables list TNM classifications of STSs depending on their site of origin (**Table 2**: extremities, retroperitoneum, and trunk; **Table 3**: head and neck, **Table 4**: abdomen and thoracic viscera) and presence of metastases (**Table 5**: lymph node metastasis, **Table 6**: distant metastasis).

Primary Tumour (T): Extremities, Retroperitoneum, and Trunk	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	≤ 5cm or less in greatest dimension
T2	>5cm, ≤ 10cm in greatest dimension
T3	>10cm, ≤ 15cm in greatest dimension
T4	>15cm in greatest dimension

Table 2 *STS-staging with TNM-system according to the AJCC-classification: T for extremities, retroperitoneum, and trunk.*

Primary Tumour (T): Head and Neck	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	≤ 2cm
T2	>2cm, ≤ 4cm
T3	>4cm,
T4a	Tumour infiltrates: orbital cavity, cranial base, dura, facial bone, musculi pterygoidei
T4b	Tumour infiltrates: brain, prevertebral muscles, arteria carotis

Table 3 *STS-staging with TNM-system according to the AJCC-classification: T for head and neck.*

Primary Tumour (T): Abdominal and thoracic viscera	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Organ confined
T2	Tumour extension into tissue beyond the organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Tumour perforates the serosa (microscopical)
T4	Multifocal involvement
T4a	Multifocal (two sites) or tumour perforates the serosa (macroscopical)
T4b	Multifocal (three to five sites)
T4c	Multifocal (>5 sites)

Table 4 *STS-staging with TNM-system according to the AJCC-classification: T for abdominal and thoracic viscera.*

Regional lymph nodes (N)	
NX	Regional LN cannon be assessed
N0	No lymph node involvement or unknown lymph node status
N1	Lymph node involvement present

Table 5 *STS-staging with TNM-system according to the AJCC-classification: N for regional lymph nodes.*

Distant Metastasis (M)	
M0	No distant metastases
M1	Distant metastases present

Table 6 *STS-staging with TNM-system according to the AJCC-classification: M for distant metastasis.*

A peer review is highly recommended when STSs are classified and histologically graded because general pathologists have a high probability of misdiagnosis [32]. The histological grade is an established marker for malignancy and the occurrence of distant metastases [33]. Unsurprisingly, undifferentiated STSs are more likely to disseminate throughout the body than better-differentiated tumour cells.

The National Cancer Institute (NCI) and the French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) are the most widely accepted standard grading systems. The FNCLCC-system considers tumour differentiation, mitotic count, and extent of necrosis; whereas the NCI-system defines the specific histological subtype instead of differentiation. Beside mitotic rate and extent of necrosis, the NCI adds two further features: pleomorphism and degree of cellularity [34].

The TNM classification and the histological grade are combined to separate sarcomas into different stages (I–IV), whereby stage I and III are again divided into A and B. The stages are prognostic relevant, and the treatment is adjusted accordingly [35] (**Table 7**).

Stage	T	N	M	Grade
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 7 *Staging of STS according to the AJCC-classification.*

6. Treatment

As mentioned above, STSs are a group of rare tumour entities, best treated in specialised centres with a large number of cases. The LR rate of affected patients not referred to a centre is 2.4 times higher compared to patients who received a multidisciplinary therapy approach at an adequate clinic [36]. Pathologists, radiologists, surgeons of diverse specialisations, radiation therapists, medical oncologists as well as physiotherapists meet in these specialised centres and discuss each case separately to ensure best medical care [37].

A referral scheme, adapted from Smolle et al., for the first contact with a suspicious lump is described in **Figure 4** [38].

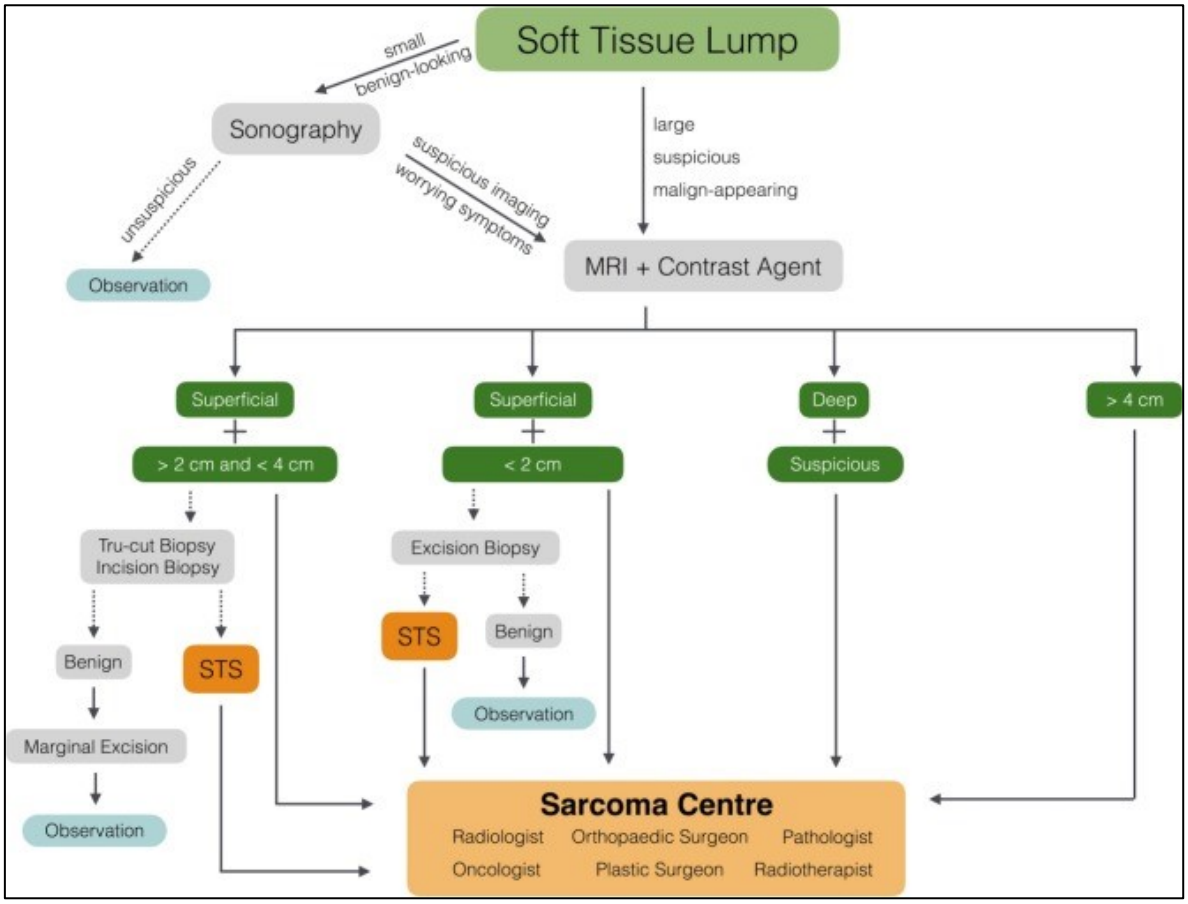

Figure 4 *Referral algorithm for soft tissue lumps.*

Patient age, performance status, general condition, comorbidities, histological subtype, as well as the disease stage will be considered for the treatment plan. Then the attending physician defines realistic goals along with the patient.

Surgery

Up to the 1970s amputation has been the preferred technique in the treatment of sarcomas affecting the extremities. Amputation results in less LRs but has the same risk of distant metastases like limb-sparing surgery with equal survival rates [39]. Surgical resection is still the method of choice when it comes to the treatment of a local primary sarcoma. An experienced surgeon aims to achieve complete en bloc excision of the tumour including, if applicable, the biopsy and drain tract with a margin of tumour-free tissue [40]. Achieving good results of local tumour control depends on the resection margins. A vast majority of STSs is surrounded by a so-called pseudocapsule. It consists of inflammatory tissue, which may be infiltrated by cancer cells. Thus, surgeons must always consider pseudocapsules as tumorous tissue [31].

There are two main classifications for evaluating the tumour margins: on the one hand, the so-called R-classification and, on the other, the residual tumour classification of the UICC, both described in **Table 8**. The former distinguishes R0–R2. R0 resection has a microscopical free tumour cell margin without a defined minimum distance to the tumour. The category R1 includes margins contaminated with tumour cells or resection along the pseudocaspule. A margin with tumour cells visible to the unaided eye is rated R2 [41]. The UICC classification has a clear border within the resection margin. R0 describes tumour-free resection margins with ≥1mm distance to the tumour itself. R1, thus, states infiltrated resection margins <1mm and R2 is equal to R2 of the Residual Classification [42].

	R-classification	UICC-classification
R0	No residual tumour	Resection margin ≥ 1mm
R1	Microscopic residual tumour	Resection margin <1mm
R2	Macroscopic residual tumour	Macroscopic tumour residual

Table 8 *Definition of resection margins according to the R- and UICC-classification.*

Metastasectomy

In the last decades, tumour treatment improved enormously due to a multidisciplinary treatment approach in the clinical setting and progress in research, practice, and science. Nowadays, a cure is very likely for some selected patients with metastatic tumours (e.g.

testicular tumour) by using chemotherapy (CTX), RTX, and surgery. At this time, metastatic STSs cannot be cured, and the focus should be on best supportive care (BSC). Most patients with advanced STS, as for many other tumours, do not die because of the local tumour growth or LRs but from the metastatic spread. A treatment scheme, adapted from the National Comprehensive Cancer Network, for metastatic STS is visualised in **Figure 5** [43].

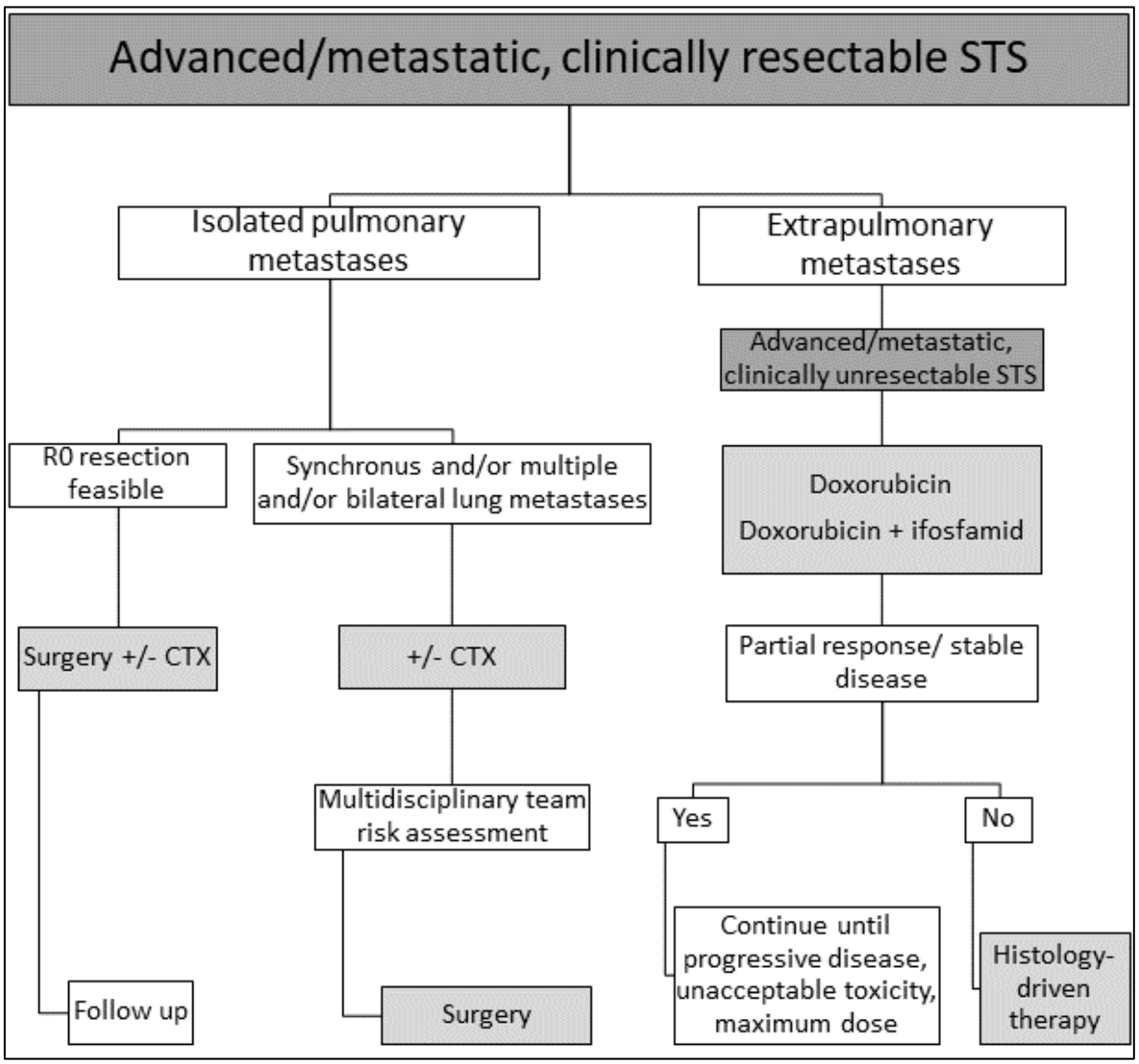

Figure 5 *Management of advanced/metastatic clinically un-/resectable STS.*

At this time, a randomised trial observing the effects of metastasectomy is still missing and will probably not happen in the future either, so the current recommendations rely on non-controlled observative studies. All these studies point out that, in certain circumstances, patients can benefit from pulmonary metastasectomy [44-59]. There are various criteria used for decision making, whether surgeons should perform pulmonary metastasectomy or not. The ability to achieve a complete resection, a low number of metastatic nodules (e.g. 1–2),

and a long metastasis-free interval (MFI) (i.e. period from treatment of the primary tumour to diagnosis of metastasis) before the occurrence of metastases (>12–18 months) are beneficial factors [44, 51-58, 60, 61]. Unsurprisingly, the complete resection of all distant metastases turned out to be the most crucial factor. It is achievable in about one-third of patients with isolated metastases [44]. Exclusion criteria are an uncontrolled primary tumour, impracticability of complete surgical resection of all metastatic nodules, and involvement of extrapulmonary tissue [62-64] though the impact of extrapulmonary metastases is a subject of controversial discussion [65]. There are no defined limitations for pulmonary metastasectomy regarding the metastatic tumour burden. More than two pulmonary nodules are adverse factors, but some surgeons are willing to resect three or even more metastases at once, depending on the individual experience and the treatment scheme of the referral centre.

The standard method for staging is still chest-CT – further CT scans of the abdomen and pelvis are necessary for sarcomas arising within the mid and lower trunk, particularly for tumours situated in the retroperitoneum. Specific histological subtypes with a slightly different dissemination pattern could benefit from further staging methods, such as a PET scan or MRI [66]. The current guidelines of the National Comprehensive Cancer Network, however, do not recommend a PET scan to search for occult extrapulmonary metastatic disease [43]. Although metastases outside the chest are still an exclusion criterion, Blackmon et al. have shown that patients undergoing extrapulmonary metastasectomy are associated with a better outcome [65].

Thoracotomy and wedge resection are commonly performed in the metastatic setting, followed by lobectomy or even pneumonectomy. A less invasive method is the video-assisted thoracoscopy (VATS). On the one hand, it is a safe and minimal invasive surgery, but, on the other hand, surgeons might overlook radiographically occult ipsilateral metastases. Thus, there is no consensus on when VATS is suitable for pulmonary metastasectomy. Some use it only for patients with solitary pulmonary nodule because they are associated with a low likelihood of further clinically occult metastases. Other argue that initially unresected nodules detected later by surveillance CT-scans, have no adverse impact on survival if removed in a second step [67]. Up to now, data of randomised trials comparing the difference between VATS and thoracotomy is non-existent. The favourable outcomes of VATS might base on selection bias. Thus, it should be used for populations with a limited disease extent.

Excision of lung nodules is a potentially curative approach though there is a high rate of disease recurrence within these patients. Reoperation is feasible for a part of them and may result in a survival benefit [68, 69]. Favourable prognostic factors are clear resection margins, less than two nodules with size ≤ 2cm, and well-differentiated histology [70].
The limited data regarding hepatic metastasectomy suggest resection of isolated metastases for specific histological subtypes such as GIST or leiomyosarcoma [71-73]. Selection bias is again not excludable, for example, the use of tyrosine kinase inhibitors, such as imatinib, achieves favourable long-term outcomes of patients suffering from GIST. High-grade subtypes, leiomyosarcoma, and no resection free margins turned out to be adverse prognostic factors [74].
If surgical excision is not possible due to patient comorbidities, then there are still methods of local interventional therapies such as radiofrequency ablation [71], cryoablation [75], stereotactic body radiation therapy [76, 77], and hepatic arterial embolisation. One must keep in mind that these techniques are performed to get control over distant metastases, and data for improved patient survival is still missing.

Radiotherapy

There are two forms of RTX: brachytherapy and conventional RTX. The first one is ionising radiation applied inside one's body and is frequently used for palliative settings. The second one is commonly known as conventional RTX. It produces radioactive beams outside of the patient and has a vast field of indications. A commonly used technique is fractional RTX, where the total dose is administered over several days in small single doses (usually 1.5–2.5Gy).

Referring to STS, adjuvant RTX is considered as the standard therapy approach whenever histological examination reveals an intermediate or high-grade STS. Patients with compartment resection, amputation, or low-grade subtypes do not need adjuvant RTX unless resection margins are contaminated. RTX enables less radical surgical resection and preservation of function without having consequences on LR rates compared to a more radical approach (i.e. amputation/compartment excision) [78].

There is still no agreement whether pre- or postoperative RTX is advantageous because both have equal tumour control rates. Differences exist in the harmful secondary effects made by RTX. Possible postoperative complications of RTX of the extremities are wound healing problems. The dosage applicated for preoperative RTX is 50Gy over 5 weeks. After 4–6 weeks, the surgery takes place. The dosage utilised for postoperative RTX ranges between 66–70Gy. The higher dosage is needed to cover the whole tumour bed. Consequently, late toxicity complications of RTX (e.g. tissue fibrosis) are more common [79].

Nevertheless, some patients with radiosensitive tumours (e.g. myxoid liposarcomas) benefit from neoadjuvant RTX and have a satisfying treatment response. It decreases the tumour volume, resulting in better limb-sparing surgery [80].

Definitive RTX is an option whenever patients have unresectable sarcomas because of advanced size, the grade of invasion, or no limited metastatic disease (i.e. if surgery is not feasible or unreasonable). Unfortunately, satisfying local control rates do not correlate with overall survival (OS). Exact balancing of the dose is necessary because of the thin line between curative and palliative approach. 68Gy are recommended limits because higher doses raise the number of complications without an obvious treatment benefit [81]. RTX is also used as a palliative treatment option in patients with advanced STS. The main indications are osteolytic bone lesions at risk of fracture or painful bone metastases [82].

Proton therapy

Proton therapy is a kind of RTX with high accuracy of the maximal radiation field. Surrounding tissue is less affected by the ionisation, which is useful for STSs situated near sensitive structures (e.g. spinal cord) [83].

Chemotherapy

The use of adjuvant CTX is, with a few exceptions, still controversial in the treatment of sarcomas in adult patients. A multicentre randomised trial tested the efficiency of adjuvant CTX with doxorubicin, ifosfamide, and lenograstim. It showed no positive impact on local control, relapse-free survival or OS [84]. On the other hand, Frustaci et al. showed a positive impact of adjuvant CTX with doxorubicin and ifosfamide on disease-free survival (DFS)

and OS in high-risk extremity STSs [85]. Therefore, the ESMO Clinical Practice Guidelines recommend adjuvant CTX in extremity STS with following features: high-grade histology, situated in the deep, and a size >5cm or patients treated within clinical trials [37].

Aggressive CTX has its place within a multimodality therapy. It enables surgery of tumours appearing to be borderline resectable or limited metastases not being resectable at the moment. In this scenario, neoadjuvant CTX with high toxicity (e.g. full-dose anthracyclines plus ifosfamide) is used, especially for chemosensitive subtypes such as synovial sarcoma or myxoid liposarcoma to create limb-sparing surgery conditions [86, 87]. Currently, a randomised controlled phase III trial has compared the combination of epirubicin plus ifosfamide versus histology-driven CTX and has reported a survival benefit for STS patients receiving the standard CTX with epirubicin and ifosfamide in comparison to histology-driven CTX [88].

If long-term survival is unlikely and the patient suffers from the disease, symptom-oriented therapy is paramount, always considering the toxic side effect of CTX. For a long time, the four-drug combination CyVADIC, consisting of cyclophosphamide, vincristine, adriamycin, and dacarbazine, was the standard CTX treatment for advanced STS [89]. A randomised trial, however, showed no benefit against single-agent doxorubicin used in patients with advanced STS, and a new gold standard in the palliative setting was established [90]. Therefore, single-dose with anthracyclines (e.g. doxorubicin) is the first choice to control metastasis and extend lifetime.

There are a lot of substances and combinations available as second-line therapies depending on histological subtypes, patient's performance status, and their toxicity. Doxorubicin, in combination with ifosfamide, is used to achieve quick tumour response and palliate pain caused by fast-growing metastases, whenever a tumour subtype is sensitive to ifosfamide [91].

Trabectedin monotherapy has its place in the therapy of patients with previously treated metastatic STS without any chance of a cure. This substance, initially gained from sea squirt, combines a good quality of life with remarkable tumour stabilisation [92]. The PALETTE study showed an average increase of 3 months in progression-free survival (PFS) for Pazopanib, a tyrosine-kinase inhibitor first approved in renal cell carcinoma, in patients with

non-adipogenic STS [93]. Eribulin, a substance inhibiting the microtubule dynamic, such as vinca alkaloids and taxane, extended the OS compared to dacarbazine in patients with leiomyosarcomas and liposarcomas. For the latter, the median OS difference was up to 7 months [94]. Maki et al. showed in a randomised phase II study that gemcitabine/docetaxel is superior to gemcitabine alone as second-line CTX. The dual therapy, however, also has higher toxicity and is reserved for leiomyosarcoma and undifferentiated pleomorphic sarcoma (UPS) [22].

Hyperthermic Limb Perfusion

Local advanced extremity STS can be downsized with isolated hyperthermic limb perfusion to avoid amputation. With the help of a heart-lung machine cannulated to a major vessel, it is possible to intervene in a limb's blood circulation. A proximal affixed tourniquet makes sure that no systemic application happens. At first, the temperature of the limb is raised to 39°C causing optimal conditions for the used medications. Then TNF-α and Melphalan are injected, whereas former harms the vascularisation of tumours and stimulates the uptake of Melphalan by tumour cells [95].
According to a systematic review, including 18 studies with 1030 patients, response rates of 72% were achieved, and limb-salvage surgeries were possible in 81% of the cases [96]. A randomised phase III study in patients with localised high-risk STS (G2–G3, >5cm, deep situated) showed a benefit from regional hypothermia in combination with systemic CTX on PFS [97].

Immune Checkpoint Inhibitors

Cancer immunotherapy is an active area of research that is still in its infancy. The basic principle of all immunotherapies is to inactivate the tumour's ability to evade immune surveillance.

The programmed cell death protein 1 (PD-1) is a transmembrane protein expressed by T-cells, B-cells, and natural killer cells. It binds to the programmed death ligand 1 (PD-L1), his natural ligand located on many tissues, especially on hematopoietic cells, as well as on specific tumour cells. The binding of PD-L1 to PD-1 triggers signals that inhibit apoptosis, cause T-cell exhaustion, and increase the occurrence of regulatory T-cells (anti-

inflammatory, suppressive T cells) to avoid cytotoxic autoimmune reactions or as in the case of tumour cells to bypass the immune system [98, 99].

Humanised monoclonal antibodies that target either PD-1, such as pembrolizumab and nivolumab, or PD-L1, such as durvalumab and atezolizumab, are used in clinical practice. A phase II trial tested pembrolizumab in advanced STS and revealed a new, potential treatment approach, especially for UPSs and dedifferentiated liposarcomas [100, 101].

7. Tumour Entities

The World Health Organisation (WHO) differentiates more than 100 histological subtypes of STSs in the 2013 published "WHO Classifications of Tumours of Soft Tissue and Bone". The classification arranges the sarcomas into subgroups according to their morphology, immunohistochemistry, and molecular status [102]. The two last methods gain more and more attention, but classic morphology remains crucial even in the future. Not uncommonly the histogenesis is unclear (i.e. unknown line of differentiation), in this case, pathologists describe the histological architecture of tumour cells, such as alveolar sarcoma, epithelioid sarcoma, clear cell sarcoma, or UPS [102]. Until today, the mechanism of sarcoma genesis is not fully solved, and the theory that every neoplasm has his mature standard counterpart has not yet been proved. Molecular patterns do not only help to understand dysfunctional pathways within the cell cycle but may also open new ways to classify sarcomas.
Pathologists use immunohistochemical staining (IHC) and molecular genetic analysis to confirm their initial suspicion based on the histological pattern. Structural chromosomal aberrations, especially non-random chromosomal translocations, seem to play an essential role in the pathogenesis and disease process of specific sarcomas. The genetic abnormality is gathered for sarcomas to understand the mechanism of downregulating tumour suppressor genes and activating proto-oncogenes. This genetic knowledge helps to understand the pathway to unlimited growth and creates a basis for new approaches, like targeted therapy.

The following table lists subtypes of STSs according to their histology and malignancy (**Table 9**). The second table shows some known translocations of particular STS subtypes (**Table 10**).

1. Adipocytic tumours
Benign
Lipoma
Lipomatosis
Lipomatosis of nerve
Lipoblastoma/Lipoblastomatosis
Angiolipoma
Myolipoma
Chondroid lipoma
Extrarenal angiomyolipoma
Extra-adrenal myelolipoma
Spindle cell/pleomorphic lipoma
Hibernoma
Intermediate (locally aggressive)
Atypical lipomatous tumour/Well-differentiated liposarcoma
Malignant
Dedifferentiated liposarcoma
Myxoid liposarcoma
Round cell liposarcoma
Pleomorphic liposarcoma
Mixed-type liposarcoma
Liposarcoma, not otherwise specified

2. Fibroblastic/Myofibroblastic tumours
Benign
Nodular fasciitis
Proliferative fasciitis
Proliferative myositis
Myositis ossificans
Ischaemic fasciitis
Elastofibroma
Fibrous hamartoma of infancy
Myofibroma/Myofibromatosis
Fibromatosis colli
Juvenile hyaline fibromatosis
Inclusion body fibromatosis
Fibroma of tendon sheath
Desmoplastic fibroblastoma
Mammary-type myofibroblastoma
Calcifying aponeurotic fibroma
Angiomyofibroblastoma
Cellular angiofibroma
Nuchal-type fibroma
Gardner fibroma
Calcifying fibrous tumour
Giant cell angiofibroma
Intermediate (locally aggressive)
Superficial fibromatoses (Dupuytren disease, Mb. Ledderhose)
Desmoid-type fibromatoses
Lipofibromatosis
Intermediate (rarely metastasising)
Solitary fibrous tumour and haemangiopericytoma

7. Vascular tumours
Benign
Haemangiomas
Epithelioid haemangioma
Angiomatosis
Lymphangioma
Intermediate (locally aggressive)
Kaposiform haemangioendothelioma
Intermediate (rarely metastasising)
Retiform haemangioendothelioma
Papillary intralymphatic angioendothelioma
Composite haemangioendothelioma
Kaposi sarcoma
Malignant
Epithelioid haemangioendothelioma
Angiosarcoma of soft tissue

8. Chondro-osseous tumours
Soft tissue chondroma
Mesenchymal chondrosarcoma
Extraskeletal osteosarcoma

9. Tumours of uncertain differentiation
Benign
Intramuscular myxoma
Juxta-articular myxoma
Deep ("aggressive") angiomyxoma
Pleomorphic hyalinising angiectatic tumour
Ectopic hamartomatous thymoma
Intermediate (rarely metastasising)
Angiomatoid fibrous histiocytoma

4. Smooth muscle tumours
Angioleiomyoma
Deep leiomyoma
Genital leiomyoma
Leiomyosarcoma

5. Pericytic (perivascular) tumours
Glomus tumour
Myopericytoma

6. Skeletal muscle tumours
Benign
Rhabdomyoma (adult/fetal/genital type)
Malignant
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma

Intermediate (rarely metastasising)
Plexiform fibrohistiocytic tumour
Giant cell tumour of soft tissues
Malignant
Undifferentiated pleomorphic sarcoma
Undifferentiated pleomorphic sarcoma with giant cells
Undifferentiated pleomorphic sarcoma with prominent inflammation

2. Fibroblastic/Myofibroblastic tumours	9. Tumours of uncertain differentiation
Intermediate (locally aggressive)	**Intermediate (rarely metastasising)**
Inflammatory myofibroblastic tumour	Ossifying fibromyxoid tumour
Low-grade myofibroblastic sarcoma	Mixed tumour/Myoepithelioma/Parachordoma
Myxoinflammatory fibroblastic sarcoma	**Malignant**
Infantile fibrosarcoma	Synovial sarcoma
Malignant	Epithelioid sarcoma
Adult fibrosarcoma	Alveolar soft part sarcoma
Myxofibrosarcoma	Clear cell sarcoma of soft tissue
Low-grade fibromyxoid sarcoma	Extraskeletal myxoid chondrosarcoma
Sclerosing epithelioid fibrosarcoma	PNET/Extraskeletal Ewing tumours
3. So-called fibrohistiocytic tumours	Desmoplastic small round cell tumour
Benign	Extra-renal rhabdoid tumour
Giant cell tumour of tendon sheath	Malignant mesenchymoma
Diffuse-type giant cell tumour	Neoplasms with perivascular epithelioid cell differentiation (PEComa)
Deep benign fibrous histiocytoma	Intimal sarcoma

Table 9 *Histological classification of STSs defined by the WHO in 2013.*

Sarcoma	Translocation	Fusion protein
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14) t(1;13)(p36;q14)	PAX3-FKHR PAX7-FKHR
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	TFE3-ASPL
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	FUS-ATF1
Clear cell sarcoma	t(12;22)(q13;q12)	EWS-ATF1
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	PDFGB-COL1A1
Desmoplastic small round cell tumour	t(11;22)(p13;q12)	EWS-WT1
Endometrial stromal sarcoma	t(7;17)(p15;q21)	JAZF1-JJAZ1
Ewing's sarcoma/ Peripheral primitive neuroectodermal tumour	t(11;22)(q24;q12) t(21;22)(q22;q12) t(7;22)(p22;q12) t(2;22)(q33;q12) t(17;22)(q12;q12) t(16;21)(p11;q22)	EWS-FLI1 EWS-ERG EWS-ETV1 EWS-FEV EWS-E1AF FUS-ERG
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23)	TPM3-ALK TPM4-ALK CLTC-ALK
Low grade fibromyxoid sarcoma	t(7;16)((q33;p11)	FUS-CREB3l2
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12) t(9;15)(q22;q21) t(9;17)q22;q11)	EWS-CHN TFC12-CHN TAF2N-CHN
Myxoid liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q12)	TLS-CHOP EWS-CHOP
Synovial Sarcoma	t(X;18)(p11;q11)	SSX1-SYT SSX2-SYT SSX4-SYT

Table 10 *Chromosomal translocations associated with different sarcomas [103].*

The following passages include short descriptions of common sarcomas, such as angiosarcoma, epithelioid sarcoma, fibrosarcoma, leiomyosarcoma, liposarcoma, UPS, synovial sarcoma, and rhabdomyosarcoma.

Angiosarcoma

Angiosarcomas originate from blood or lymphatic vessels and count for 1% of all STSs. Its preferred site is the head and neck, followed by the trunk. The site can also differ from deep locations (e.g. viscera) to superficial ones, particularly the skin. The tumour can arise at any age but has a peak incidence in the seventh decade of life [104].

Referring to aetiology, the literature describes two risk factors: patients with breast cancer, who have undergone RTX, might develop an angiosarcoma within the exposed zone as a late complication, and lymphangiosarcomas of the upper extremity often appear together with an acquired lymphoedema caused by a mastectomy (Stewart-Treves syndrome) [105]. First clinical signs are an enlarging, blue, purple lesion, which is easily mistaken for a bruise or nonhealing ulceration [106].

The standard therapy is wide resection with subsequent application of adjuvant RTX if necessary. CTX is used for the treatment of locally advanced or metastatic angiosarcomas. Taxanes (e.g. paclitaxel, docetaxel) are preferred instead of the standard doxorubicin-based CTX [107]. The general survival rate depends on several factors such as the site, age, tumour size, and resectability and is considered as rather poor [104].

Epithelioid Sarcoma

The tumour is usually found on sites such as the fingers, hand, forearms, and pretibial region belonging to young men between 20 and 30 years [108, 109].

The acidophilic tumour cells differentiate from both epithelial and mesenchymal tissue. The histology differentiates between epithelioid, spindled, and mixed varieties. The clinical signs, in the beginning, are a single node, which can spread local along tendons, fascial planes, and aponeuroses [108]. Epithelioid sarcomas grow indolent and have often central ulcerations. Therefore, they might be mistaken for granulomatous processes, resulting in late diagnosis and reduced survival chances [108, 110]. The tumour disseminates along subdermal lymphatic/blood vessels and creates frequently distant metastases in the lung [108].

LRs appear particularly within the first 2 years after excision but might also be diagnosed after several years in remission. They occur in up to 85% of the treated patients, depending on site (e.g. tumours proximal to the elbow or knee are associated with a worse survival rate) and tumour size at diagnosis. About 30% of the patients develop distant metastases, which reduce the chances of a cure enormously [108, 109]. Therefore, a radical tumour excision with negative borders is necessary to achieve the best possible results for OS.

Fibrosarcoma

In the past, the adult fibrosarcoma was often misinterpreted and led to a high number of false diagnoses. Since 2002 it is a diagnosis of exclusion due to a revised classification of sarcomas by the WHO [3]. There are many subtypes imitating the adult fibrosarcoma including low-grade fibromyxoid sarcomas, sclerosing epithelioid fibrosarcomas, and fibrosarcomas arising from dermatofibrosarcomas protuberans; as well as monomorphic synovial sarcomas, malignant peripheral nerve sheath tumours (MPNST), and spindle cell variants, such as angiosarcomas, rhabdomyosarcomas, and epithelioid sarcomas. Non-mesenchymal tumours that might be mistaken for a fibrosarcoma are melanoma and sarcomatoid carcinoma [111].

Adult fibrosarcomas arise preferably at the median age of 50 years and affect slightly more males. The main sites of its origin are deep soft tissues of the lower extremities, head and neck, followed by the trunk, and upper extremities [111]. Vimentin and minimal smooth muscle actin are relevant immunohistochemistry markers used for detecting fibrosarcomas though a more substantial part of actin-binding antibodies is an indicator for a myxofibrosarcoma [111].

Myxofibrosarcoma, previously called myxoid malignant fibrous histiocytoma, arises in older people's extremities. The tumour has a diffuse infiltrative growth and high amount of LR [112].

Fibromyxoid type or low-grade fibromyxoid sarcoma, sclerosing epithelioid type, and juvenile/infantile fibrosarcomas are different types of fibrosarcomas according to the WHO [102].

The OS of patients with fibrosarcoma is less than 70% for the first 2 years and less than 55% for 5 years of follow up [111]. Fibrosarcomas are aggressive tumours with a high tendency

of LR. The recurrence rate depends more on surgical margins than on tumour grade. They tend to disseminate haematogenously to the lungs, similarly to other STSs.

Leiomyosarcoma

The group of adult leiomyosarcomas account for 5 to 10% of all STSs [113]. Leiomyosarcomas consist of three main groups, which differ in site, prognosis, and treatment. One feature all groups have in common is their origin out of smooth muscle cells or progenitor cells [114]. Therefore, leiomyosarcomas can occur in almost every site of the body. Most leiomyosarcomas develop within the retroperitoneum and the pelvis [115]. Specific symptoms are rare, so leiomyosarcomas often gather a big size and have a bad surgical resectability at the time of surgery.

The second group of leiomyosarcomas is affecting the big vessels of the lower pressure system, notably inferior vena cava, pulmonary artery, and rarely peripheral arteries [116]. Depending on tumour progress and the site, different symptoms occur. Above the liver, a Budd-Chiari syndrome might develop. A tumour which is situated below the liver, in turn, causes oedema of the extremities.

Leiomyosarcomas, arising from non-retroperitoneal soft tissue (i.e. somatic soft tissue), represent the third group and occur commonly in the limb [117]. A so-called atypical intradermal smooth muscle neoplasm (i.e. cutaneous leiomyosarcoma) belongs to the latest named group. This entity has an excellent prognosis and has a low metastatic potential because of its growth limitations within the dermis [118].

Well-differentiated tumours show spindle cells gathered to fascicles. These fascicles, in turn, are arranged at right angles and cause the typical histological pattern of leiomyosarcomas [102].

Liposarcoma

Liposarcomas arise from adipocytic tissue and consist of four main groups, including well-differentiated, dedifferentiated, myxoid, and pleomorphic liposarcomas. These subtypes encompass about 20% of all adult STSs [102].

Well-differentiated or low-grade liposarcomas are the most common subtypes, accounting for 40–45% of all liposarcomas. They are often situated in the retroperitoneum and the limbs, followed by rarer sites such as the para-testicular area and the mediastinum. Referring to

malignancy, this subtype is unable to spread metastasis though further dedifferentiation is possible. Microscopically, well-differentiated liposarcomas have adipocytes and pleomorphic lipoblasts with an atypical nucleus surrounded by large intracytoplasmic vacuoles. Sometimes the term atypical lipomatous tumour is used in clinical routine to describe a well-differentiated and completely resectable liposarcoma [119].

Dedifferentiated liposarcomas represent the second group and usually arise de-no. However, 10% develop from existing well-differentiated liposarcomas within an average period of 7.7 years [120, 121].

Dedifferentiated liposarcomas have the potential to metastasise, unlike well-differentiated types. Distant metastases occur in 15–20% of the cases although most patients die because of uncontrollable LR. Their favourite site is the peritoneum, followed by the deep soft tissue of the limb and trunk [120].

Myxoid liposarcomas are the second largest group of liposarcomas with 30–35%. These tumours tend to originate from the lower limbs of a far younger age group compared to other liposarcomas types. Distant metastasis to retroperitoneum, soft tissue, abdominal cavity, and bones are common in this subtype. In some cases, only extra-pulmonary metastases were described, which is unusual for other STSs [122, 123].

The last subtype of liposarcomas is the pleomorphic one. The preferred site is the lower extremity. Histological samples show pleomorphic spindle cells with scattered lipoblasts. Despite its rareness, up to 30% of all pleomorphic liposarcomas metastasise during disease progression and show comparable figures of overall mortality [124].

Undifferentiated Pleomorphic Sarcoma

Malignant fibrous histiocytoma (MFH) was a collective term for all unclassifiable tumours with a suspected origin of soft tissue. This fact led to immense overdiagnoses because diagnostic methods such as IHC, cytogenetics, and molecular examinations were not available at that time. Therefore, it was considered as the most common STS of late adult life [125]. The WHO reclassification in 2002 introduced a new term for STS of unknown origin: UPS. Today it is a diagnosis of exclusion and counts for 5% of all STSs [126].

Histologically, there are four subtypes: undifferentiated high-grade pleomorphic sarcoma, myxofibrosarcoma, and the rare types of UPSs with either giant cells or inflammation. Myxofibrosarcoma is still the most common entity among STSs of old patients and mostly

found in the subcutaneous tissue of the lower extremities. UPSs occur in the deep soft tissue of the lower limbs, and 5% of the patients have already an advanced disease at presentation. Both show increasing incidences at an older age. The 5-year DFS ranges between 40–65% with a 5-year OS rate between 50–70% [127].

Synovial Sarcoma

The name of this tumour entity might mislead because the original tissue of synovial sarcoma is not familiar to cells of the synovial membrane. The term has historical reasons since the entity occurs near large joints [128].

The Synovial sarcoma can occur at any age but usually affects older children or young adults and is responsible for about 5–10% of all malignant STSs in adulthood [129].

Although no distinctive progenitor cell is described, the classification divides synovial sarcomas into subgroups with histological specifications. The two main types are biphasic synovial sarcomas with spindled and epithelioid components. Monophasic ones show only spindled like cells under the microscope [128]. Referring to genetics variants, the translocations t(X;18) and t(p11;q11) are a unique characteristic and appear in almost every synovial sarcoma [130]. This type of tumour arises from the deep soft tissue of extremities close to joints, especially the knee. Further sites are the head and neck, retroperitoneum, and mediastinum [131].

Age above 25 years, size bigger than 5cm, and poorly differentiated subtypes of synovial sarcomas are markers for high-risk groups associated with poor prognosis. Due to its aggressive behaviour, about half of the affected patients develop distant metastases to the lung or pleura. This results in a 5-year survival rate of 60% [132].

Rhabdomyosarcoma

The rhabdomyosarcoma is the most common STS in children and adolescents and is responsible for 5% of all paediatric cancers. It is right behind neuroblastoma and Wilms' tumour regarding the incidence of extracranial solid child tumours. Furthermore, rhabdomyosarcomas are part of the group of tumours with small, round, blue cells apart from lymphoma, neuroblastoma, and primitive neuroectodermal tumours [133]. There are three histological variants of rhabdomyosarcomas including embryonal, alveolar, and pleomorphic types.

The first two types occur mainly in children and adolescents but can arise at any age and any site throughout the body. However, embryonal rhabdomyosarcomas prefer to arise in the head and neck region, while alveolar types affect the extremities [134].
Although rhabdomyosarcomas are more common in children, they account for 3% of all adult STSs [135]. Pleomorphic and rhabdomyosarcomas not otherwise specified are the most common types in adults [136]. These types occur at the age of 45 years or older and arise in the deep soft tissue of the extremities [137].

8. Hereditary Tumour Syndromes

Some heritable cancer predisposition syndromes are responsible for the development of STSs. Affected people develop tumours early in their lifetime. Patients might have family members who died or suffered from the same disease or develop multiple malignancies within one lifespan. Germline mutations, which lead either to overexpression of proto-oncogenes or downregulation of tumour suppressor proteins, are the reason for hereditary cancer.

Li-Fraumeni Syndrome

In 1990, Malkin et al. could prove the association between Li-Fraumeni families and the mutation of the TP53 gene. A pivotal tumour suppressor gene leads to the loss of apoptosis and cell repair mechanism [138]. The risk of developing any tumour is much higher than in the average population, particularly for types such as STSs, osteosarcoma, pre-menopausal breast cancer, brain tumours, and adrenocortical carcinomas [139]. Patients with atypical tumours for their age and suspicious family history should be considered for genetic testing.

Beckwith-Wiedemann Syndrome

The Beckwith-Wiedemann syndrome is a paediatric overgrowth disorder caused by different methylation errors on chromosome 11p that encodes for the *insulin-like growth factor 2* [140]. Children show height and weight above the 90th percentile and sometimes present further features such as macroglossia, visceromegaly, naevus flammeus, hypoglycaemia, and abdominal wall defects (e.g. omphalocele and gastroschisis) [141]. The genetic mutation

comes along with a predisposition to embryonal malignancies, particularly Wilms' tumour and hepatoblastoma [142].

Maffucci Syndrome

In the late 19th century, two different cases of enchondromatosis were described: Maffucci syndrome and Ollier's disease, former with simultaneously occurring haemangiomas [143]. Although the syndrome is nonhereditary, it manifests at early childhood. The enchondromas are most times located in the bones of the hand. Affected people have a high risk of developing malignancies such as chondrosarcomas, which develop from benign chondromas [144].

Carney Complex

The Carney Complex is an autosomal dominant mutation of the PRKAR1 gene. It encodes for the regulatory subunit type 1A of the protein kinase A [145]. The syndrome features cardiac and skin myxomas, spotty skin pigmentation (e.g. blue lentigines), and adrenocortical disease. Besides the common myxomas, a small part of the patients might develop osteochondromyxomas too [146].

Neurofibromatosis Type I

Neurofibromin 1 is a protein responsible for the regulation of cellular proliferation by influencing the Ras signal transduction pathway. This protein is absent or non-functional among patients with Neurofibromatosis Type 1 due to a mutated gene on chromosome 17 [147, 148]. Besides cafè-au-lait spots, numerous neurofibromas can arise, depending on the extent of the mutation. Plexiform types of neurofibromas have even the potential to degenerate into MPNSTs [149]. Further malignancies seen in young patients with Neurofibromatosis Type 1 are rhabdomyosarcomas and leukaemia [150].

Retinoblastoma Syndrome

The tumour suppressor protein Retinoblastoma regulates the cell cycle. When activated, it sets in motion several intracellular processes which finally stop proliferation [151]. Patients with a retinoblastoma syndrome have a mutated RB1 gene either hereditary or non-hereditary. Germline mutations, which are rarer than somatic mutations, are predominantly found in patients with binocular retinoblastoma [152]. Heritable retinoblastomas are associated with secondary malignancies, such as osteogenic sarcomas (e.g. osteosarcoma), leiomyosarcomas or malign melanomas. Thus, patients with a successfully therapied hereditary retinoblastoma have to be informed of their lifetime risk and should take part in an appropriate screening programme [153].

9. The Aim of the Study

STSs encompass a large group of heterogeneous and rare tumours. There are up to 100 subtypes, arising from mesenchymal cells. UPS, adipocytic sarcoma, leiomyosarcoma, MPNST are common types. Treatment modalities for metastatic STS includes surgery, RTX, CTX, and targeted therapy.

Distant metastasis is a common feature of STS, up to 50% of all high-grade sarcomas disseminate during disease progression [85]. Treatment may be challenging, taking their heterogeneity and rareness into account. OS rates, after the diagnosis of metastasis, vary from 12 to 18 months [37, 154, 155]. UPS, angiosarcoma, and sarcoma not otherwise specified have the lowest OS with a prognosis below 12 months [155].

The influence of metastasectomy on the survival outcomes in patients with metastatic STS was examined in several non-controlled studies. As early as 1999, Billingsley et al. showed median OS rates of 15 months after surgical excision of metastases. Meanwhile, some studies report median OS rates of up to 47 months [45, 46, 50, 53, 54, 58].

Unfortunately, there are no randomised controlled studies comparing the long-term effects of metastasectomy to non-invasive treatment [156]. The retrospective study design cannot entirely avoid selection bias. In most cases, patients within the surgery group present with favourable clinical parameters such as a low score in the Eastern Co-operative of Oncology Group Scale of Performance Status (ECOG-PS), lower tumour burden, and a slow disease progression with prolonged DFS [52, 57, 154, 157, 158]. Most non-controlled observational

studies did not take unequal patients' distribution into account, which might skew the positive results achieved with metastasectomy [60, 156]. Many metastatic STSs are indeed high-grade tumours with a rather aggressive behaviour [85]. A study by Harris et al. reported median OS rates of 17.5 months for patients with metastatic STS, receiving systemic cancer therapy (e.g. palliative CTX) [155]. Therefore, it is doubtful that patients with high-grade metastatic STS survive more than 5 years without any specific treatment. Patients undergoing metastasectomy, in turn, have an improved OS [47-49, 51, 55, 56, 59, 71].

This study aims to quantify possible benefits of a surgical approach (e.g. pulmonary metastasectomy) versus non-invasive therapies (e.g. BSC ± RTX ± CTX) in patients with metastatic STS. We used a propensity score model to reduce the impact of selection bias. An inverse propensity of treatment weighting (IPTW) was applied to minimise the difference between the two study groups and ensure a non-influenced result. The full advantage of metastasectomy can only be answered by a randomised prospective clinical trial, delivering results from an equal patient distribution. Such a study will most probably never be realised. For that reason, retrospective data will remain the best available evidence supporting the advantage of metastasectomy among patients with metastatic STS.

10. Material and Methods

This retrospective study gathered data of 517 patients with histologically confirmed STS treated between 1998 and 2017 at the Medical University of Graz. Eighty-seven patients matched the inclusion criteria that we will explain later. The gathered data include epidemiological information such as gender, date of birth, date of last follow up or death, and disease-specific parameters like anatomical site (upper limb, lower limb, trunk), depth (deep or superficial), histological subtype, histological grade, and size. Resection margins, classifications based on the UICC references, as well as the type of surgery were documented. Information of other treatments such as CTX, RTX, and isolated limb perfusion was collected, plus the setting they were applied for (adjuvant, neoadjuvant, or palliative), the composition of the CTX, and the total number of Grey administered.

Likewise, the date of LRs and their treatment (resection, RTX, CTX, a combination of RTX/CTX, amputation) were notated.

Information about primary and secondary metastasis such as the total amount, treatment start/discontinuation, and anatomical site were collected, especially for pulmonary metastases. Level of haemoglobin/albumin and the ECOG-PS were gathered for each patient before undergoing the therapy for metastases.

The follow-up period reached from the date of diagnosed metastases to death or the end of records. The baseline date was defined as the day where imaging (i.e. chest X-ray, MRT, CT, PET) substantiated the suspicion of metastatic spread, which was later confirmed by an increase of size, further dissemination, or histological examination of resected metastases. The primary endpoint of this study was OS.

Inclusion/exclusion Criteria

Patients included in the analysis had to fit the following criteria: a histologically confirmed STS with metastasis. We compared a non-surgical group to a surgical group to quantify the benefit of metastasectomy. The first group included patients who received a non-surgical treatment approach for advanced STSs (e.g. BSC ± CTX ± RTX). Patients in the intervention group underwent surgery to resect metastatic disease.

Statistical analysis

IBM SPSS Statistics, Version 25.0, STATA 15.1 and *Microsoft Excel for Windows 2016, Version 16.0* were used for collecting and analysing data. The primary endpoint of the study was OS, which was calculated from the time of diagnosed metastases to death of any cause. A p-value ≤ 0.05 was regarded as statistically significant. Descriptive analysis was used to determine the frequency rate of categorical scales of measurement (e.g. frequencies of nominal values, like gender or ordinal values like the tumour size: <5cm, 5–10cm, and >10cm). Metric/continuous variables underwent explorative analysis to examine the median, mean, variance, standard deviation, minimum and maximum (e.g. haemoglobin values), and 95% confidence interval (95% CI). Bivariate correlation analysis was ascertained with *Pearson's chi-squared test* for categorical values (e.g. gender vs surgical intervention). The comparison of two means was performed with *T-test for independent samples* and *Wilcoxon-rank-sum-/Mann-Whitney-U-test.* The first was applied for metric and normally distributed data (e.g. haemoglobin values between the two study groups: surgical intervention vs. no surgical intervention). The latter compared non-metric and distribution free scales (e.g. size of primary tumour between the two study groups). The *Shapiro-Wilk-test* and the *Kolmogorov-Smirnov-test* were used to examine continuous variables for normal distribution. OS was analysed with *Kaplan-Meier-Survivorship Curves*. Survivor functions were compared with the *Log-Rank (Mantel-Cox) test.* A propensity score approach with IPTW was used to reduce selection bias due to different performance status (e.g. haemoglobin/albumin level, ECOG-PS) between patients receiving best non-surgical treatment and those who underwent surgery. The influence of risk factors on survival was estimated with uni- and multivariate Cox proportional hazard models, presenting p-values calculated with the *Wald test* (e.g. impact of metastasectomy on OS).

11. Results

Patient Characteristics

The analysis of the 87 patients included 38 females (43.7%) and 49 males (56.3%). The mean age of first diagnosed metastases was 64 years, with a range between 19 to 95 years. The site of STSs sorted in ascending order: 6 STSs of the trunk (6.9%), 17 in the upper limb (19.5%), and the lower limb with an amount of 65 STSs (73.6%). **Figure 6** shows the amount of diagnosed metastases from STSs depending on age and gender.

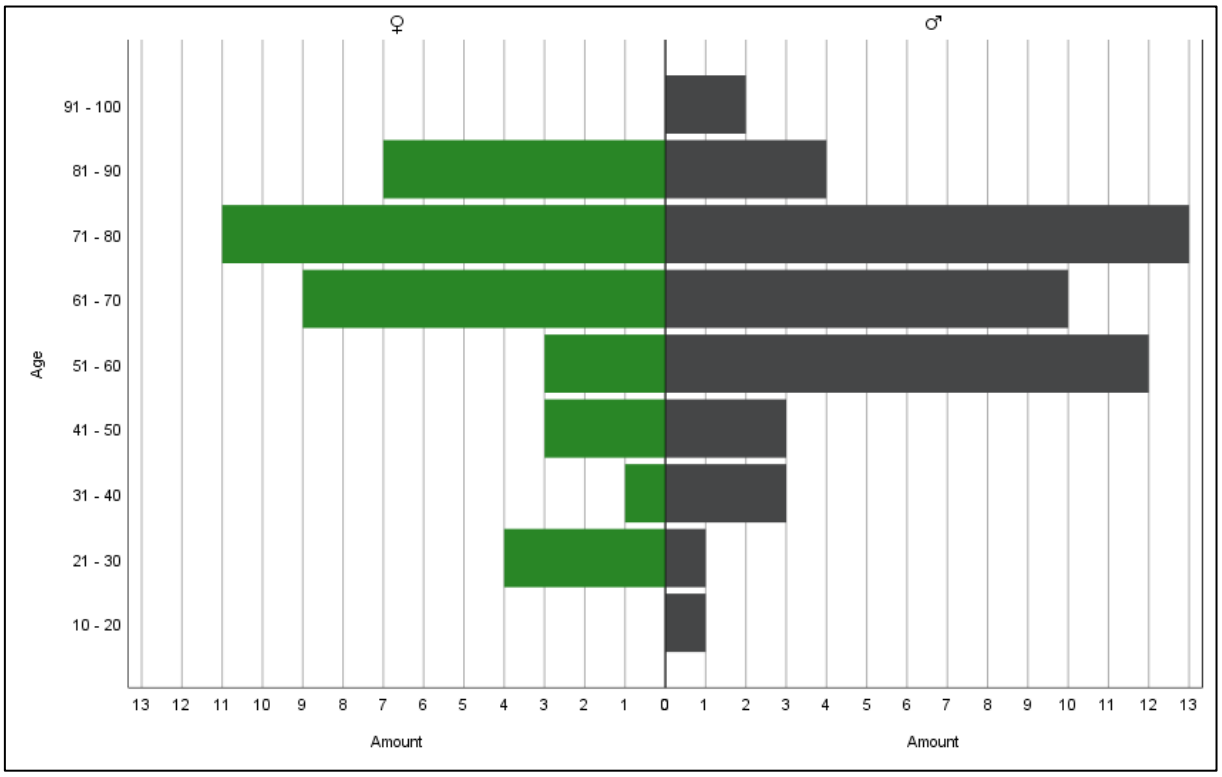

Figure 6 *Metastasis distribution depending on age in decades and gender.*

Tumour Characteristics

Myxofibrosarcoma, found in 31% of the cases (n=27), was the most frequent histological entity among advanced STSs, followed by UPS in 10.3% (n=9), synovial sarcoma in 8% (n=7), liposarcoma/spindle cell sarcoma both in 5.7% (n=5), and angiosarcoma/MPNST both in 3.4% (n=3). The remaining 32.2% (n=28) subtypes were not further categorised and grouped into “other entities” (**Figure 7**).

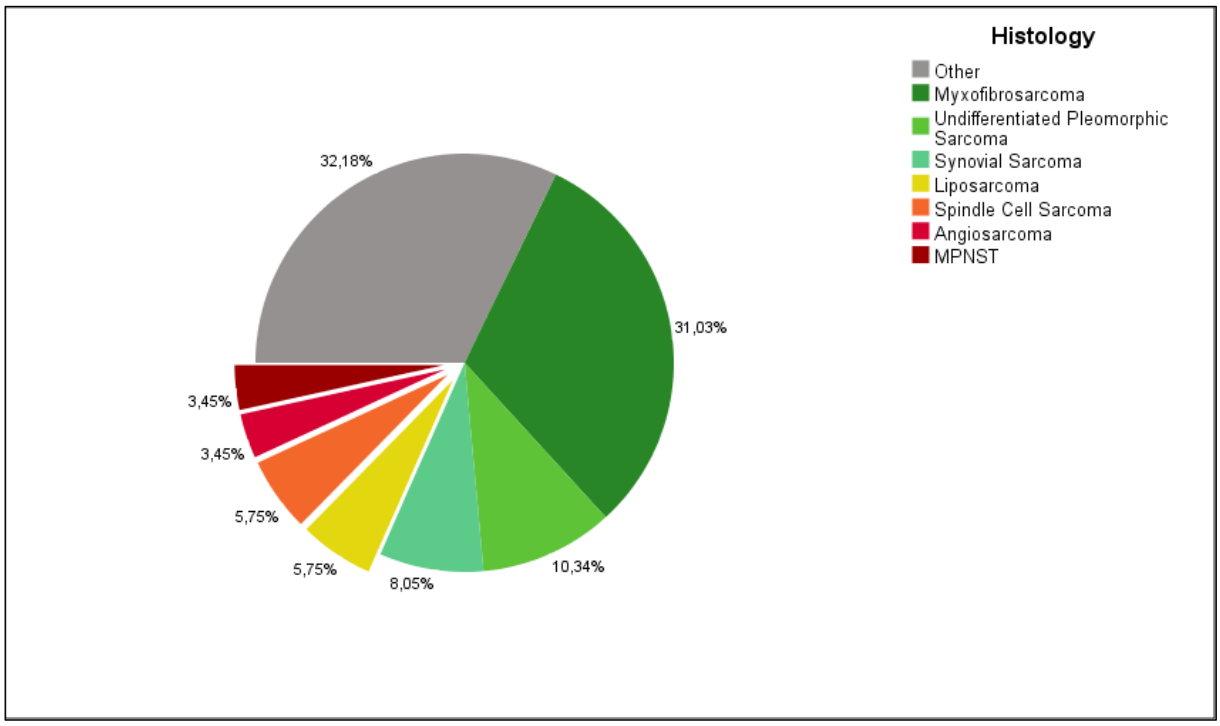

Figure 7 *Piechart depicting the frequency of histological subtypes.*

The tumours were categorised into three sizes: 18 were smaller than 5cm (20,7%), 32 ranged between 5cm to 10cm (36.8%), and 36 were larger than 10cm (41.4%).

STSs of the upper limb had an average size of 8.6cm (SD +/- 4.3cm), followed by the lower limb with 9.9cm (SD +/- 5.5cm). The largest tumours arose from the trunk with an average size of 14.5cm (SD +/- 7.9cm).

Most tumours, 77% (n=67), were poorly differentiated and rated high-grade (G3). Fifteen patients presented tumours with intermediate histological differentiation (G2; 17.2%) and 2 patients with well-differentiated tumour histology (G1; 2.3%) (**Figure 8**).

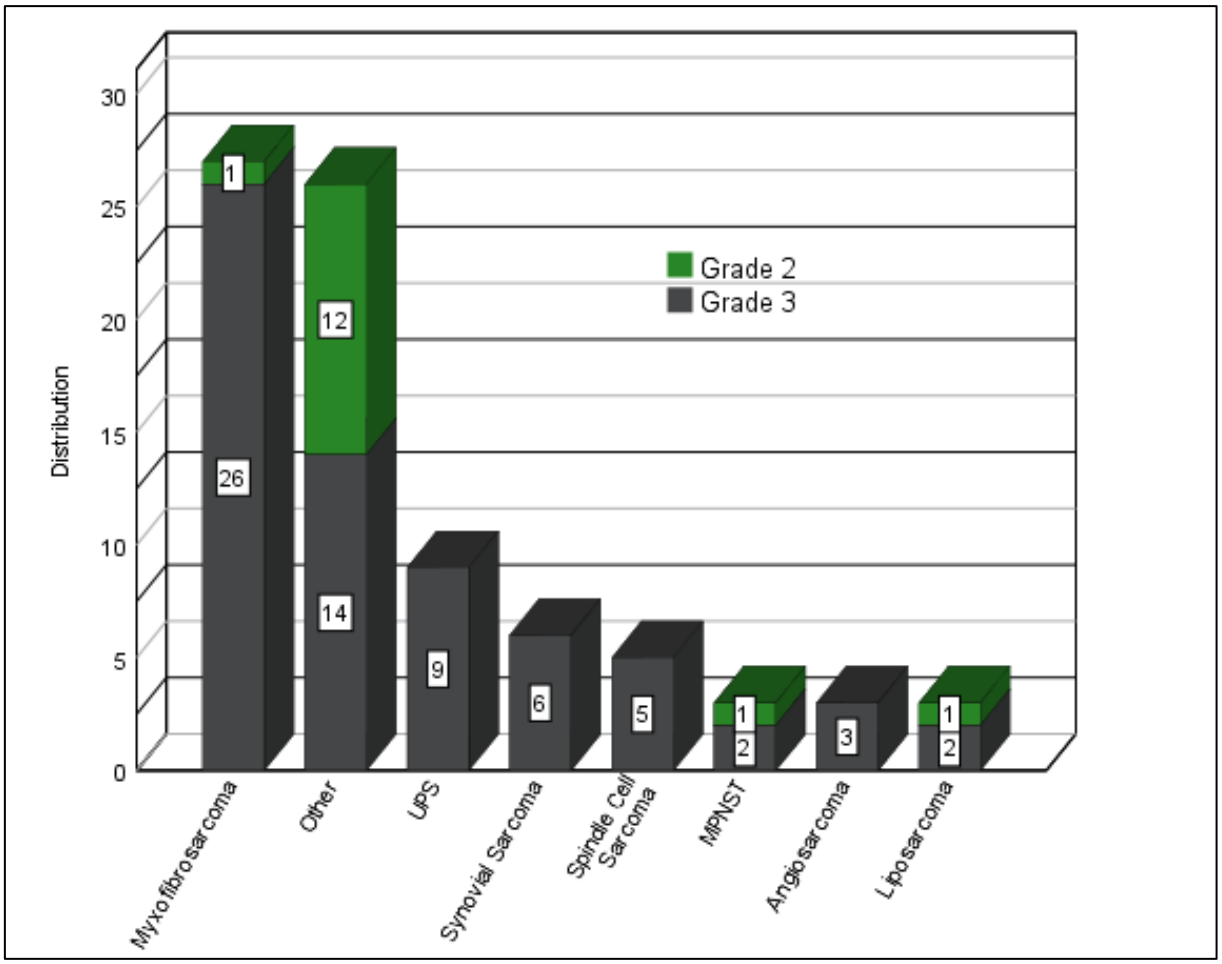

Figure 8 *The amount of G2 and G3 graded tumours depending on their histological subtype.*

Treatment Characteristics of the primary Tumour

Chemotherapy and Radiotherapy

The mean follow-up was 44.4 months, with a minimum of 3 months and a maximum of 208.8 months.

For 39 patients, no data about administered CTX were documented (44.8%). Of the other 48 patients (55.2%), 23 received no CTX (47.9%). Adjuvant CTX was used in 4 patients (8.3%), neoadjuvant CTX in 1 patient (2.1%), and palliative CTX in 7 patients (14.6%). Thirteen patients received CTX in an adjuvant and palliative setting (27.1%) (**Figure 9)**.

In the group with RTX treatment, data of 39 patients were missing (44.8%). Of the remaining 48 patients (55.2%), the vast majority (n=31, 64.6%) received RTX in an adjuvant setting. Both, adjuvant and palliative RTX, was used for the remaining 3 patients (6.2%). Fourteen patients received no RTX (29.2%) (**Figure 9**).

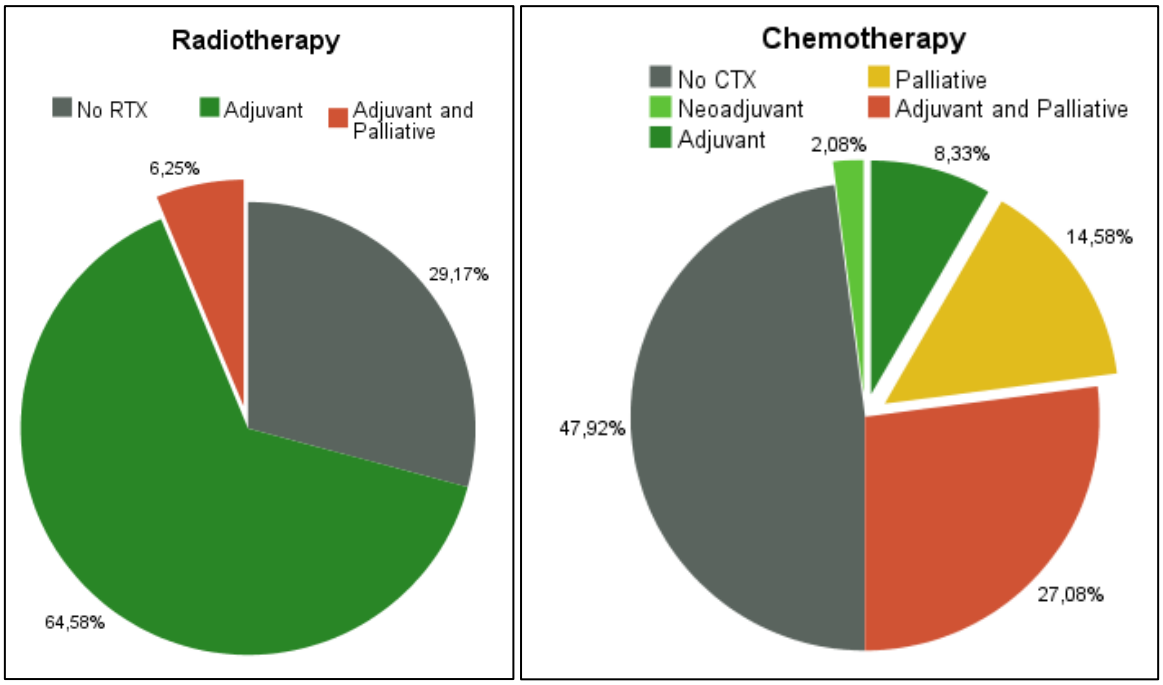

Figure 9 *Piechart illustrating the percentage use of RTX and CTX.*

Surgery

Fifty-seven patients underwent planned surgery for the primary tumour (65.5%). In 51 patients, a tumour resection was sufficed (89.5%). Amputation was performed in 6 patients (10.5%). Wide resection margins could be achieved in 43 patients (79.6%), and marginal resections between 0.1–2mm were documented in 11 patients (20.4%).

Metastasis Characteristics

The median age of the study group at diagnosis of metastases was 64 years (25^{th}–75^{th} percentile: 53–76 years). The median follow-up from diagnosis to the development of lung metastases (25^{th}–75^{th} percentile: 3–20 months) was 17.3 months. Sixty-one patients initially presented with lung metastases (70.1%). Twenty-two of them with a single pulmonary nodule (36.1%) and 39 with multiple metastases (63.9%). Unilateral lung metastases (i.e. metastases affecting one side of the lung) arose in 30 patients (49.2%) whereas 31 patients had metastases in both lungs (50.8%). Sixteen patients presented with metastatic lesions to the soft tissue and/or lymph nodes (18.4%), and 4 with metastases to the bone (4.6%). Of the 5 remaining patients, 3 had skip lesions (3,4%) and 2 solid organ metastases (excluding lung and brain) (2.3%). No site of metastases could be figured out in 1 patient (1%). Multiple

metastases were found in 47 patients (54%) whereas 40 patients had singular lesions (46%). Additional metastases, after diagnosis of the first ones, occurred in 41 patients (47.1%).

Metastasectomy was performed in 47 patients (54%). Of the remaining 40 patients with no surgical intervention (46%), 27 received BSC (67.5%) and 13 were administered CTX ± RTX (32.5%). Of the 47 patients with metastasectomy (54%), 7 patients underwent wedge-resections (14.9%), 19 lobectomies (40.4%), 10 lymph node extirpations (21.3%), and 11 resections of peripheral metastases (23.4%).

Variables		n (% missing)	Overall	<4 years PMS		>4 years PMS		p-value
			(n=87)	(n=73)	%	(n=14)	%	
Gender	*Male*	*87 (0%)*	*49*	41	83.7	8	16.3	0.946
	Female		*38*	32	84.2	6	15.8	
Primary Tumour Site	*Upper limb*	*87 (0%)*	*17*	17	100	0	0.0	**0.050**
	Lower limb		*64*	50	78.1	14	21.9	
	Trunk/Retroperitoneum		*6*	6	100.0	0	0.0	
Histology	*Angiosarcoma*	*87 (0%)*	*3*	3	100.0	0	0.0	0.629
	MPNST		*3*	3	100	0	0.0	
	Myxofibrosarcoma		*27*	24	88.9	3	11.1	
	Synovial Sarcoma		*7*	6	85.7	1	14.3	
	MFH/UPS		*9*	6	66.7	3	33.3	
	Spindle Cell Sarcoma		*5*	4	80.0	1	20.0	
	Liposarcoma		*5*	5	100.0	0	0.0	
	Other		*28*	22	78.6	6	21.4	
Tumour Grade	*G1*	*84 (3.4%)*	*2*	2	100	0	0.0	0.770
	G2		*15*	12	80.0	3	20.0	
	G3		*67*	56	83.6	11	16.4	
Tumour Size	*0–5cm*	*86 (1.1%)*	*18*	12	66.7	6	33.3	0.087
	5–10cm		*32*	28	87.5	4	12.5	
	>10cm		*36*	32	88.9	4	11.1	

Table 11 *Patient- and tumour-related parameters compared between patients surviving less or more than 4-years after the development of metastases.*

There was no significant association between the post-metastasis survival (PMS) rate (i.e. time from occurrence of metastases to death) and gender (p=0.946, χ^2-test), histological subtype (p=0.629, χ^2-test), tumour grade (p=0.770, χ^2-test), or tumour size (p=0.087, χ^2-test) (**Table 11**).

However, the tumour site correlated significantly with the 4-year PMS (p=0.050, χ^2-test). Fourteen patients with advanced tumours situated in the lower limb were still alive after 4 years (n=14 out of 74; 21.9%) whereas patients with metastasised tumours arising from the upper limb (n=0 out of 17; 0%) or trunk/retroperitoneum (n=0 out of 6; 0%) did not live longer than 4 years (**Table 11**).

Table 12 lists the baseline characteristics of the study population in terms of distribution between the groups with and without surgical intervention.

Thirty-one patients who underwent a limb salvage surgery had a metastasectomy (68.8%). Of the 6 performed amputations, only 1 patient had further surgical excisions of metastases (p=0.039, χ^2-test) (**Table 12**).

No significant differences between the rate of metastasectomy and non-surgical approaches could be determined for gender (p=0.523, χ^2-test), primary tumour site (p=0.440, χ^2-test), histology (p=0.524, χ^2-test), grading (p=0.248, χ^2-test), or tumour size (p=0.087, χ^2-test). Unsurprisingly, also the exact tumour size did not interfere whether excisions of metastases were performed or not (p=0.879, U-test) (**Table 12**).

Patients that had a neo-/adjuvant therapy approach with either RTX (n=13 out of 21; 61.9%), CTX (n=3 out of 5; 60.0%) or both (9 out of 13; 69.2%) had better chances to receive surgical intervention in terms of metastasectomy (p=0.037, χ^2-test). In contrast, resection of metastases, without previous administered CTX or RTX, was performed in only 1 patient (11.1%) (**Table 12**).

Singular metastases were resected significantly more frequent (n=28 out of 40, 70.0%) as compared with multiple (>1 metastasis) metastases (n=19 out of 40, 40.4%; p=0.006, χ^2-test) (**Table 12**).

Variables		n (% missing)	Overall	No surgical intervention		Surgical Intervention		p-value
			(n=87)	(n=40)	%	(n=47)	%	
Gender	*Male*	*87 (0%)*	49	24	49.0	25	51.0	0.523
	Female		38	16	42.1	22	57.9	
Primary Tumour Site	*Upper limb*	*87 (0%)*	17	10	58.8	7	41.2	0.440
	Lower limb		64	28	43.8	36	56.3	
	Trunk/Retroperitoneum		6	2	33.3	4	66.7	
Histology	*Angiosarcoma*	*87 (0%)*	3	1	33.3	2	66.7	0.524
	MPNST		3	3	100.0	0	0.0	
	Myxofibrosarcoma		27	14	51.9	13	48.1	
	Synovial Sarcoma		7	3	42.9	4	57.1	
	MFH/UPS		9	3	33.3	6	66.7	
	Spindle Cell Sarcoma		5	1	20.0	4	80.0	
	Liposarcoma		5	2	40.0	3	60.0	
	Other		28	13	46.4	15	53.6	
Size of Primary Tumour		*86 (1.1%)*	9.0 [6.0–13.4]	10.0 [6.0–13.1]		8.0 [6.0–14.0]		0.879
Tumour Grade	*G1*	*84 (3.4%)*	2	0	0.0	2	100.0	0.248
	G2		15	9	60.0	6	40.0	
	G3		67	31	46.3	36	53.7	
Tumour Size	*0–5cm*	*86 (1.1%)*	18	7	38.9	11	61.1	0.087
	5–10cm		32	15	46.9	17	53.1	
	>10cm		36	18	50.0	18	50.0	
Surgery Primary Tumour	*Limb Salvage*	*57 (34.5%)*	51	20	39.2	31	60.8	**0.039**
	Amputation		6	5	83.3	1	16.7	
Adjuvant Therapy	*No Adjuvant Therapy*	*48 (44.8%)*	9	8	88.9	1	11.1	**0.037**
	(Neo-)Adjuvant RTX		21	8	38.1	13	61.9	
	(Neo-)Adjuvant CTX		5	2	40.0	3	60.0	
	Both		13	4	30.8	9	69.2	
Count of Metastases	*Singular*	*87 (0%)*	40	12	30.0	28	70.0	**0.006**
	Multiple		47	28	59.6	19	40.4	
Site of Metastasis	*Lung*	*86 (1.1%)*	61	35	57.4	26	42.6	**0.007**
	Soft tissue ± Lymph nodes		16	2	12.5	14	87.5	
	Bone		4	0	0.0	4	100.0	
	*Solid organs**		2	1	50.0	1	50.0	
	Skip lesions		3	1	33.3	2	66.7	
Age at Metastasis (years)		*87 (0%)*	68 [53–76]	68 [57–77]		61 [47–73]		0.151
MFI (months)		*86 (1.1%)*	11.5 [3–20.5]	6 [2–20]		11 [3–19]		0.179
ECOG-PS	*0*	*65 (25.3%)*	18	6	33.3	12	66.7	0.148
	1		32	13	40.6	19	59.4	
	2		9	6	66.7	3	33.3	
	3		4	3	75.0	1	25.0	
	4		2	2	100.0	0	0.0	
Haemoglobin (g/dL)		72 (17.2%)	13.1 [11–14.6]	12.1 [9.6–13.2]		13.9 [10.9–14.8]		**0.0006**
Albumin (g/dL)		50 (42.5%)	4.1 [3.4–4.6]	3.7 [3.1–4.1]		4.5 [4.0–4.8]		**0.0002**

Table 12 *Patient-, tumour-, and treatment-related parameters divided by the presence of metastasectomy - *solid organs (excluding brain and lung.)*

Depending on the site of the metastases, some patients had better chances that a metastasectomy was carried out (p=0.007, χ^2-test). Metastases of the soft tissue and/or lymph nodes (n=14 out of 16, 87.5%), bone (n=4 out of 4, 100.0%), and skip lesions (n=2 out of 3, 66.7%) displayed high rates of excisions. Of the patients with metastatic spread to solid organs (excluding lung and brain), 1 received a surgical approach (n=1 out of 2, 50.0%). Twenty-six patients with lung metastases were treated surgically (42.6%) (**Table 12**).

Neither the age of the patients with metastases (p=0.151, U-test) nor the time from diagnosis of the primary tumour to metastasis (p=0.179, U-test) had an impact on the decision whether surgical intervention was performed or not. Additionally, there was no difference regarding the ECOG-PS compared to the likelihood of undergoing metastasectomy (p=0.148, χ^2-test) (**Table 12**).
Patients in the surgical group had statistically higher haemoglobin ($\bar{x}$=13.9 g/dL, p=0.0006, T-test) and albumin ($\bar{x}$=4.5 g/dL, p=0.0002, T-test) values compared to patients in the non-surgical group (haemoglobin: $\bar{x}$=12.1 g/dL, albumin: $\bar{x}$=3.7 g/dL) (**Table 12**).

Prognosis

The 5- and 10-year OS rates of patients after diagnosed metastatic STSs were 22.8% and 12.3%. The median OS was 17 months (**Figure 10**).

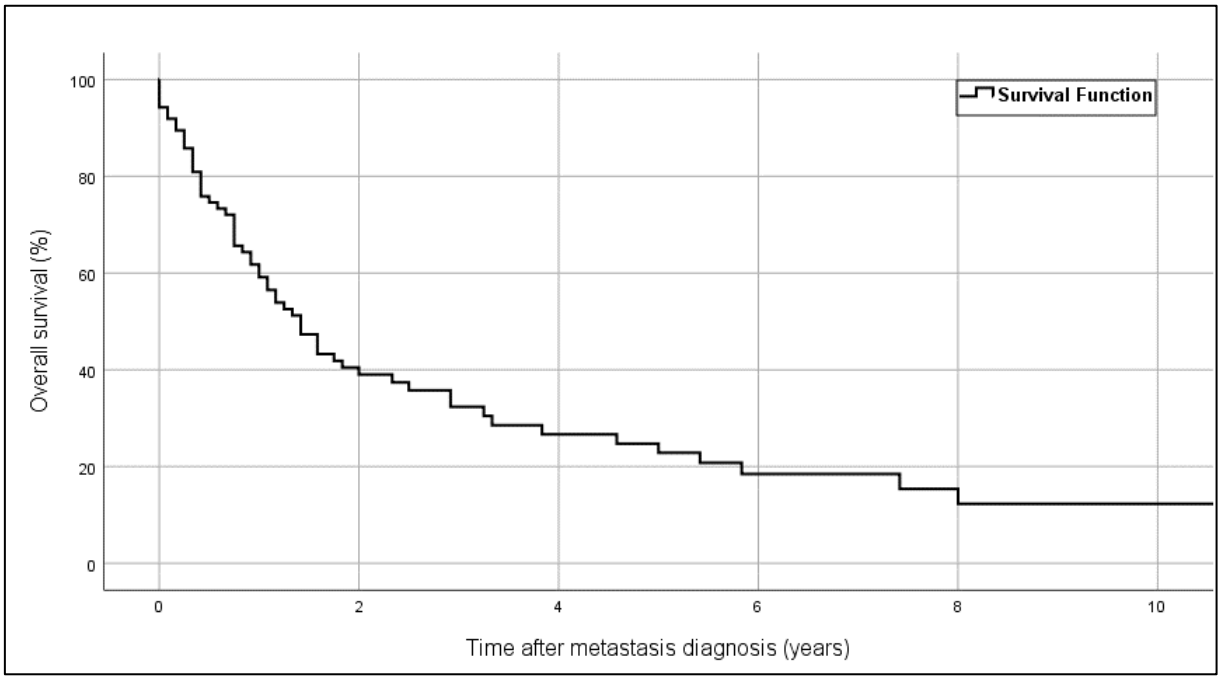

Figure 10 *Kaplan-Meier survivorship curve showing the OS of all patients with a metastatic STS (n=87).*

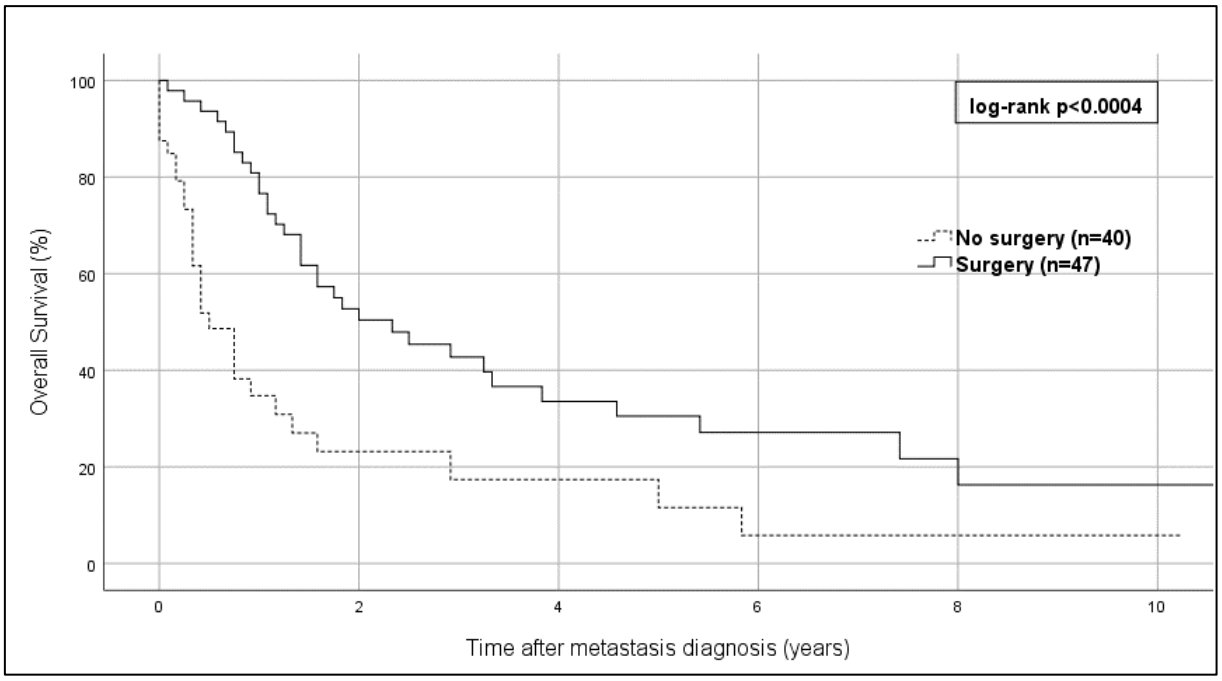

Figure 11 *Kaplan-Meier survivorship curve showing the influence of metastasectomy on OS (n=87).*

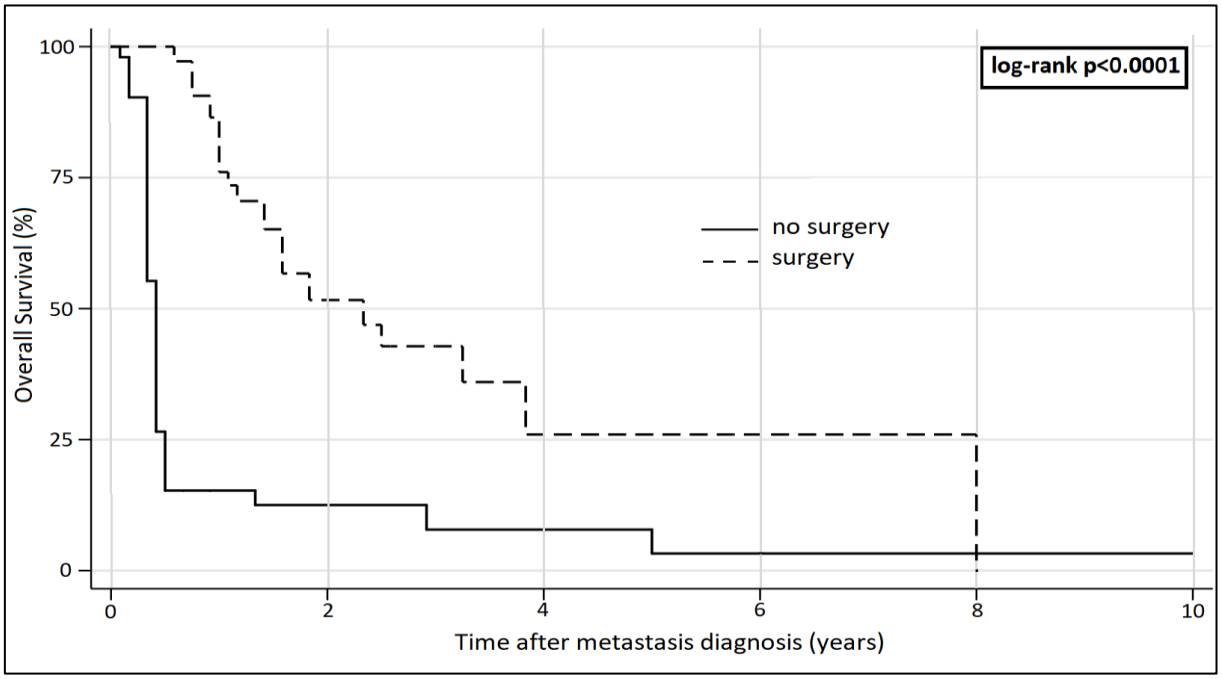

Figure 12 *Kaplan-Meier survivorship curve showing the influence of metastasectomy recalculated with IPTW (n=87). Surgery (n=47), No surgery (n=40).*

Patients who had a metastasectomy had a significantly better OS rate in comparison to patients who received palliative RTX/CTX or no therapy at all (p<0.0004, Log-Rank test). Patients without surgical excision of their metastases had 5- and 10-year OS rates of 11.6% and 5.8% whereas patients undergoing metastasectomy achieved 5- and 10-year OS rates of

30.5% and 16.3%. The median OS of the treated group was 28 months, and 6 months for patients treated non-surgical (**Figure 11**).

After weighing all patients for the IPTW-score and recalculating the survival function, metastasectomy remained a decisive factor in OS (p<0.0001, Log-Rank test) (**Figure 12**).

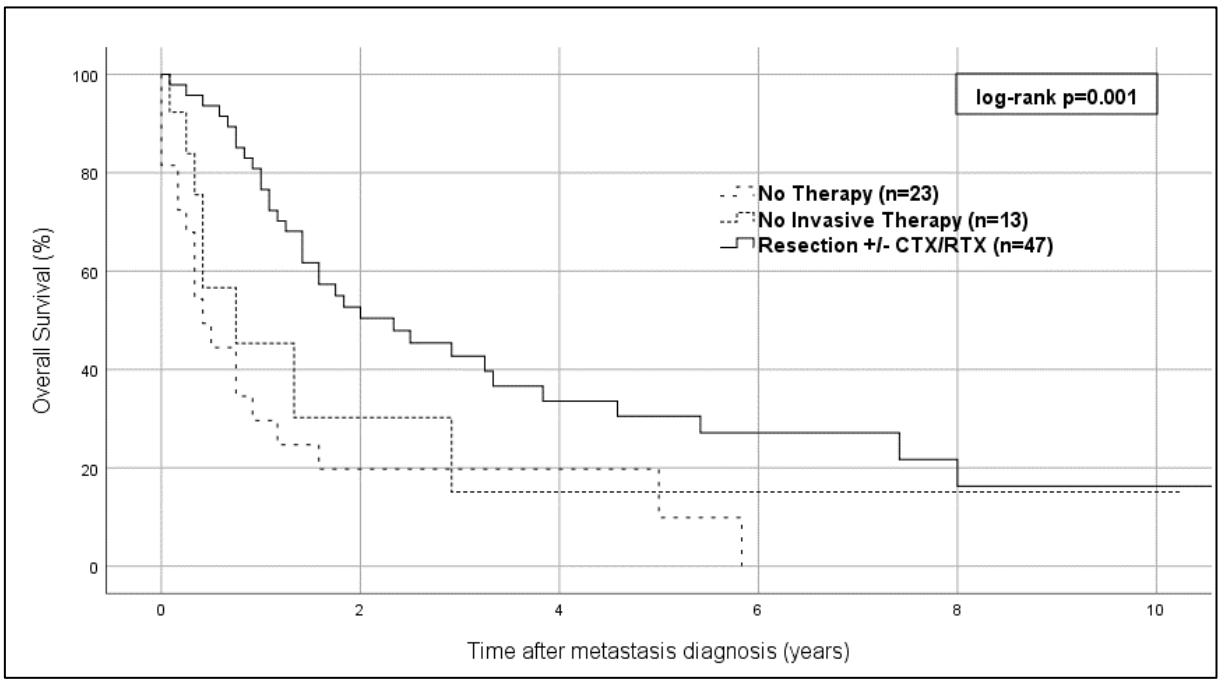

Figure 13 *Kaplan-Meier survivorship curve displaying OS depending on the treatment option (n=87).*

As shown in **Figure 13**, the non-surgical group was split into patients receiving CTX or RTX and patients receiving no treatment at all. Unsurprisingly, there was still a significant difference between the two new groups (p=0.001, Log-Rank test). The former group had identical 5- and 10-year OS rates of 15.1%. The 5-year OS rate of patients without further treatment was 9.9% with a median OS of 5 months. CTX or RTX treated patients had a median OS of 9 month (**Figure 13**).

The different histological characteristics affected significantly the prognosis of patients (p<0.0004, Log-Rank test). Patients suffering from spindle cell sarcoma had the best outcome in comparison to MPNST and angiosarcoma with a rather poor OS (**Figure 14**).

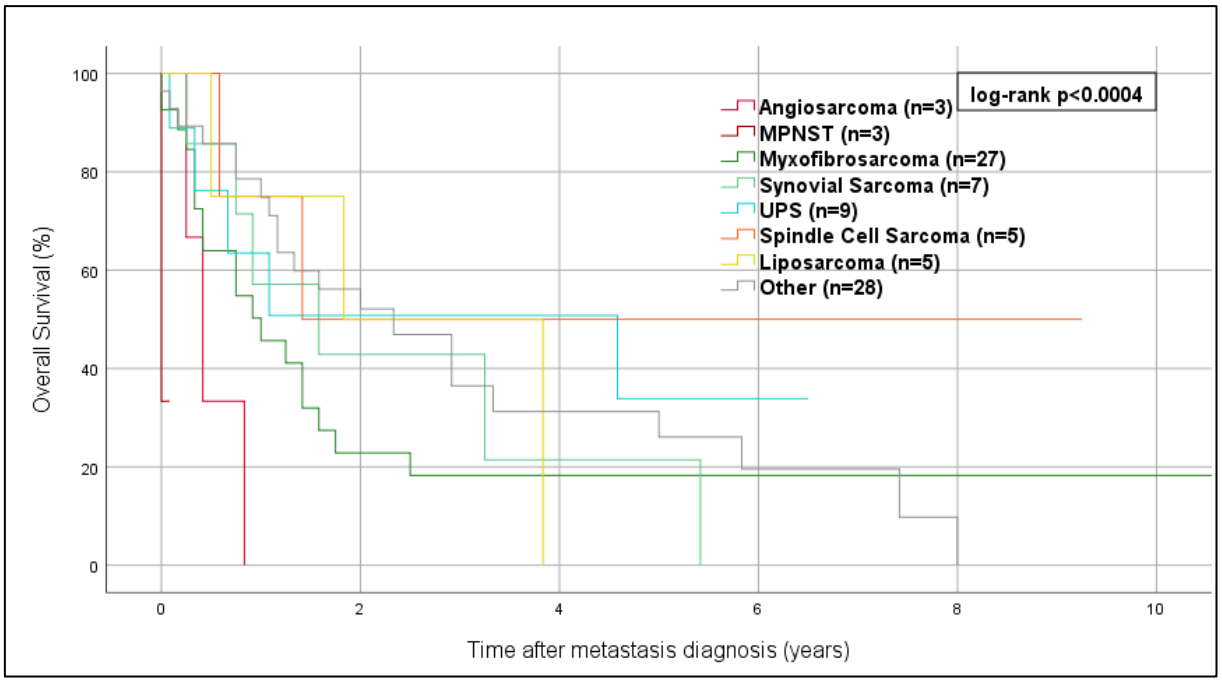

Figure 14 *Kaplan-Meier survivorship curve depicting the influence of the different histological subtypes on OS (n=87).*

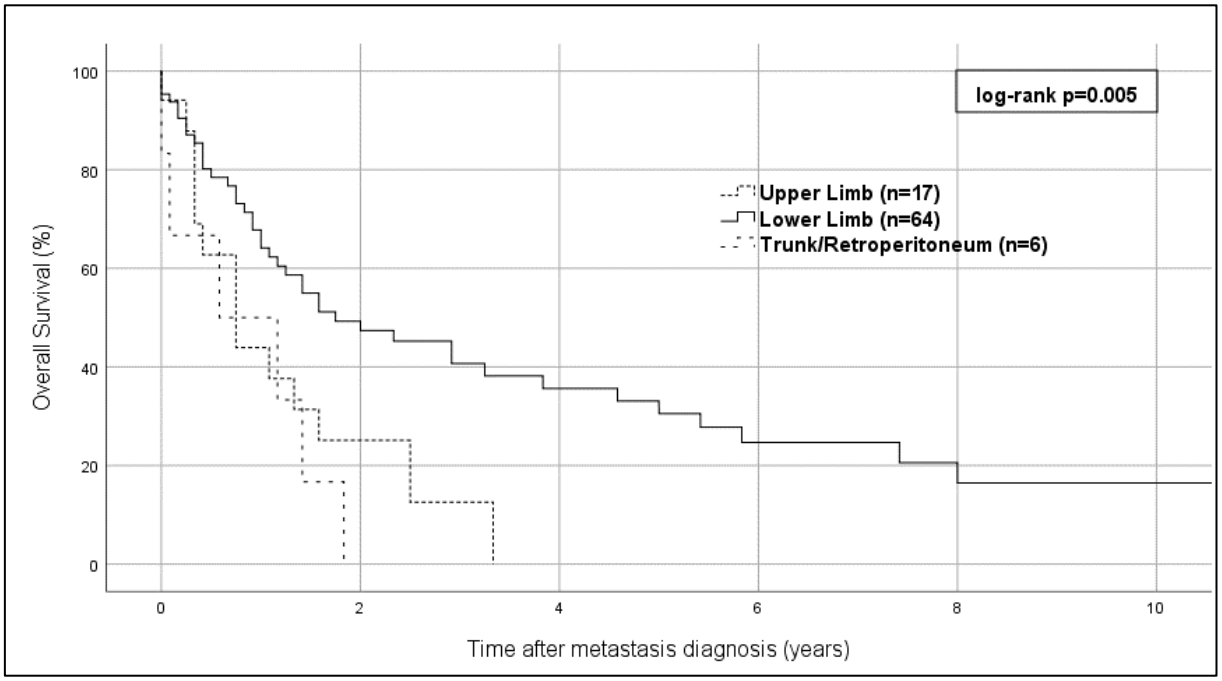

Figure 15 *Kaplan-Meier survivorship curve showing the impact of the tumour site on OS (n=87).*

Patients whose tumours arose in the lower limb had a significantly better OS compared to tumours arising from the upper limb, trunk or retroperitoneum (p=0.005, Log-Rank test). The 5- and 10-year OS rates as well as the median OS were 30.5%, 16.4% and 21 months for sarcomas of the lower limb. The median OS was 9 months for sarcomas of the upper

limb and 7 months for sarcomas of the trunk/retroperitoneum. Both tumour sites had a 5-year OS rate of 0.0% (**Figure 15**).

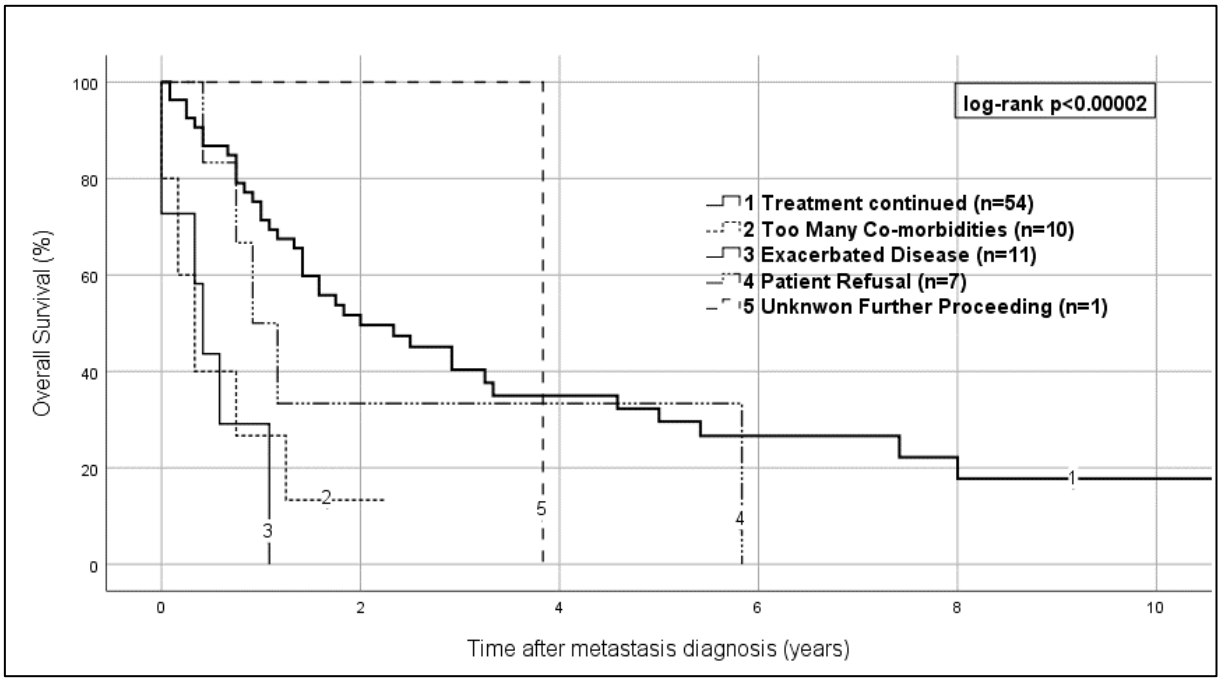

Figure 16 *Kaplan-Meier OS function by treatment stop for a variety of reasons (n=83).*

As expected, the 5- and 10-year OS rates of patients who received further treatment after metastasis were significantly better when compared to untreated patients (p<0.00002, Log-Rank test). Patients who refused further treatment lived longer than patients who did not receive further treatment likely due to comorbidities or disease-exacerbation that led to treatment stop (**Figure 16**).

Gender (p=0.751), histological grade (p=0.672), tumour size of <5cm/5–10cm/>10cm (p=0.807), administration of adjuvant therapy (RTX/CTX, p=0.052), whether singular metastasis or multiple metastases were diagnosed (p=0.169), and the absolute amount of metastasis (p=0.424) showed no significant influence on OS when examined with the Log-Rank test.

Given the fact that STSs spread mainly to the lungs, survival functions were made for these patients.

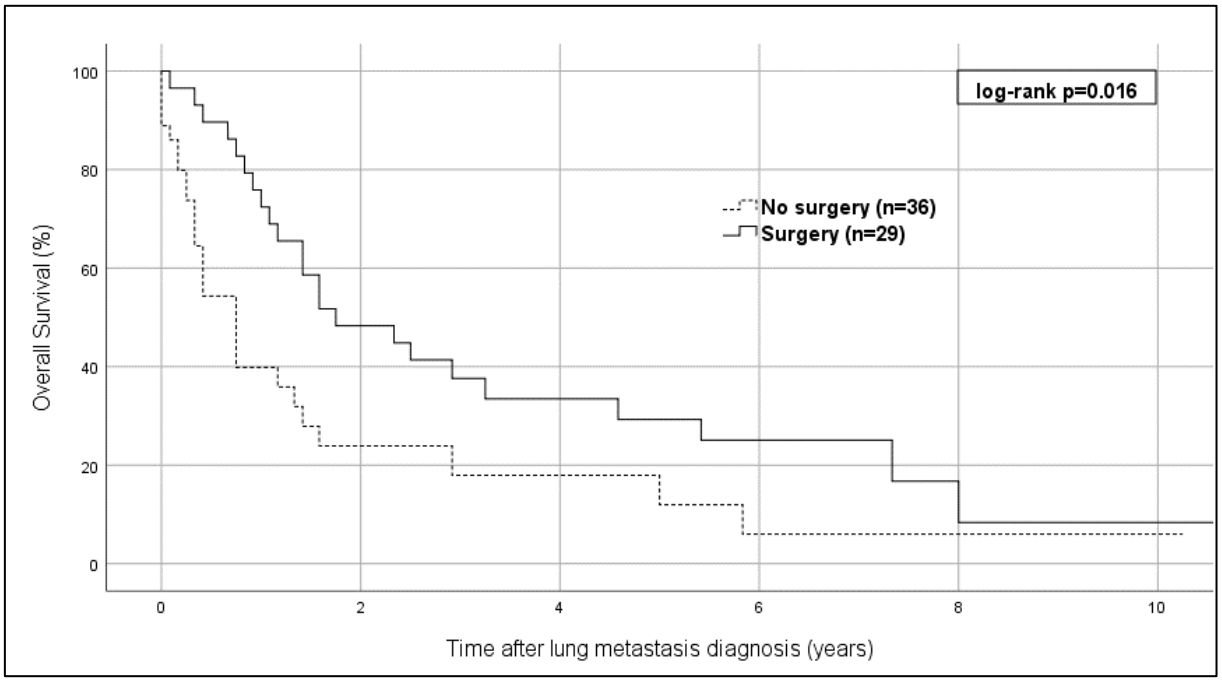

Figure 17 *Kaplan-Meier OS function by surgical treatment group lung metastasis (n=65).*

The 5- and 10-year OS rates of patients with initial lung metastasis were 21.3% and 0.08%. The median OS was 16 months. Increased OS rates in the metastasectomy group were confirmed for patients with initial metastasis to the lung (p=0.016, Log-Rank test). Metastatic excision increased the median OS from 9 months to 21 months, the 5-year OS rates from 12% to 29.3% and the 10-year OS rates from 6% to 8.4% when compared to patients treated non-surgical (**Figure 17**).

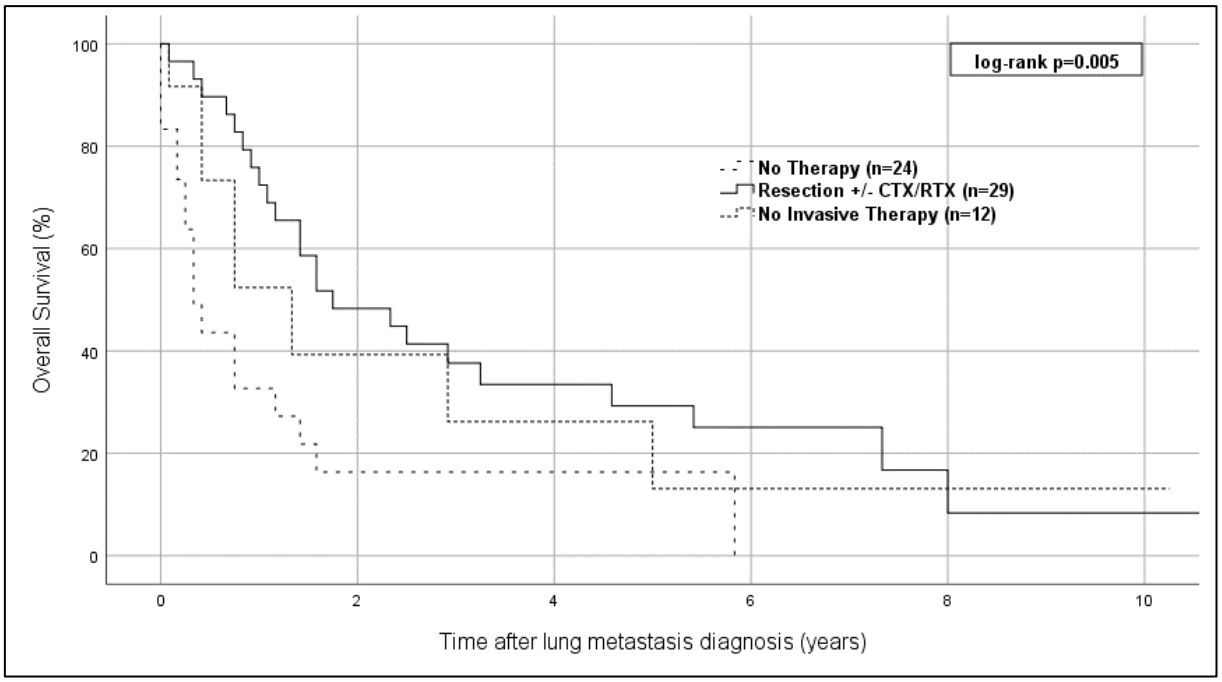

Figure 18 *Kaplan-Meier OS function by treatment group of lung metastasis (n=65).*

Patients without surgical intervention were divided into patients receiving BSC and patients who were administered RTX or CTX. As above, there was still a significant difference between the two different treated groups (p=0.005, Log-Rank test). Metastases treated with RTX or CTX had 5- and 10-year OS rates of 13.1% and 0% – with a median OS of 16 months. BSC attained a median OS of 4 months and 5- and 10-year OS rates of 16.3% and 0% (**Figure 18**).

Gender (p=0.710), singular or multiple pulmonary metastases (p=0.658), and unilateral or bilateral pulmonary metastases (p=0.773) turned out to be without any significant influence on OS according to the Log-Rank test.

Univariate/Multivariate Analysis

Univariate Analysis

The MFI was negatively influenced by no administration of adjuvant RTX (p=0.009). Gender (p=0.206, Wald test), age at surgery of the primary tumour (p=0.572, Wald test), primary tumour site (p=0.710, Wald test), grade (p=0.079, Wald test), primary tumour size (p=0.205, Wald test), resection margins (p=0.254, Wald test) and adjuvant CTX (p=0.949, Wald test) were nonsignificant factors (**Table 13**).

Variables		**All patients**			
n=87		**HR**	**95% CI**		**p-value**
			Lower	**Upper**	
Gender	*Male*	1			0.206
	Female	0.754	0.486	1.169	
Age at Surgery (years)	*≤50*	1			0.572
	>50	1.034	0.684	1.991	
Primary Tumour Site	*Extremity*	1			0.710
	Non-Extremity	1.096	0.675	1.780	
Grade	*1-2*	1			0.079
	3	1.626	0.945	2.799	
Primary Tumour Size (cm)	*≤10*	1			0.205
	>10	1.334	0.854	2.084	
Resection Margins (UICC)	*R1*	1			0.254
	R0	0.676	0.346	1.324	
Adjuvant RTX	*No*	1			**0.009**
	Yes	0.394	0.196	0.795	
Adjuvant CTX	*No*	1			0.949
	Yes	1.020	0.558	1.864	

Table 13 *Univariate Cox-regression analysis of prognostic factors for MFI in patients with advanced STS.*

Variables		All patients			
n=87		HR	95% CI		p-value
			Lower	Upper	
Gender	*Male*	1			0.754
	Female	0.922	0.555	1.533	
Age at metastasis (years)	*≤70*	1			0.182
	>70	1.415	0.850	2.358	
Primary Tumour Site	*Non-Extremity*	1			**<0.005**
	Extremity	0.422	0.240	0.741	
Primary Tumour Size (cm)	*≤10*	1			0.523
	>10	1.183	0.707	1.980	
ECOG-PS	*0–1*	1			**<0.005**
	>1	8.486	3.873	18.591	
Grade	*1–2*	1			0.384
	3	1.315	0.709	2.439	
Any soft tissue ± lymph node metastasis	*Yes*	1			**0.042**
	No	0.519	0.275	0.977	
Any bone metastasis	*No*	1			0.931
	Yes	1.041	0.415	2.613	
Any solid organ metastasis (excluding lung and brain)	*No*	1			0.970
	Yes	1.015	0.460	2.241	
Any brain metastasis	*No*	1			0.165
	Yes	1.697	0.804	3.583	
Any lung metastasis	*No*	1			0.435
	Yes	1.286	0.683	2.422	
MFI (months)	*≤12*	1			0.064
	>12	0.064	0.370	1.029	
Multiple Metastases	*Solitary*	1			0.177
	Multiple	1.416	0.855	2.347	
Surgery Type of Primary Tumour	*Amputation*	1			**0.043**
	Resection	0.406	0.243	0.681	
Haemoglobin (g/dl)	*≤12.5*	1			**0.047**
	>12.5	0.554	0.309	0.992	
Albumin (g/dl)	*≤4*	1			**0.031**
	>4	0.484	0.250	0.937	

Table 14 *Univariate Cox-regression analysis of prognostic factors for OS in patients with advanced STS.*

The OS of patients suffering from metastatic STS was significantly influenced by the primary tumour site ($p<0.005$, Wald test), ECOG-PS ($p<0.005$, Wald test), any metastases of the soft tissue and/or lymph nodes ($p=0.042$, Wald test), surgery type of the primary

tumour (p=0.043, Wald test), albumin level (p=0.031, Wald test), and haemoglobin level (p=0.047, Wald test) (**Table 14**).

Gender (p=0.754, Wald test), patient's age at the occurrence of the first metastasis (p=0.182, Wald test), tumour size (p=0.523, Wald test), grade (p=0.384, Wald test), any bone metastasis (p=0.931, Wald test), any solid organ metastasis (excluding lung and brain) (p=0.970, Wald test), any brain metastasis (p=0.165, Wald test), any lung metastasis (p=0.435, Wald test), MFI (p=0.064, Wald test), and multiple metastasis (p=0.177, Wald test) revealed themselves as nonsignificant factors (**Table 14**).

Variables		**Lung metastases**			
n=61		**HR**	**95% CI**		**p-value**
			Lower	**Upper**	
Gender	*Male*	1			0.204
	Female	0.724	0.44	1.192	
Age at Surgery (years)	*≤50*	1			0.572
	>50	1.167	0.684	1.991	
Primary Tumour Site	*Extremity*	1			0.710
	Non-Extremity	1.096	0.675	1.780	
Grade	*1-2*	1			0.079
	3	1.626	0.945	2.799	
Primary Tumour Size (cm)	*≤10*	1			0.205
	>10	1.334	0.854	2.084	
Resection Margins (UICC)	*R1*	1			0.378
	R0	0.725	0.355	1.483	
Adjuvant RTX	*No*	1			**0.039**
	Yes	0.452	0.213	0.961	
Adjuvant CTX	*No*	1			0.897
	Yes	0.958	0.558	1.844	

Table 15 *Univariate Cox-regression analysis of prognostic factors for MFI in patients with first metastasis to the lung.*

The same univariate analysis was calculated for patients with metastases affecting the lung, the favourite organ of distant metastasis from STSs.

Gender (p=0.204, Wald test), age at surgery of the primary tumour (p=0.572, Wald test), primary tumour site (p=0.710, Wald test), grade (p=0.079, Wald test), primary tumour size (p=0.205, Wald test), resection margins (p=0.378, Wald test), and adjuvant CTX (p=0.897, Wald test) were not associated with an effect on the MFI (**Table 15**).

No administration of adjuvant RTX (p=0.039, Wald test) was a significant factor contributing to the appearance of lung metastases (**Table 15**).

Variables		All patients			
n=61		HR	95% CI		p-value
			Lower	Upper	
Gender	*Male*	1			0.716
	Female	0.900	0.511	1.586	
Age at metastasis (years)	*≤70*	1			**0.016**
	>70	2.047	1.140	3.676	
Primary Tumour Site	*Non-Extremity*	1			**0.043**
	Extremity	0.506	0.262	0.978	
Primary Tumour Size (cm)	*>10*	1			0.798
	≤10	0.928	0.521	1.650	
ECOG-PS	*0–1*	1			**<0.005**
	>1	10.963	4.071	29.525	
Grade	*1–2*	1			0.659
	3	1.164	0.593	2.286	
MFI (months)	*≤12*	1			0.089
	>12	0.606	0.340	1.080	
Multiple Metastases	*Solitary*	1			0.614
	Multiple	1.158	0.654	2.051	
Surgery Type of the Primary Tumour	*Resection*	1			0.095
	Amputation	1.509	0.931	2.446	
Haemoglobin (g/dl)	*≤12.5*	1			0.085
	>12.5	0.556	0.285	0.611	
Albumin (g/dl)	*≤4*	1			**0.027**
	>4	0.427	0.201	0.907	

Table 16 *Univariate Cox-regression analysis of prognostic factors for OS in patients with first metastasis to the lung.*

Variables influencing the OS of patients with lung metastases proved to be age at first lung metastasis (p=0.016, Wald test), primary tumour site (p=0.043, Wald test), ECOG-PS (p<0.005), and albumin level (p=0.027, Wald test) (**Table 16**).

Factors without any impact on OS were gender (p=0.716), tumour size (p=0.798, Wald test), grade (p=0.659, Wald test), MFI (p=0.089, Wald test), multiple metastases (p=0.614, Wald test), surgery type of the primary tumour (p=0.095, Wald test), and haemoglobin level (p=0.085, Wald test) (**Table 16**).

Multivariate Analysis

After analysing each factor on his own, a multivariate analysis was performed. In this analysis, no administration of adjuvant RTX (p=0.009, Wald test) remained a significant factor that influenced the time to metastatic spread (**Table 17**).
Age at surgery (p=0.334), primary tumour site (p=0.478, Wald test), grade (p=0.075, Wald test), primary tumour size (p=0.348, Wald test), resection margins (p=0.087, Wald test), and administration of adjuvant CTX (p=0.966, Wald test) were not associated with any effect on MFI (**Table 17**).

Variables		All patients			
n=87		HR	95% CI		p-value
			Lower	Upper	
Age at Surgery (years)	*>50*	1			0.334
	≤50	0.628	0.244	1.615	
Primary Tumour Site	*Extremity*	1			0.478
	Non-Extremity	1.390	0.560	3.446	
Grade	*1-2*	1			0.075
	3	2.126	0.928	4.871	
Primary Tumour Size (cm)	*≤10*	1			0.348
	>10	1.382	0.703	2.719	
Resection Margins (UICC)	*R1*	1			0.087
	R0	0.495	0.221	1.108	
Adjuvant RTX	*No*	1			**0.009**
	Yes	0.373	0.179	0.781	
Adjuvant CTX	*No*	1			0.966
	Yes	1.019	0.438	2.372	

Table 17 *Multivariate Cox-regression analysis of MFI in patients with advanced STS.*

Surgical resection of metastases (p=0.050, Wald test), a ECOG-PS of 0 or 1 (p=0.046, Wald test), and a primary tumour not arising from the trunk, retroperitoneum, or upper limb (p=0.011, Wald test) affected the OS of patients with advanced STS in multivariate Cox-regression analysis in a positive way whereas age at first metastasis (p=0.115, Wald test), MFI (p=0.106, Wald test), multiple metastases (p=0.566, Wald test), haemoglobin (p=0.873, Wald test), and albumin (p=0.752, Wald test) did not have an influence on OS (**Table 18**).

Variables		All patients			
n=87		HR	95% CI		p-value
			Lower	Upper	
Metastasectomy	*No*	1			**0.050**
	Yes	0.307	0.094	1.000	
Age at metastasis (years)	*≤70*	1			0.115
	>70	2.323	0.841	6.626	
ECOG-PS	*0–1*	1			**0.046**
	>1	3.848	1.022	14.487	
MFI (months)	*>12*	1			0.106
	≤12	0.402	0.133	1.215	
Multiple Metastases	*Solitary*	1			0.566
	Multiple	0.757	0.292	1.960	
Primary Tumour Site	*Extremity*	1			**0.011**
	Non-Extremity	0.259	0.091	0.737	
Haemoglobin (g/dl)	*≤12.5*	1			0.873
	>12.5	0.913	0.300	2.777	
Albumin (g/dl)	*>4*	1			0.752
	≤4	1.214	0.364	4.051	

Table 18 *Multivariate Cox-regression analysis of OS in patients with advanced STS.*

Variables		All patients			
n=61		HR	95% CI		p-value
			Lower	Upper	
Age at Surgery (years)	*>50*	1			0.841
	≤50	0.916	0.389	2.158	
Primary Tumour Site	*Extremity*	1			0.501
	Non-Extremity	1.372	0.546	3.447	
Grade	*1-2*	1			**0.017**
	3	3.426	1.243	9.442	
Primary Tumour Size (cm)	*>10*	1			0.877
	≤10	0.944	0.456	1.957	
Resection Margins (UICC)	*R1*	1			0.097
	R0	0.494	0.215	1.138	
Adjuvant RTX	*No*	1			**0.031**
	Yes	0.435	0.204	0.927	

Table 19 *Multivariate Cox-regression analysis of MFI in patients with first metastasis to the lung.*

Referring to the MFI, G3 tumours (p=0.017, Wald test) and no adjuvant RTX approach (p=0.031, Wald test) were adverse factors (**Table 19**).

Factors with no impact on MFI turned out to be: age at surgery (p=0.841, Wald test), primary tumour site (p=0.501, Wald test), primary tumour size (p=0.877, Wald test) (**Table 19**)

Age at first lung metastasis (p<0.005, Wald test) and a low ECOG-PS score (p<0.005, Wald test) correlated with a better OS in patients with lung metastases (**Table 20**).

Following factors had no influence on OS in multivariate setting: metastasectomy (p=0.339, Wald test), primary tumour site (p=0.989, Wald test), haemoglobin (p=0.236, Wald test), and albumin level (p=0.891, Wald test) (**Table 20)**.

Variables		**All patients**			
n=61		**HR**	**95% CI**		**p-value**
			Lower	**Upper**	
Metastasectomy	*No*	1			0.339
	Yes	0.540	0.153	1.907	
Age at metastasis (years)	*≤70*	1			**<0.005**
	>70	10.335	2.702	39.679	
ECOG-PS	*0–1*	1			**<0.005**
	>1	35.071	3.560	345.479	
Primary Tumour Site	*Non-Extremity*	1			0.989
	Extremity	0.992	0.302	3.257	
Haemoglobin (g/dl)	*≤12.5*	1			0.236
	>12.5	0.417	0.174	1.539	
Albumin (g/dl)	*≤4*	1			0.891
	>4	0.910	0.236	3.509	

Table 20 *Multivariate Cox-regression analysis of OS in patients with first metastasis to the lung.*

12. Discussion

STSs represent a rare group of malignancies with many different histological subtypes. One feature that all STSs have in common is their mesenchymal origin. Leiomyosarcoma, UPS, MPNST and adipocytic sarcomas are frequent representatives of these tumour entities. There are different treatment approaches for each subtype. Referral to specialised centres is highly recommended to grant the best medical treatment and avoid a delay in diagnosis or even worse an unplanned excision. A surgical resection with wide resection margins represents the gold standard in the treatment of patients with non-metastatic tumours, depending on the tumour's anatomical site and extent. The latter may depend again on a quick diagnosis. However, a delay in diagnosis is rather the rule than the exception because of the painless growth of the tumour and a delayed referral from some GPs, who do not suspect a malign process. This delay results in an average time of 4 months from symptoms onset to the final diagnosis and represents one reason why 11.6% of the patients with STS have already developed metastases at the time of diagnosis (i.e. synchronous metastatic disease) [8, 9]. Most metastases, approximately 50%, are from high grade sarcomas [85]. In our cohort, 77% of all metastases developed from poorly histologically differentiated tumours. Metachronous metastatic disease (i.e. after successful treatment of the primary tumour) occurs in approximately 25% of patients with STS. Adverse Prognostic factors for the metastatic recurrence rate are primary tumours being larger than 5cm in size, situated deep to the fascia, being graded G2 or G3, histological subtype (e.g. leiomyosarcoma), and positive microscopic margins [159, 160]. Our study revealed that no administration of adjuvant RTX is an independent adverse factor for the MFI. A randomised prospective study by Yang et al., however, proved that administration of adjuvant RTX decreased the risk of LR but did not improve OS [78]. STSs have the ability of haematogenous dissemination. The lung is their primary metastatic site [44]. Some histological subtypes of STSs can metastasise to the skin, soft tissues, bone, liver, or brain, but, compared to the lung, these organs are much less affected (e.g. leiomyosarcoma commonly spreads to the liver) [161]. The mortality rate of STS depends highly on the occurrence of metastasis, whereas LR plays a minor role in patients' outcome. The rareness and the great variety of STSs complicate the treatment. Most STS patients with advanced disease are incurable. A palliative therapy approach includes careful use of systemic therapy to relieve pain, slow down disease progression, and perhaps prolong survival. However, some patients with metastatic STS have potentially curative options. Metastasectomy is an established treatment approach to improve OS of patients with

STS, as substantiated by non-controlled studies [45, 46, 50, 53, 54, 58]. Selection bias, which may interfere with the results, are unavoidable when using a retrospective study design. Therefore, we used a propensity score matching with the aim of avoiding this source of error. Our study compares the outcomes of patients undergoing a surgical resection of their metastases (e.g. pulmonary metastasectomy) with the outcomes of patients receiving a non-invasive treatment (e.g. BSC ± RTX ± CTX) and aims to quantify possible benefits of a surgical approach.

According to the literature, the median OS of patients with metastatic STS lies between 12 and 19 months, depending on the histologic subtype and the treatment strategies.[44, 162, 163]. In line with these findings, we found in our study population a median OS of 17 months for all patients and 16 months for patients with first metastasis to the lung.
The present study indicates an independently significant association between metastasectomy and beneficial outcome in metastatic STS patients.

Billingsley et al. reported a survival benefit for resection of pulmonary metastasis in a large single-institution series with 719 STS patients [44]. The study demonstrated a 5-year OS of 37% with a median OS of 33 months. In the present study, resection of metastases in STS patients showed equally improved OS rates, respectively. Patients in the metastasectomy group had a 5- and 10-year OS rate of 30.5% and 16.3% whereas non-invasive treated patients (BSC ± CTX ± RTX) had a 5- and 10-year OS rate of 11.6% and 5.8%. The median OS rate of metastasectomy was 28 months versus 6 months in the non-surgical group – a median OS prolongation of almost 2 years for surgically treated patients. The 5- and 10-year OS for patients undergoing pulmonary metastasectomy increased from 12% to 29.3% and from 6% to 8.4% when compared to STS patients who did not undergo surgery for lung metastases. The median OS rate was 9 months for patients treated conservative (BSC ± CTX ± RTX) versus 21 months in the surgery group.

Furthermore, we identified low serum albumin and haemoglobin, primary tumour site other than the extremities, an age over 70 years at diagnosis of metastasis, and a high ECOG-PS score as adverse prognostic factors in our cohort.

Patients with low serum albumin levels showed an independent association with decreased survival in several cancers. In STS, Barreto-Andrade et al. observed in 61 patients that a low albumin level is an independent prognostic factor for poor survival [164]. Additionally, a study by Iqbal et al. demonstrated in metastatic STS that low albumin levels

correlate with decreased survival [158]. Similarly, our study confirmed that serum albumin is a negative prognosticator of survival in patients with metastatic STS in univariate setting.

In a study by Szkandera et al., low pre-operative haemoglobin levels were significantly associated with poor survival in STS patients [165]. Additionally, a study by Iqbal et al. observed a correlation between low haemoglobin levels and a decreased survival in STS patients suffering from metastatic disease. In context with these studies, we demonstrated the negatively influence of a low haemoglobin level on outcome as well. On multivariate analysis, however, neither albumin nor haemoglobin level proved to be significant prognostic factors.

We identified that STS patients with a low score in the ECOG-PS showed an independent association with an increased OS. Similarly, a study of 2185 metastatic STS patients published by Van Glabbeke et al. reported that a better performance status of patients with an advanced disease significantly correlated with an improved OS [163].

In context with the previously published study, patient's age was an independent prognostic factor for OS. In our study, an age over 70 years at diagnostic of metastasis was an adverse prognostic factor in uni- and multivariate analysis for patients with first metastasis to the lung.

The primary tumour site is a well-recognised independent prognostic factor for OS in STS patients [166]. In the current study, primary tumour site independently predicted OS. For patients suffering from pulmonary metastasis, however, the primary tumour site was not significantly related to OS in multivariate analysis.

Any metastases of the soft tissue and/or lymph nodes and resection of the primary tumour in comparison to amputation were also significant, favourable factors for OS in the univariate setting. However, both were not considered for multivariate analysis due to the rareness of extrapulmonary metastases and the low number of patients who received amputation (n=6 out of 87).

As with all retrospective study designs, our cohort is not without limitations. First, the low number of patients for this study must be mentioned. Although we used the IPTW analysis to reduce selection bias, it is not comparable to a randomized trial. Further limitations are the heterogeneity of STSs, the aggressive behaviour, and the variation in the response to treatment. Moreover, the surgical and systemic treatment improved over the years, resulting in different therapy approaches for patients with a similar diagnosis. Furthermore, although we used the ECOG-PS, the study does not include all factors interfering with the target variable (i.e. OS) such as comorbidities. Finally, wrong defined, independent variables (e.g.

characteristics should effect the aim of the study and not the treatment allocation) may influence the propensity score-matching and consequently the IPTW analysis.

Conclusion

STSs are rare solid tumours with the ability to raise in any part of the body. If the main target is cure, a complete resection of the primary tumour is a crucial aspect of the treatment. Nevertheless, about 10% of the patients present with synchronous metastasis, and in some cases, a complete resection of the primary tumour is not feasible [167]. Furthermore, approximately 25% of patients develop distant metastases after proper treatment of the primary tumour. The number increases up to 40–50% for tumours larger than 5cm, situated deep to the fascia, and a G2 or G3 differentiation [159, 160]. In our time-to-event analysis the application of adjuvant RTX significantly extended the disease-free interval (HR=0.373). Altogether, about one-third of the patients with STS is suffering from advanced disease (e.g. lung metastasis) [167]. As mentioned above, there are lots of observational studies supporting the hypothesis that surgical intervention is a beneficial treatment approach to prolong the survival of patients with metastatic STS. Long-term relapse-free survival can be achieved by surgical resection of metastases, although there are strict criteria. For example, metastasectomy is recommended for isolated pulmonary metastasis whenever resection free margins are feasible. However, guidelines for synchronous pulmonary metastasis with multiple or bilateral lung metastases are not as straightforward and hand over the final treatment decision to a multidisciplinary team assessment [43].

This retrospective study of metastatic STSs compared the effectiveness of metastasectomy regarding OS and supports the findings of previous non-controlled observational studies. In our cohort, patients with metastasectomy had a significantly improved OS in comparison to patients treated with BSC/RTX/CTX. Most of the previous non-controlled studies have not taken favourable clinical features of patients among the surgery group into account. Therefore, it might be possible that selection bias skews the positive effects of metastasectomy. In this study, the significant difference between the OS of a surgical and non-surgical approach remained even after recalculating the analysis with balanced adverse factors for all patients. Therefore, the results underline the benefit of metastasectomy among patients with advanced STS matching the inclusion criteria. These results should help clinicians in the process of treatment decision-making for patients with metastatic STS.

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