Thesis

Local recurrence in soft tissue sarcoma. Frequency and prognostic relevance of “upgrading”

-

a retrospective study

submitted by

Bernd Manuel Golja

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under the supervision of

Univ. FÄ Priv.-Doz. Dr.med.univ. Dr.scient.med Maria Anna Smolle

Univ.-Prof. Dr.med.univ. Andreas Leithner

Thames, 16. November 2025

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Thames, 16. November 2025 Bernd Manuel Golja, m.p.

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Zusammenfassung in Deutsch

Einleitung

Weichteilsarkome (STS) sind hochmaligne und relativ selten, mit einer Inzidenz von nur 3–5 Patient:innen pro 100.000 Einwohner:innen pro Jahr. Da STS nur mäßig chemosensibel sind, besteht die primäre Therapie in einer weiten En-bloc-Resektion unter Einhaltung eines adäquaten Sicherheitsabstands. Die lokale Therapie kann durch eine prä- und/oder postoperative Strahlentherapie ergänzt werden. Diese Kombination reduziert das Risiko lokaler Rezidive (LR) signifikant. Dennoch erleiden etwa 10% der Patient:innen ein LR, und etwa 30% entwickeln Fernmetastasen (FM). Sowohl der Primärtumor als auch das Rezidiv werden gemäß dem FNCLCC-System graduiert, welches den Malignitätsgrad des STS angibt. Ziel dieser Studie ist es, die Häufigkeit sowie die prognostische Relevanz eines Upgradings zu evaluieren, indem Primärtumor und Rezidiv verglichen werden.

Patient:innen und Methoden

Zwischen 1998 und 2016 wurden 504 Patienten mit primär lokalisiertem STS, die in der Abteilung für Orthopädie und Traumatologie der Medizinischen Universität Graz operativ behandelt wurden, retrospektiv auf die Entwicklung von LR, FM oder beidem untersucht. Von diesen wurden 143 Patienten mit einem Rezidiv (entweder lokal oder fern) während des Follow-ups, d. h. zwischen 1998 und bis 2022, eingeschlossen. Die Kohorte bestand aus 78 Männern (54,6%) und 65 Frauen (45,5%) im Alter von 10 bis 99 Jahren. Untersucht wurden die Häufigkeit eines Upgradings im Rezidiv im Vergleich zum Primärtumor sowie dessen Einfluss auf die Prognose mithilfe von deskriptiver Statistik sowie univariater Cox-Regressions-Analyse und Kaplan-Meier-Analyse. Die Datenerhebung erfolgte über Medocs. Für die Datenauswertung wurden Microsoft Excel (Version 2506), IBM SPSS Statistics (Version 30.0.0) und Stata (StataCorp Version 16.1 für Mac) verwendet.

Ergebnisse

Bei 84 von 143 Patient:innen lagen Daten zum Grading der LR und FM vor. Die häufigsten histologischen Subtypen waren Myxofibrosarkom (31%), undifferenziertes pleomorphes Sarkom (17,9%) und Leiomyosarkom (13,1%). Unter diesen 84 Patienten entwickelten 45 (53,6%) ein LR, 63 (75%) ein FM und

24 (28,6%) sowohl FM als auch LR. Im Hinblick auf Grading-Veränderungen im Rezidiv zeigten 10 Patienten (11,9 %) mindestens ein Upgrading, während bei 4 Patienten (4,8 %) ein Downgrading beobachtet wurde.
Statistische Tests ergaben keinen signifikanten Unterschied im Post-Rezidiv-Überleben zwischen den Gruppen (p = 0,856).

Schlussfolgerung

Zusammenfassend zeigte sich bei begrenzter statistischer Aussagekraft kein Hinweis darauf, dass ein histologisches Upgrading bei rezidivierenden STS mit einer schlechteren Prognose einhergeht. Zukünftige Studien mit größeren Patient:innenkollektiven sind notwendig, um verlässlichere Aussagen treffen zu können.

Abstract in english

Introduction

Soft tissue sarcomas (STS) are highly malignant and relatively rare with an incidence of only 3–5 patients per 100,000 patients per year. Because STS are just moderately chemosensitive, the primary treatment of STS consists of a wide resection (en bloc) therefore minding a reasonable safety margin. Local therapy may be accompanied by pre- and/or postoperative radiation therapy. This combination reduces the risk of local recurrences (LR) significantly. Nonetheless, 10% of the patients suffer from local recurrences and about 30% develop a distant metastasis (DM). The primary tumor as well as the LR are graded using the FNCLCC-system, which indicates the grade of malignancy of STS. The aim of this study is to evaluate the frequency and the prognostic relevance of upgrading by comparing the primary tumor and the recurrence (LR, DM).

Patients and Methods

Between 1998 and 2016, 504 patients with primary localized STS surgically treated at the *Department of Orthopaedics and Trauma, Medical University of Graz* were retrospectively screened for development of LR, DM or both. Of these, 143 patients with a recurrence (either local or distant) during follow-up, i.e. between 1998 and up to 2022 were included.

The patient collective consists of 78 men (54.6%) and 65 women (45.5%) ranging from the age 10 to 99. The frequency of upgrading in recurrences compared to the primary tumor and its influence on the prognosis will be statistically analyzed using descriptive statistics and univariate Cox-Regression analysis and Kaplan-Meier-Curve. All the data has been collected via Medocs. Data collection and statistical analyses were conducted using Microsoft Excel for Windows (version 2506), IBM SPSS Statistics (version 30.0.0) and Stata (StataCorp Version 16.1 for Mac).

Results

For 84 out of 143 patients (58.7%), data on grading of LR and DM were available. The most frequent histological subtypes were myxofibrosarcoma (31%), undifferentiated pleomorphic sarcoma (17.9%), and leiomyosarcoma (13.1%). Among these 84 patients, 45 (53.6%) developed LR, 63 (75%) developed DM while 24 (28.6%) developed both DM and LR. In terms of grading changes at

recurrence, 10 patients (11.9%) showed at least one instance of upgrading, while 4 patients (4.8%) had one instance of downgrading
Statistical tests revealed no significant difference in post-recurrence survival rate between groups ($p = 0.856$).

Conclusions

In conclusion, while the statistical evidence was limited, the study did not reveal a trend suggesting that histological upgrading in recurrent STS is associated with worse outcomes. Further studies with larger patient cohorts are necessary to draw more reliable conclusions.

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Abbreviations and explanations

AJCC	American Joint Committee on Cancer
AS	Angiosarcoma
CT	Computed tomography
CTX	Chemotherapy
DDLPS	Dedifferentiated liposarcoma
DM	Distant metastasis
ES	Epitheloid sarcoma
FDG	Fluorodeoxyglucose
FNCLCC	Fédération Nationale des Centres de Lutte Contre Le Cancer
FS	Fibrosarcoma
HPF	High-powered field
ILP	Isolated hyperthermic limb perfusion
IQR	Interquartile range
LMS	Leiomyosarcoma
LPS	Liposarcoma
LR	Local recurrence
MFS	Myxofibrosarcoma
MLPS	Myxoid liposarcoma
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnet resonance imaging
NCI	National Cancer Institute
NOS	Not otherwise specified
OS	Overall survival
PET-CT	Positron emission tomography-computed tomography
PLPS	Pleomorphic liposarcoma
RMS	Rhabdomyosarcoma
RTX	Radiotherapy

SS	Synovial sarcoma
STS	Soft tissue sarcoma
SUV	Standardized uptake value
TNFα	Tumor necrosis factor-alpha
TNM	Tumor, node, metastasis
UPS	Undifferentiated pleomorphic sarcoma
US	Ultrasonography
WDLPS	Well differentiated liposarcoma

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1 Introduction

Sarcomas can be roughly divided into bone sarcomas (e.g. osteosarcoma, chondrosarcoma and Ewing sarcoma) and soft tissue sarcomas (STS)(1). STS are a rare and heterogeneous group of malignant neoplasms derived from mesenchymal cells, comprising approximately 1% of all malignancies diagnosed every year. They originate from mesodermal tissues and can develop in various organs and connective tissues throughout the body(2). The incidence of STS in Austria is 4.2 per 100.000 patients per year(3). Notably, malignant neoplasms are outnumbered by benign soft tissue tumors(4,5). STS have the potential to manifest in any part of the body, with the highest prevalence observed in the extremities (59%), followed by the trunk (19%), the retroperitoneum (15%), and the head and neck region (9%)(6).

The exact etiology of most cases remains unclear, although specific genetic factors may play a role. For example, individuals with neurofibromatosis type I (Mb. Recklinghausen), caused by mutations in the NF1 gene, have a 10% lifetime risk to develop malignant peripheral nerve sheath tumors (MPNST)(7). Likewise, those with a family history of retinoblastoma, associated with RB gene mutations, have a higher chance of developing bone sarcomas as well as STS. Additionally, families with Li-Fraumeni syndrome, characterized by mutations in the TP53 tumor suppressor gene, also exhibit an increased vulnerability to sarcomas and other malignancies(8).

1.1 Tumor entities

According to "*The 2020 WHO Classification of Soft Tissue Tumours",* benign and malignant soft tissue tumours are divided into more than 70 subtypes (Table 1), each distinguished by unique characteristics that influence their clinical behavior and treatment strategies. Additionally, many of these subtypes are extremely rare (9). Unsurprisingly, a pathologist outside of a high-volume center may never diagnose one of them in a lifetime. Obtaining specialized expertise in diagnosis and treatment of STS (and bone sarcoma as well) is thus always recommended, not only for pathologists, but for any physician involved, including orthopedic surgeons, radiologists, oncologists, and radiotherapists(10). Sarcoma oncology is a fast-evolving medical field, continuously revealing new histological subtypes and

individual treatments. In 2013, for example, only 50 histological subtypes were distinguished, which is roughly 20 subtypes less than nowadays(11).

Table 1: The 2020 WHO classification of soft tissue tumours with a list of major entities under each category. Adapted from Bansal et al. (12).

CATEGORY	BENIGN	LOCALLY AGGRESSIVE	RARELY METASTASISING	MALIGNANT
ADIPOCYTIC	Lipoma	Atypical Lipomatous Tumour		Liposarcoma
	Lipomatosis			Well-differentiated
	Lipoblastoma			Dedifferentiated
	Angiolipoma			Myxoid
	Myolipoma			Pleomorphic
	Chondroid Lipoma			Myxoid pleomorphic
	Spindle Cell Lipoma			
	Atypical Spindle Cell/Pleomorphic Lipomatous Tumour			
	Hibernoma			
FIBROBLASTIC AND MYOFIBROBLASTIC	Nodular Fasciitis	Solitary Fibrous Tumour	Dermatofibrosarcoma Protuberans	Solitary Fibrous Tumour, malignant
	Proliferative Fasciitis	Fibromatosis	Solitary Fibrous Tumour	Fibrosarcoma
	Proliferative Myositis	Palmar/Plantar	Inflammatory Myofibroblastic Tumour	Myxofibrosarcoma
	Elastofibroma	Desmoid Type	Myofibroblastic Sarcoma	Low-grade fibromyxoid sarcoma
	Fibrous Hamartoma of Infancy	Lipofibromatosis	Superficial Cd34 Positive Fibroblastic Tumour	Sclerosing epitheloid fibrosarcoma
	Fibroma of Tendon Sheath	Giant Cell Fibroblastoma	Myxoinflammatory Fibroblastic Sarcoma	

	Desmoplastic Fibroblastoma		Infantile Fibrosarcoma	
	Myofibroblastoma			
	Calcifying Aponeurotic Fibroma			
	Ewsr1- Smad3 Positive Fibroblastic Tumour			
	Angiomyofibroblastoma			
	Cellular Angiofibroma			
	Angiofibroma Of Soft Tissue			
	Nuchal Fibroma			
	Acral Fibromyxoma			
	Gardner Fibroma			
SO-CALLED FIBROHISTIOCYTIC TUMOURS	Tenosynovial Giant Cell Tumour	Plexiform Fibrohistiocytic Tumour		Malignant Tenosynovial Giant Cell Tumour
	Deep Benign Fibrous Histiocytoma	Giant Cell Tumour Of Soft Parts		
VASCULAR TUMOURS	Hemangioma	Kaposiform Hemangioendothelioma	Retiform Hemangioendothelioma	Epithelioid Hemangioendothelioma
	Epithelioid Hemangioma		Papillary Intralymphatic Angioendotheliom a	Epitheloid Hemangioendothelioma
	Acquired Tufted Hemangioma		Composite Hemangioendothelioma	With Yap1- Tfe3 Fusion
			Kaposi Sarcoma	Angiosarcoma

			Pseudomyxogenic Hemangioendothelioma	
PERICYTIC TUMOURS	Glomus Tumour			Malignant Glomus Tumour
	Myopericytoma			
	Angioleiomyoma			
SMOOTH MUSCLE TUMOURS	Leiomyoma	Smooth Muscle Tumour Of Uncertain Malignant Potential		Leiomyosarcoma
				Inflammatory Leiomyosarcoma
SKELETAL MUSCLE TUMOURS	Rhabdomyoma			Rhabdomyosarcoma
				Embryonal
				Alveolar
				Pleomorphic
				Spindle Cell
				Ectomesenchymoma
GASTROINTESTINAL STROMAL TUMOUR				
CHONDRO-OSSEOUS TUMOURS	Chondroma			Extraskeletal Osteosarcoma
PERIPHERAL NERVE SHEATH TUMOURS	Schwannoma			Malignant Peripheral Sheath Tumour
	Neurofibroma			Melanotic Malignant Nerve Sheath Tumour
	Plexiform Neurofibroma			Malignant Granular Cell Tumour
	Perineurioma			Malignant Perineurioma
	Granular Cell Tumour			
	Nerve Sheath Myxoma			

	Solitary Circumscribed Neuroma			
	Meningioma			
	Hybrid Nerve Sheath Tumour			
TUMOURS OF UNCERTAIN DIFFERENTIATION	Myxoma	Epithelioid Angiomyolipoma	Atypical Fibroxanthoma	Ntrk Rearranged Spindle Cell Neoplasm
	Aggressive Angiomyxoma	Hemosiderotic Fibrolipomatous Tumour	Angiomatoid Fibrous Histiocytoma	Synovial Sarcoma
	Pleomorphic Hyalinizing Angiectatic Tumour		Ossifying Fibromyxoid Tumour	Epithelioid Sarcoma
	Phosphaturic Mesenchymal Tumour		Myoepithelioma	Alveolar Soft Part Sarcoma
	Perivascular Epitheloid Tumour			Clear Cell Sarcoma
	Angiomyolipoma			Extraskeletal Myxoid Chondrosarcoma
				Desmoplastic Small Round Cell Tumour
				Rhabdoid Tumour
				Malignant Perivascular Epithelioid Tumour
				Intimal Sarcoma
				Malignant Ossifying Fibromyxoid Tumour
				Undifferentiated Sarcoma

				Undifferentiated Spindle Cell Sarcoma
				Undifferentiated Pleomorphic Sarcoma
Undifferentiated small Round Cell Sarcoma of bone and soft tissues				Ewing's Sarcoma
				Round cell sarcoma with EWSR1-non ETS fusion
				CIC rearranged sarcomas
				Sarcoma with BCOR genetic alterations

1.1.1 Epitheloid sarcoma (ES)

Epithelioid sarcomas (ES) are very rare, accounting for less than 1% of STS(13). They tend to affect males more frequently, with a male to female ratio of 2:1. The majority of documented tumors are found in adolescent and adult males, often between the age of 10 and 45 years(14). ES typically manifest as slow-growing, painless swellings in the distal upper extremity, which in some cases may also lead to ulceration. ES can be located in the dermis, subcutis, or deep to the muscular fascia. They typically infiltrate through fascial planes and follow the path of tendons and aponeuroses. The proximally located subtype of the ES is typically found in the perineal, pubic, genital, and truncal region. Of note, the classification of ES is based on its histological characteristics rather than its specific location(15).

ES are malignant lesions that exhibit histopathological features of both mesenchymal and epithelial origin. Approximately 90 % of ES display a lack of integrase interactor-1 (INI-1) expression. INI-1 is a component of the SWI/SNF chromatin remodeling complex that occurs in all normal cells. This complex plays a crucial role in biological processes by modifying nucleosomes for DNA transcription(15). Under the microscope, typical ES display a nodular or lobular structure with central regions of necrosis (16).

The prognosis of ES is primarily linked to factors such as tumor size, vascular invasion, resectability, and metastases at presentation (14). Ten years after the first diagnosis, 80% of patients will have developed a local recurrence (LR), while around 40% of patients will be diagnosed with distant metastases (DM) that are often followed by multiple LR. Under these circumstances, the prognosis is rather poor(17).

1.1.2 Leiomyosarcoma (LMS)

Leiomyosarcomas (LMS) derive from smooth muscle cells. They account for 15%-20% of all STS. LMS can develop in any location, preferably in regions where smooth muscle is physiologically present, including blood vessels and the uterus. Roughly 35% of tumors are located in the retroperitoneum or intra-abdominal region, and 30% of LMS are found in the uterus(18). Tumors in the extremities account for 19% of cases, and those in the trunk for approximately 16%(18). Women are more commonly affected in retroperitoneal and pelvic areas (due to uterine LMS), whilst for other body regions, no gender difference is present. Most patients experience a lumpy mass or swelling that grows with time, accompanied by dull pain in the affected area(19). However, pain is an overall unreliable parameter to distinguish between benign or malignant mesenchymal neoplasms(20). Under the microscope, LMS display a unique pattern, characterized by spindle cells intersecting at approximately 90° angles. Large tumors may contain hypocellular, hyalinized, and necrotic areas(21). Regarding prognosis, it is important to take into account various factors like the location and size of the tumor as well as mitotic rate, tumor depth, necrosis and vascular invasion(22). For instance, retroperitoneal LMS typically have a poor prognosis as resections with clear surgical margins are usually not achievable, often resulting in later metastatic spread, and an overall poor 5-year survival rate of 30%. LMS of vascular origin have the most unfavorable prognosis, with 50% of patients showing metastases at the time of diagnosis(23,24). The prognosis of LMS in extremities is usually better, depending on the infiltration of blood vessels(25).

1.1.3 Liposarcoma (LPS)

Liposarcomas (LPS) are malignant tumors that originate from adipose tissue. They are frequent STS subtypes and account for 15% to 20% of all STS cases. LPS are

categorized into four main subtypes: well-differentiated liposarcoma (often referred to as atypical lipomatous tumor (Figure 1),
nowadays considered an intermediate variant), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma, and pleomorphic liposarcoma(26). The tumor's resectability determines the prognosis; tumors in the retroperitoneum have the poorest outcome. Metastases are observed in 15-20% of dedifferentiated LPS, whereas LR occurs in around 40%(27).

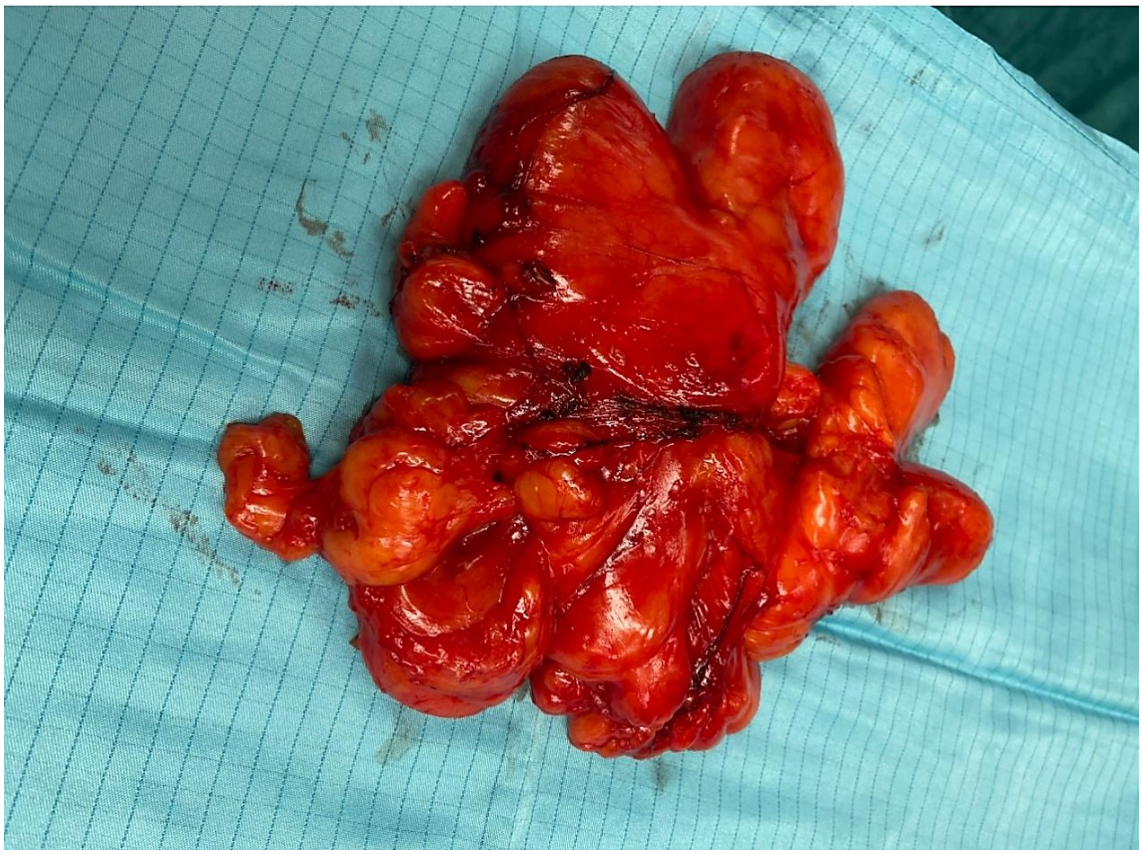

Figure 1: Atypical lipomatous tumor – an intermediate variant of a lipomatous tumour with high local recurrence rates, but nearly no potential for distant spread. Surgical treatment usually consists of marginal resection (as depicted).

1.1.4 Well differentiated liposarcoma (WDLPS) and dedifferentiated liposarcoma (DDLPS)

In case complete excision can be achieved, WDLPS / at the extremities atypical lipomatous tumors (ALT) have no metastatic potential and are associated with an excellent outcome. Nevertheless, LR and the tendency for dedifferentiation is more frequent if WDLPS develop in the retroperitoneum, mediastinum, or the paratesticular region(28). It is believed that the higher occurrence of DDLPS in deep and retroperitoneal locations is due to the delayed diagnosis owing to lack of

noticeable symptoms. During this time delay, there is a possibility for WDLPS to undergo dedifferentiation. Nonetheless, the majority of DDLPS develop spontaneously. Dedifferentiated tumors lead to more complications and a reduced overall survival (26,28).

1.1.5 Myxoid liposarcomas (MLPS)

Myxoid liposarcomas (MLPS) commonly manifest as slow-growing tumors in the lower extremities. The average age at diagnosis is 48 years, with a slight male predominance(29). Although the most prevalent location is the lower extremities, these tumors have the potential to develop in any extremity, the neck, intrathoracic areas or in the retroperitoneum. As with other STS, MLPS are also usually painless. Because of the absence of symptoms, these tumors are typically relatively large upon diagnosis(29). Under the microscope, MLPS have a myxoid stroma background with varying amounts of immature lipoblasts and very small round-to-oval, non-adipocytic mesenchymal tumor cells(26). Other than most STS subtypes, MLPS tend to metastasize to rare locations, wherefore routine follow-ups with whole body magnetic resonance imaging (MRI) are recommended(30).

1.1.6 Pleomorphic liposarcoma (PLPS)

Pleomorphic liposarcoma (PLPS) is an uncommon subtype of LPS that is clinically aggressive. PLPS typically occur in the limbs or, less frequently, in the trunk or retroperitoneum. Histologically, it presents as a high-grade undifferentiated sarcoma with no identifiable lineage and contains a varying amount of pleomorphic lipoblasts(26). Metastases occur in a high number of patients, usually in the lungs. PLPS show poor response to chemotherapy (CTX) and radiotherapy (RTX). Mortality rate is high at about 50%(26).

1.1.7 Malignant peripheral nerve sheath tumor (MPNST)

MPNST accounts for up to 5-10% of all STS and derives from Schwann cells(31). The benign counterparts are schwannomas that are usually treated by marginal resection (Figure 2, Figure 3). MPNST grow in an infiltratively way, aggressively and often metastasize. As most STS subtypes, MPNST are rare, except in patients with NF type 1. In these patients, the lifetime risk for MPNST exceeds 10%. Conversely, about 50% of patients with MPNST have NF type 1. About 10-

20% of MPNST are diagnosed in children(32). Unfortunately, the risk for LR and/or metastases is high (40-50%) and the prognosis is poor, due to the aggressive behavior of the tumor(31). Despite radiological findings sometimes suggesting the presence of MPNST, a histologic examination (as for any STS) is required for proper diagnosis. Identifying a clear source from either a peripheral nerve or a neurofibroma can assist in reaching a diagnosis(32). It is also important to observe certain histological features, such as the presence of fascicles with alternating, marble-like cellularity, palisade/rosette-like arrangements, and an asymmetric pattern(32). Presence of necrosis and numerous mitotic figures determines whether the MPNST is classified as high- or low-grade(32). Factors contributing to a worse prognosis include the presence of a NF 1 mutation, a larger tumor size, deep location relative to the fascia, higher grade of malignancy, presence of metastases at initial diagnosis, and the tumor's location in the trunk or head and neck. Ensuring the complete resection of the tumor with wide surgical margins is crucial to improve prognosis of MPNST patients, along with the appropriate use of additional treatments (CTX, RTX), as needed(33).

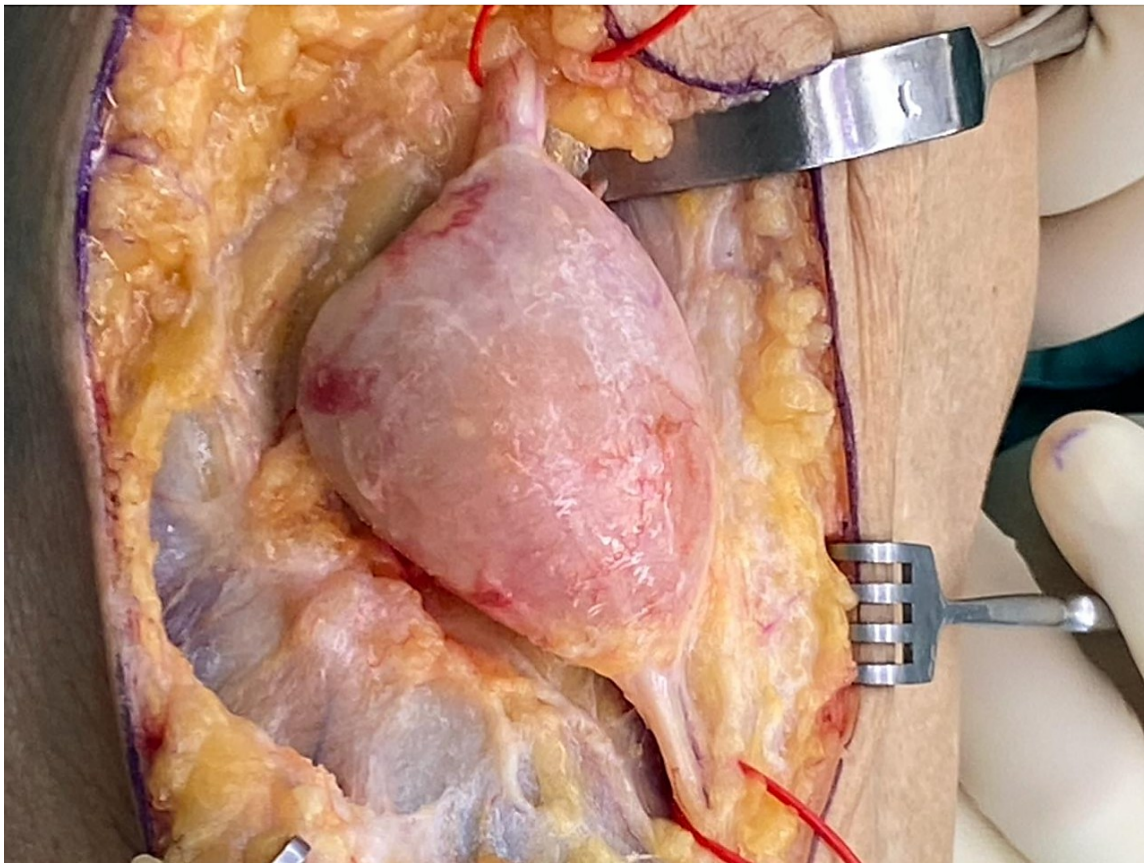

Figure 2: Intraoperative image of a schwannoma deriving from the peroneal nerve, which is a benign peripheral nerve sheath tumor (PNST).

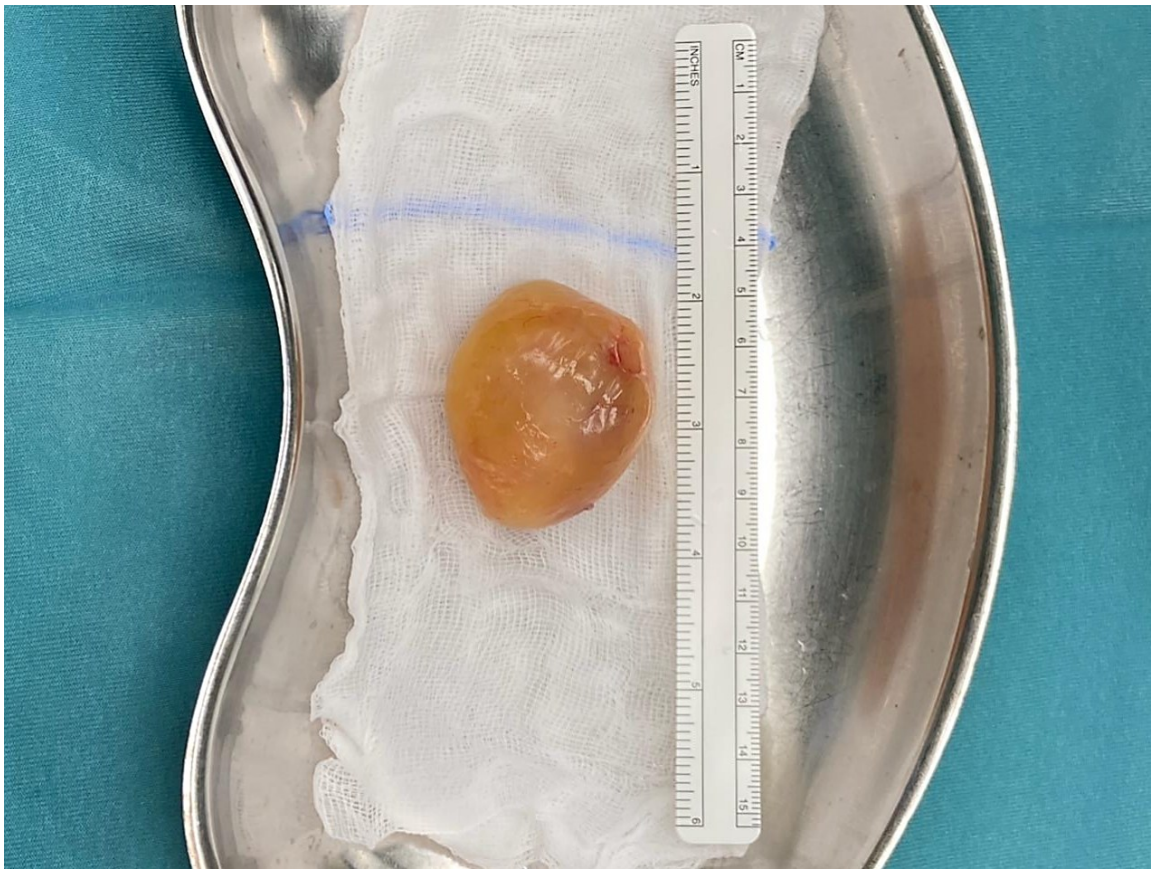

Figure 3: Schwannoma with a diameter of 2 cm following marginal resection.

1.1.8 Fibrosarcoma (FS)

Adult fibrosarcoma (FS) commonly develops from the connective tissues of the body, such as fascia and tendons. Adult FS is typically diagnosed in individuals who are middle-aged or older, and are rarely seen in children. Unlike the infantile type, adult FS is classified as a highly malignant tumor, with a tendency to metastasize(34). There is a slight predominance of male patients. The most common areas affected are the deep soft tissues of the extremities, trunk, head, and neck(35). In case the tumor infiltrates the surrounding tissue and/or organs, symptoms may occur(34). Typically, adult FS is diagnosed through a process of elimination. Histopathologically, it is defined by spindle cells with fusiform oval nuclei, lance-shaped tapering cells, and unipolar or bipolar cytoplasm(35). The "herringbone" pattern is pathognomonic. Adult FS usually displays mild to moderate pleomorphism, which is considered within the normal range. However, it is important to note that a high level of mitotic activity leads to the classification of an undifferentiated pleomorphic sarcoma(35). The majority of adult FS are classified as grade 2 or 3. These tumors have a high level of aggressiveness,

often leading to LR and the invasion of cancer cells to nearby lymph nodes and other organs. Adult FS is associated with a poor prognosis, with a survival rate of < 70% at 2, and < 55% at 5 years(35).

1.1.9 Myxofibrosarcoma (MFS)

Myxofibrosarcoma (MFS) is a frequently encountered STS subtype that typically occurs in the lower extremities of older individuals but can also be seen in the upper extremities. However, cases involving the trunk, head and neck, hands, and feet are uncommon. In addition, it is very rare that MFS develop in the retroperitoneum and abdominal cavity. This histological subtype usually appears as a lump that expands slowly and does not cause pain. It is more common in adults between 50 and 70 years and tends to affect males slightly more often. MFS has the highest LR rate of all STS, with a rate of 20% to 60% after five years(36). The current treatment choice consists of a wide resection with histologically confirmed clear surgical margins, combined with neoadjuvant or adjuvant RTX and/or CTX. Under the microscope, MFS typically show myxoid stroma, pleomorphic cells and curvilinear vessels, as well as multinodular growth and fibrous septa(36,37). Based on available data, it is estimated that around 20% to 25% of cases may develop DM(36,38). The 5-year recurrence-free survival rate of patients with MFS is 70-80%, and the overall survival about 60%. Nevertheless, the prognosis worsens with increased age and larger tumor size(38).

1.1.10 Angiosarcoma (AS)

Angiosarcoma (AS) is a rare type of STS, accounting for only 1% of STS(39). These tumors originate from lymphatic or vascular endothelial cells and are generally classified as 'high-grade'. AS can manifest in various areas of the body. Particularly aggressive forms constitute those secondary to irradiation, specifically following RTX for breast cancer(40). Treating this condition can be quite difficult, and unfortunately, the prognosis is poor, particularly in case an AS is detected at an advanced stage. Metastases are predominantly found in the lungs and brain(39,41). The 5-year survival rate for patients diagnosed with AS ranges from 30% to 40%(39). Twenty to 40% of patients experience a LR or metastasis(41). Similar to other STS cases, surgical resection with a tumor-free margin offers the most successful oncological outcomes(39). The histopathology of AS is

characterized by multiple irregular vascular channels that are lined by endothelial cells. In case of poorly differentiated AS, one may observe spindle-shaped, polygonal, epithelioid, and primitive round cells with increased mitotic activity and poorly formed vascular spaces(39). Notably, identifying AS can be quite challenging due to the diverse cytoarchitectural features found in poorly differentiated tumors(41).

1.1.11 Rhabdomyosarcoma (RMS)

Rhabdomyosarcoma (RMS) is a type of pediatric malignant STS deriving from skeletal muscle. The majority of cases is diagnosed in children who are younger than 6 years of age. The estimated annual incidence ranges between 4 and 7 cases per a million children aged 15 or younger(42). Similarly to other STS subtypes, the etiology contributing to this condition is still largely unknown. The vast majority of RMS cases occur spontaneously, although there is a connection to certain inherited syndromes such as NF type 1, Noonan syndrome, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Costello syndrome(43). The four different types of RMS are embryonal, alveolar, pleomorphic, and spindle/sclerosing RMS, with decreasing frequency. Head and neck involvement is more common in children and young adolescents, typically of the embryonal type(44). Extremity RMS tend to be more prevalent among adolescents, usually presenting as the alveolar type.

Histologically, the cells exhibit an eccentric eosinophilic granular cytoplasm, containing plenty thick and thin filaments, and can have a variable shape, either round or elongated(44). They are also known as strap cells or tadpole cells, depending on their appearance(44). When examining patients with metastatic disease from different protocols in Europe and America, certain factors emerged as important indicators of prognosis; these include age (> 10 years is worse), the location of the primary tumor, number of metastatic sites, and the extent of tumor involvement(45). Localized disease in children with RMS can often be effectively treated through multimodal therapy, resulting in a survival rate of > 70% at five years post-diagnosis. Unfortunately, around 15% of patients diagnosed with RMS have metastases at time of diagnosis, and thus a poor prognosis(46).

1.1.12 Synovial sarcoma (SS)

Synovial Sarcoma (SS) is thought to originate from primitive mesenchymal cells and has a pathognomonic translocation of the t(X;18) chromosome. Therefore, its development is driven by several SS18:SSX oncogenic fusion proteins that are expressed as a result of this translocation. The fact that the tumor sometimes develops close to joints provides reason for the term "SS". The name persisted even though this association is untrue, and the tumor has nothing to do with synovial epithelium(47). Approximately 5% to 10% of all STS are synovial sarcomas. Most synovial sarcomas tend to have a slow growth rate and patients typically experience symptoms for an average of 2 years before a diagnosis is reached(48). SS has specific clinical features that set it apart from other STS subtypes. It tends to manifest at a younger age, often affecting adolescents and young adults, resulting in an average age of 39 years at diagnosis(48). Additionally, this histological subtype affects both males and females equally. SS is the most frequent non-RMS STS subtype in children, accounting for approximately 30% of all childhood STS cases(47). SS can be subdivided into monophasic and biphasic SS. Whilst the monophasic type consists only of spindle cells, the biphasic type includes epithelial and spindle cells at varying amounts(49). SS is generally classified as a high-grade sarcoma and has a poor prognosis. In adult patients, the anticipated 5-year survival rate ranges from 50% to 60%, while the 5-year metastasis-free survival rate is between 40% and 60%(50). Notably, in some studies, the 5-year survival rate in children reaches 90% (51).

1.1.13 Undifferentiated pleomorphic sarcoma (UPS)

Undifferentiated pleomorphic sarcoma (UPS) is a high-grade STS that was termed malignant fibrous histiocytoma in the past, as it is very likely that the tumor originates from mesenchymal stem cells, rather than histiocytes as previously believed(52). UPS are typically considered as a diagnosis of exclusion. They account for approximately 10% of STS cases in adults. Soft tissues, bone, and retroperitoneum can all be affected. Also, UPS are more frequently observed in white males, and the occurrence tends to rise with age, particularly above the age of 60(53). Histopathologically, UPS displays atypical, pleomorphic spindle cells

with numerous mitotic figures. The invasion of soft tissues frequently reaches deep through dermis, subcutis, fascia and skeletal muscle and should be resected as shown in Figure 4 and Figure 5. The tumor can exhibit a storiform, fascicular, or sheet-like arrangement within a fibrous stroma(52). Factors such as advanced age, metastases at the time of diagnosis, tumor size and depth relative to the fascia have a significant impact on overall survival that is approximately 60% at 5 years, and 48% at 10 years(54,55).

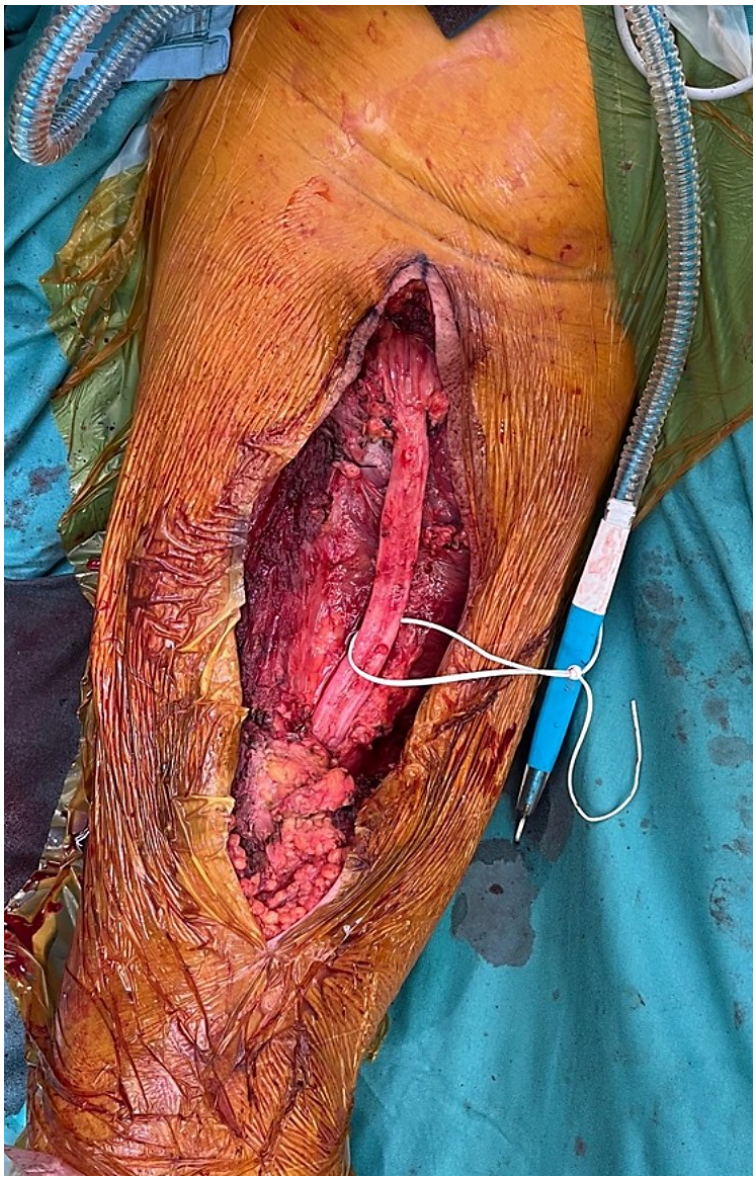

Figure 4: Intraoperative situs after resection of an UPS in the dorsal thigh with neurolysis of the sciatic nerve (marked with a white loop).

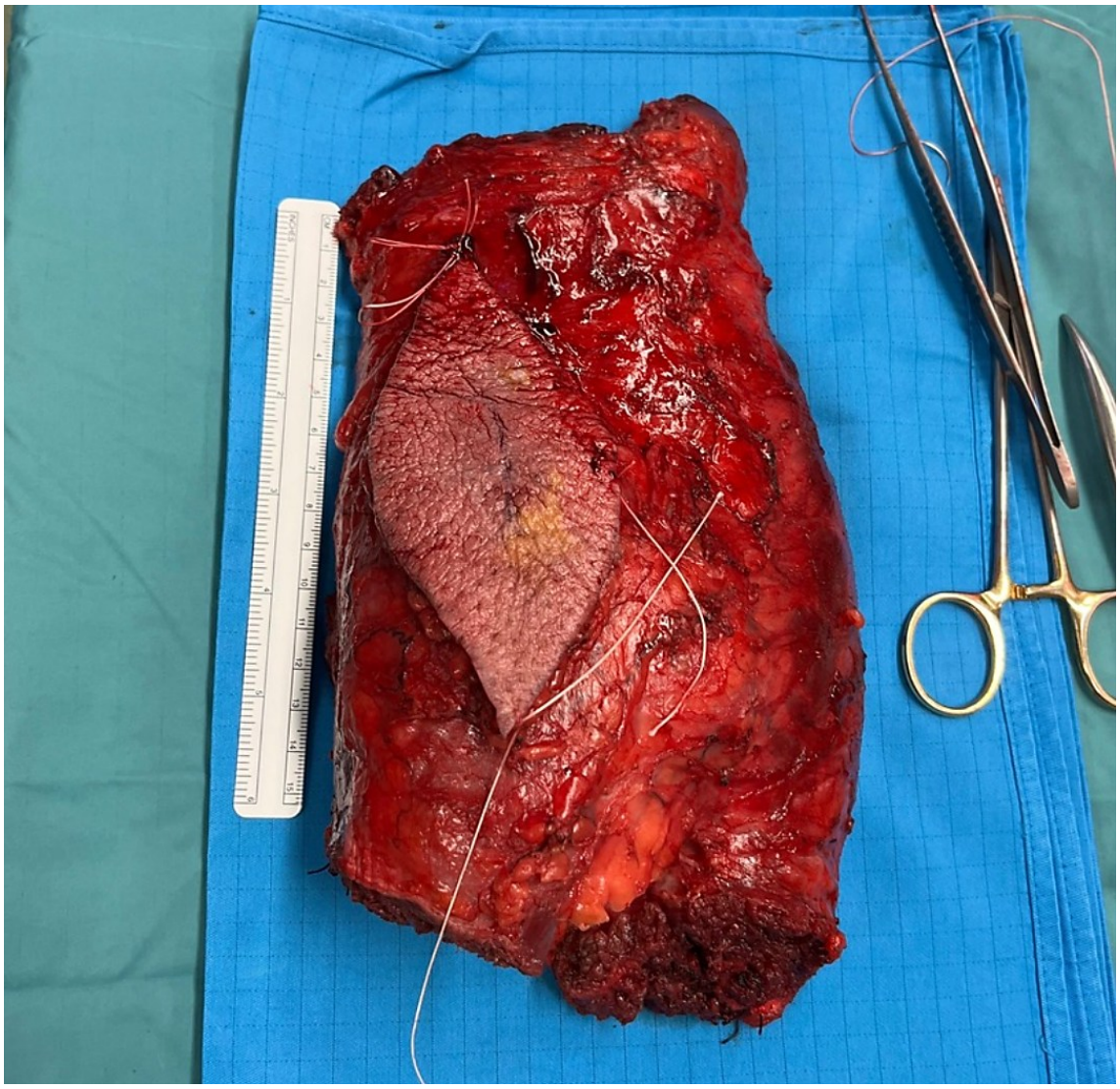

Figure 5: Resection of an undifferentiated pleomorphic sarcoma (UPS) in the dorsal thigh [see also Figure 4].

1.2 Clinical presentation

Generally, it is favorable to detect STS as soon as possible, but it can be difficult to diagnose these tumors at an early stage. Firstly, STS are often clinically silent, as patients do not experience any pain despite a growing mass. It often takes considerable time until a swelling or lump is detected and/or pain is felt. Secondly, STS can occur anywhere and at every age. Frequently, tumors have already reached a considerable size and patients may - due to the indolent behavior - see the massive lump more as a cosmetical issue instead of a life threatening disease. Therefore, early diagnosis is often complicated(56).

Yet, there are a few important clinical features that are crucial to differentiate whether the lesion is malignant or benign. Size matters, especially in STS(57).

Studies showed that malignancy is more likely, the larger the soft tissue swelling is(57,58). Even tough, size combined with age and R_{ALD} (ratio of lateral to axial diameter) is a more accurate way of discriminating between benign and malign(59).

Lumps that exceed 4 cm, or the size of a golfball, are considered suspicious and should therefore be checked(57). An increase in size is indicative of aggressive behavior and cellular dedifferentiation. As previously mentioned, STS often do not cause pain, wherefore this feature alone is unreliable to differentiate whether a lesion is rather benign or malignant. Last but not least, it is important to consider the location of the tumor relative to the fascia; more worrisome than a superficially located lump that can be moved easily is a lesion that is located in the deep and attached to the muscular fascia, and can thus not be moved(60). The presence of a lesion > 4 cm, a history of growth, and adherence to the fascia are thus important features to differentiate between benign and potentially malignant soft tissue swellings(61). To determine the exact size and its malignancy, different diagnostic methods are needed. A referral algorithm for soft tissue lumps is shown in Figure 6

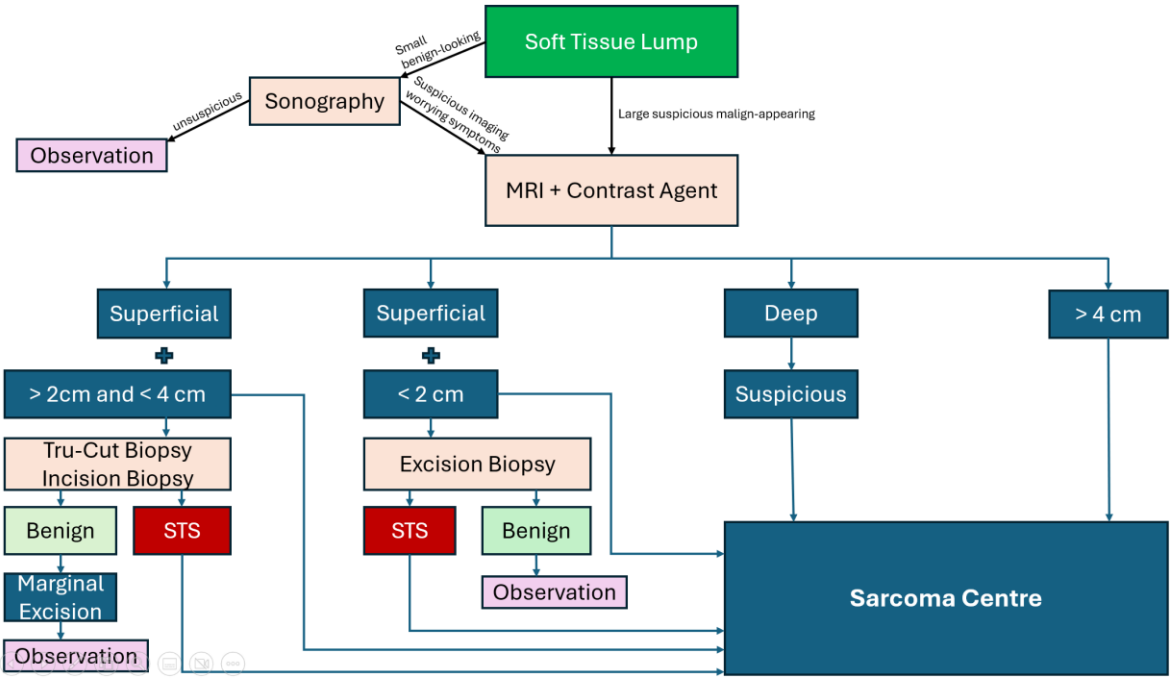

Figure 6: Suggested referral algorithm for soft-tissue lumps, (STS, soft-tissue sarcoma). Adapted from Smolle et al. (60)

1.3 Diagnostics

1.3.1 Imaging

Table 2 shows different imaging modalities that are used in musculoskeletal radiology together with their implications in diagnosis of musculoskeletal tumours.

Table 2: A comparison of imaging modalities commonly used in musculoskeletal tumors. Adapted from Caracciolo et al. (62)

MODALITY	ADVANTAGES	DISADVANTAGES	INDICATIONS/ USEFULNESS
DIAGNOSTIC RADIOGRAPHY, ORTHOGONAL ROENTGENO-GRAM	• Diagnostic • Accessible • Inexpensive • Critical in evaluating bone tumors • Demonstrates tumor mineralization and adipocytic tumors	• Ionizing radiation • Limited evaluation of nonadipocytic STS	• Evaluation of bone tumor margin, matrix, and periosteal reaction • STS density and internal mineralization
CT	• Accessible • Short scan time • Imaging of large anatomic regions • Greater spatial & temporal (comp. to MRI)	• Ionizing radiation • Less soft tissue contrast (comp. to MRI)	• Evaluate tumor matrix • Involvement of cortical bone • Tumor staging (incl. chest CT for pulm. metastases) • CT-guided biopsy
MRI	• Greater soft tissue contrast resolution (comp. to CT) • No ionizing radiation • Direct multiplanar imaging	• Small confined space (claustrophobia) • Cost • Contraindications to MRI	• Evaluation of internal tumor composition • Local extent of disease including neurovascular involvement

			• Bone marrow involvement, skip lesions
ULTRASOUND	• Real time imaging • Asses solid vs. cystic mass and tumor vascularity (doppler)	• Limited ability to differentiate soft tissue masses	• Ultrasound guided biopsy
PET	• Tumor/tissue viability, assessment of metabolic activity	• Ionizing radiation • Reimbursement in sarcomas	• May help differentiate benign and malignant tumors (i.e., neurogenic tumors) • Evaluate tumor response to neoadjuvant therapy
WHOLE BODY BONE SCAN	• Assessment of the entire skeletal system in a single examination	• Ionizing radiation	• Assessment of skeletal metastases and osteomyelitis

1.3.1.1 Ultrasonography (US)

Ultrasound (US) is fast, cheap and widely available. Also, no side effects are associated with the use of US as a diagnostic tool. It is particularly useful to evaluate superficial soft tissue masses. US can be used to confirm a mass, measure the length, width, and depth and evaluate its echotexture as well as vascularity(63). This information helps to differentiate between a few well known benign tumors or cysts and potentially malignant soft tissue swellings(64). Yet, any suspect lesion should undergo further diagnostic work-up with MRI. The downside of US includes limitation in large and deeply located or hidden lesions (for example behind bones)(65). The specificity and sensitivity of US in differentiating between benign and malignant soft tissue masses is average but also highly dependent on the pretest probability. Additionally, US imaging does require an experienced assessor, otherwise the results are not reliable(66,67). With MRI nowadays being

the gold standard in diagnostic work up of any suspicious bone and soft tissue mass, US still has a role to guide biopsy, or as an alternative in rare cases when MRI and CT scans are not an option(64).

1.3.1.2 Plain radiographs

A radiograph is in many cases the initial diagnostic test ordered when a patient complains about limb pain or a mass/swelling. It is important to have at least two different views that are perpendicular to each other. Plain radiographs are easily accessible, relatively inexpensive, critical in evaluating bone tumors, and show potential mineralization of tumors that can help in establishing a diagnosis or narrowing down the possibilities(62). For example, myositis ossificans can be differentiated from other soft tissue masses by showing a lucent zone in the center, and reflecting zonal pattern of mineralization, and layering of calcium(64,68). The pattern of mineralization can also be helpful in ruling out a benign lesion as the cause of the mass. The disadvantages lie in ionizing radiation and limited possibility to evaluate soft tissue tumors in general. Rather than for evaluation of questionable soft tissue lesions, plain radiographs are therefore particularly useful to assess bone tumors, including their border, matrix, periosteal reaction, as well as a potential soft tissue component(62).

1.3.1.3 Magnetic resonance imaging (MRI)

MRI is the preferred imaging technique to assess STS (gold-standard), especially for determining the precise size and location of the tumor, its matrix, and contrast enhancement(63). The absence of ionizing radiation, the capacity to capture images from several angles, and the exceptional contrast across tissues make it well-suited for assessing the characteristics and size of the lesion in question (69). It also detects infiltration of the compartments and critical anatomical features such as nerves, blood vessels, and joints(64). Certain STS subtypes may be differentiated based on how they appear in T1- and T2-weighted sequences. For instance, FS show a high signal intensity with sporadic low signal patches on T2 weighted sequences, and a medium signal intensity on T1 weighted pictures. Conversely, bigger SS show heterogeneity on T2 weighted images and homogeneity on T1 weighted images(70). The downsides of MRI are associated costs, the limited availability, and that patients with claustrophobia or other

contraindications (e.g. cochlear implants) are not allowed to undergo MRI, or only after careful preparation (e.g. patients with pacemaker). Due to the fact that one can evaluate size and inner tumor composition, neurovascular and bone marrow involvement, as well as skip metastases, MRI is a helpful tool for locoregional staging, thus having an impact on further therapeutical management and prognosis(62).

1.3.1.4 Computed tomography (CT)

For locoregional staging of STS, computed tomography (CT) is inferior compared to MRI, as the soft tissue resolution is worse(64). However, CT is a valuable modality for local monitoring when MRI is contraindicated or unavailable(71). For detection of potential metastases and thus staging in general, the CT scan is the gold standard(62). Compared to radiographs of the chest, thoracic CT scans are able to show lesions earlier and more accurately, as well as the number of lesions and segments that need to be addressed(62). On one hand, CT scan is easily accessible, takes a short amount of time, has a greater spatial and temporal resolution than MRI, and is helpful in assessing the bone (i.e. for pathological fractures) or involvement of soft tissue tumors. On the other hand, patients are exposed to ionizing radiation and the soft tissue contrast of CT scans is inferior to MRI(62).

1.3.1.5 Positron emission tomography-computed tomography (PET-CT)

In positron emission tomography-computed tomography (PET-CT), a glucose analogue called Fluorodeoxyglucose (FDG) is used. It acts similar to glucose and can therefore show the rate of metabolism in cells. Combined with a CT scan, one receives detailed anatomical data with information about metabolic activity. This can be used for diagnosis or staging of a malignant tumor in question. Additionally, PET-CT monitors treatment response, distinguishing between viable tumor tissue and post-therapeutic changes, and enables early detection of recurrences(64). The advantages of PET-CT include enhanced sensitivity and specificity by combining functional and anatomical imaging, comprehensive whole-body assessment in a single session, and quantitative analysis through standardized uptake values (SUV)(72).

1.3.2 Biopsy

A biopsy plays a vital role in diagnosing bone and soft tissue tumors. Certain guidelines, as shown in Table 3, must be followed to ensure accurate tissue collection and effective treatment planning. For masses over 4 cm or those located deep within tissues, prompt referral to a specialized tumor center is advisable(60). Tru-Cut™ needle biopsies that are carried out under local anesthesia, are preferred for larger, easily accessible tumors. For deeper or smaller masses, open or image-guided biopsies might be necessary. Although open biopsies provide a higher amount of tissue, they are more invasive and have a higher risk of tumor cell spread. To reduce complications like bleeding, hematoma formation and consecutive spread of tumor cells, careful procedural planning is critical. Studies show that biopsies performed outside specialized centers have a greater risk of diagnostic errors and later recurrence, highlighting the need for expert referral if malignancy is suspected(60).

Table 3: Ten rules to aid planning and evaluation of a biopsy. Adapted from Smolle et al.(60)

	RULES	HOW TO ACHIEVE
1	Do not hurry	Take time and carefully plan your next steps
2	Do not contaminate neurovascular structures or joints	Plan your biopsy according to anatomy and eventual future surgery
3	Do adequate imaging before any operation	Arrange MRI (with contrast agent)
4	Send biopsy specimen to a pathologist specialised in bone and soft tissues tumours	Check with your nearby pathology department whom to contact
5	Take the shortest way through one compartment only	Keeping in mind rules II, VI
6	Plan your biopsy in view of eventual resections	Cut in longitudinal direction of the extremity
7	Gain sufficient and representative tissue	Take samples from the peripheral area, not central necrotic regions
8	(If possible) store small fraction of tissue fresh frozen (-80°) for research purposes	Get in contact with the pathologist
9	Operate as atraumatically as possible	Minimise incision or use CT-guided biopsy for deep lesions

10	Avoid any post-operative haematoma	Perform thorough haemostasis, use a drain (passed directly through skin incision) and apply compression dressing

1.4 Classification

1.4.1 Histological grading

The accurate histological classification is a crucial part of the diagnostic pathway, as there are many different subtypes of STS (Table 1) with various therapy approaches(60). In the majority of STS, histological grade is an important prognostic indicator, especially in predicting LR-free survival, DM-free survival, and disease-specific survival(73).

Histological grading assesses the biological behavior of a primary tumor based on its intrinsic histological features, such as differentiation and aggressiveness, to predict how aggressively it behaves clinically(73). Unlike staging that examines the tumor's spread, grading evaluates the tumor's quality at the cellular level.

Today, two grading systems are commonly used whose criteria focus on cell differentiation, necrosis, and mitotic count. For these parameters, multivariate analysis has shown to be most predictive for prognosis. These standardized grading systems help to predict the tumor's aggressiveness and treatment response(73).

The two predominantly used grading systems for STS are the NCI system by the US National Cancer Institute and the FNCLCC by the French Federation of Cancer Centers. The NCI classification system categorizes tumors into grades from 1 to 3 based on histological characteristics including subtype, pleomorphism, cell density, and the rate of cell division (reflected by the Ki-67 index). The amount of necrosis is essential to differentiate between grades 2 and 3, as a necrotic rate over 15% indicates rapid cell turnover and aggressive growth.

The FNCLCC system assesses three critical histological factors: the extent of necrosis, cellular differentiation, and mitotic rate (Ki-67 index) as shown in

Table 4. The FNCLCC system integrates these three factors into a scoring system, with each parameter scored individually, rather than categorizing STS by subtype. The tumor's grade is subsequently determined by the total score(74,75).

Table 4: FNCLCC Histologic Grading System (76)

TUMOR DIFFERENTIATION	
SCORE 1	Sarcoma closely resembling normal adult mesenchymal tissue (e.g., well-differentiated liposarcoma)
SCORE 2	Sarcomas for which histologic typing is certain (e.g., myxoid liposarcoma)
SCORE 3	Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, and synovial sarcomas
MITOTIC COUNT	
SCORE 1	0–9 mitoses per 10 HPF
SCORE 2	10–19 mitoses per 10 HPF
SCORE 3	≥20 mitoses per 10 HPF
TUMOR NECROSIS	
SCORE 0	No necrosis
SCORE 1	<50% tumor necrosis
SCORE 2	≥50% tumor necrosis

1.4.2 Staging

STS are staged according to the AJCC staging system, that is loosely based on the tumor, node, metastasis (TNM) system, developed in collaboration by the UICC (Union for International Cancer Control) and AJCC (American Joint Committee on Cancer). The TNM system assesses tumor size (T), lymph node involvement (N), and the presence or absence of distant metastases (M)(77). It can be used for any malignant tumor. The AJCC staging system incorporates information from TNM together with histologic grade (G) to establish the final stage of STS. The AJCC staging system for STS was updated to the 8th edition in 2017(77).

STS are categorized into stages 1 to 4, with lower stages indicating less extent of tumor spread. Stage IV means that the tumor has spread to distant organs. In each step, preceding letters imply lesser degrees of growth.

Until the 7th edition, the staging system for STS utilized a uniform classification irrespective of their anatomical site. Nonetheless, the 8th edition presented specific staging systems customized to the tumor's site. The sites are classified into four categories: trunk and extremities (Table 5), retroperitoneum, head and neck, and abdominal and thoracic visceral organs(77). Another key difference between the 7th vs. 8th version is the interpretation of the T factor that had been divided into only 2 different categories before 2017: T1 ≤5 cm and T2 >5. In the current 8th version, there are 4 subdivisions: T1 ≤5 cm; T2 >5 and ≤10 cm; T3 >10 and ≤15 cm; and T4 >15 cm(78).

Table 5: STS staging of extremities and lower trunk according to the eighth edition AJCC Cancer Staging Manual(77)

CATEGORY	DEFINITION
PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 5 cm or less in greatest dimension
T2	Tumor more than 5 cm and less than or equal to 10 cm in greatest dimension
T3	Tumor more than 10 cm and less than or equal to 15 cm in greatest dimension
T4	Tumor more than 15 cm in greatest dimension
REGIONAL LYMPH NODES (N)	
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
DISTANT METASTASIS (M)	
M0	No distant metastasis
M1	Distant metastasis
DEFINITION OF GRADE (G)	
GX	Grade cannot be assessed
G1	Total differentiation, mitotic count and necrosis score of 2 or 3
G2	Total differentiation, mitotic count and necrosis score of 4 or 5
G3	Total differentiation, mitotic count and necrosis score of 6, 7, or 8
PROGNOSTIC STAGE GROUPS	
WHEN T IS... | AND N IS... | AND M IS... | AND GRADE IS...	Then the stage group is...
T1 | N0 | M0 | G1, GX	IA
T2, T3, T4 | N0 | M0 | G1, GX	IB
T1 | N0 | M0 | G2, G3	II
T2 | N0 | M0 | G2, G3	IIIA
T3, T4 | N0 | M0 | G2, G3	IIIB
ANY T | N1 | M0 | ANY G	IV
ANY T | ANY N | M1 | ANY G	IV

1.4.3 Classification of surgical margins

In the 1940s, amputations for large STS lead to better local control rates than less radical surgical procedures (e.g. marginal resection). In 1980, Enneking et al. described the connection between tumor-free surgical margins and decreased LR rates(79). Since then, a thorough removal of the tumor has been established as a significant predictor for the occurrence of LR.

In the past three decades, the frequency of amputations to manage STS has notably decreased, as limb-sparing surgeries have become the favored method of treatment. Amputation is now regarded as a last resort, only considered when extensive tumor removal would lead to significant functional limitations due to the tumor's interaction with nerves, bones, or blood vessels.

In this respect, a reasonable margin should take into account the range of the margin, as well as which anatomic barrier can be found(80,81). To help categorizing whether the tumor margins are clear or not, the R-Classification and the UICC-Classification have emerged and are used by clinicians all over the world. They do not only consider margins macroscopically, but also on a microscopic level.

1.4.3.1 Classification by Enneking et al.

In 1980, Enneking et al. established a surgical staging system for musculoskeletal sarcomas, categorizing margins into four types: intralesional, i.e. the dissection traverses the tumor, leaving residual tissue behind; marginal, i.e. the tumor is excised through its reactive zone, risking microscopic residual disease; wide, i.e. the tumor is resected with adjacent normal tissue; and radical, i.e. the removal of the tumor along with the entire anatomical compartment is removed. This approach emphasizes the correlation between the margin and the tumor's pseudocapsule, with the nearest margin dictating the classification(79).

1.4.3.2 R-Classification

The R-Classification consists of 3 different classes. R0 implies that the surgical margins are microscopically as well as macroscopically tumor cell free. R1 is macroscopically tumor cell free, but not microscopically. Last but not least, R2 defines an intralesional tumor resection(81).

1.4.3.3 UICC-Classification (R+1mm)

In 2002, the UICC-Classification was introduced. It follows the same principles as the R-Classification but includes a 1 mm safety margin. Therefore, R0 refers to a margin including 1 mm of healthy tissue which is microscopically and macroscopically tumor free. R1 indicates that the resection margin is <1mm, and R2 describes macroscopic tumor contamination(82,83).

1.5 Therapy

STS are rare and occur in many different shapes and locations. Therefore, a multidisciplinary team of radiologists, pathologists, orthopedic surgeons, oncologists, thoracic surgeons, pediatric haemato-oncologists, radiotherapists, plastic surgeons, and physiotherapists, which are normally found in a sarcoma-centre, is crucial to find the best therapy for each individual patient(60). The referral algorithm to the sarcoma center can be seen in Figure 6. The primary approach for high-grade STS involves surgery together with either neoadjuvant or adjuvant RTX, and eventually CTX. In special cases, also isolated hyperthermic limb perfusion (ILP) may be carried out(60).

1.5.1 Surgery

Surgery serves as the fundamental approach in the treatment of STS. Complete resection with wide surgical margins is the most important step in STS therapy(60). The overall outcome and risk for LR and DM heavily depend on the quality of the performed surgery(84). The tumor margins, as discussed in the classifications above, play a big role. Non-tumor-free resection margins increase the risk of LR as well as development of DM(85). Due to its rarity, importance, and difficulty, the therapy must be performed in a specialized tumor center with high case numbers managed by a multidisciplinary team(86,87).

Even though there are different classifications for margins, they have something in common: Tumor-free margins are crucial for minimizing risk for local as well as systemic relapse, and optimizing the outcome. Sometimes, achieving tumor-free margins leads to functional deficits. In case STS are located in a compartment but do not invade all of it, a functional compartmental resection can be performed. In this scenario, the surgeon ensures wide surgical margins but does not resect all

the muscle to maintain some functionality(81). Should the STS invade the entire compartment, the surgeon must perform a full compartmental resection. Even though no functional muscle will be left in this area, it is crucial for optimizing the outcome and avoiding loss of the whole limb. Depending on the location of the compartmental resection, the resulting deficit may be minor (e.g. adductor compartment of the thigh) or severe (e.g. extensor compartment of the thigh). In case the STS also invades the skin, it is necessary to resect it as well. Consecutive primary wound closure is then not always possible. In these cases, plastic reconstruction with split skin grafts or pedicled/free muscular flaps might become necessary(88).

Neoadjuvant RTX and/or CTX can be discussed to downsize the tumor and thus enable wide resection. However, only a minority of histological subtypes will actually show tumor shrinkage upon neoadjuvant therapy. In this regard, myxoid liposarcomas usually respond well to neoadjuvant RTX. In case wide tumor margins cannot be achieved with a satisfyingly functioning extremity, an amputation of the limb can be performed. Even though this leads to a significant reduction in quality of life, it may become necessary to improve the overall outcome and prognosis(81).

1.5.2 Radiotherapy (RTX)

RTX is a highly potent treatment option that can be delivered in different ways. One can deliver it as neoadjuvant/preoperative, intraoperative, or adjuvant/postoperative RTX, as well as brachytherapy(60). Especially for resectable, non-metastatic lesions in the limbs and trunk, RTX (particularly its neoadjuvant application) is a necessary part of the multimodal treatment strategy of STS. Usually perioperative, its objective is to maximize local control(89). In combination with wide resection, it increases the local control rate, but it remains unclear how the risk for distant metastases and the overall survival rate are influenced by (neo)adjuvant RTX(90,91). Both preoperative and postoperative RTX produce similar oncological outcomes. However, their toxicity profiles differ, as preoperative RTX is linked with higher wound complication rates but less long-term functional side effects due to smaller target volumes and less dosages(89). The choice which type of RTX fits best should always be made in the

interdisciplinary setting, and also depends on histological subtypes, growth dynamics, and center-specific preferences.
Although solid evidence is lacking right now, particle beam treatments could have advantages based on their different dose schedules(89).

RTX may only be considered in patients unfit for surgery, or in those with large, inoperable tumors with already proven metastatic spread(89). In addition to advanced or metastatic disease, RTX may be applied to soft tissue or bone metastases of STS as well, aiming at reducing local symptoms such as growth and pain(92).

1.5.3 Chemotherapy (CTX)

In 1973 it was discovered that anthracyclines (e.g., doxorubicin) are effective against STS(93). Since then, many clinical trials have taken place, including different drugs such as vinca alkaloid agents, taxanes, gemcitabine, and oxazaphosphorines(60,94). The number of different chemotherapeutic drugs tested is large and their characteristics and safety vary greatly. Doxorubicin is considered the best agent regarding safety and efficacy. Therefore, it is still the first-line drug in CTX for STS(95,96).
Despite the effectiveness of doxorubicin monotherapy, studies on combination regimens have been conducted. The most commonly used combination is doxorubicin plus ifosfamide, which increases objective response rate and progression-free survival time, but does not improve overall survival and pushes hematological toxicity, including anemia, compared to doxorubicin monotherapy. According to previous studies, no combination regimen so far has significantly improved overall survival compared to doxorubicin monotherapy(97–99). Therefore, this combination regimen should be used as preoperative neoadjuvant CTX of high-risk STS (i.e., deep, high-grade STS of the extremities > 5 cm) in order to reduce the risk for later metastatic spread(97,100).
CTX is applicable in neoadjuvant, adjuvant, and palliative contexts and currently is the first-line treatment for advanced, unresectable STS(97). Neoadjuvant chemotherapy, for example, can be used to eliminate skip lesions or reduce the size of a locally advanced tumor, making it easier to perform limb-sparing surgery(60).

1.5.4 Isolated hyperthermic limb perfusion (ILP)

ILP was developed In 1950(101). Since then, melphalan and tumor necrosis factor-alpha (TNFα) have been added to the procedure, as well as an independent oxygenated perfusion circuit. During the procedure, the limb to be perfused is connected to a heart-lung machine after cannulation of the afferent and efferent vessels. While for the upper limb, brachial or axillary are used, the external iliac, superficial femoral, or common femoral vessels are chosen for the lower limb(102). For vasodilatation and optimal efficacy of melphalan and TNFα, the limb must be warmed to 39°C. When the perfusion is done, the washout phase with saline starts(60). Afterwards, the used blood vessels are repaired and controlled with a Doppler sonography to ensure physiological blood flow(102). Surgery should be performed 6 to 10 weeks after successful ILP.

In general, ILP can be used for locally advanced or irresectable STS by reducing the size. It is used as an alternative to primary amputation (or in other words to avoid potential amputation due to primary tumor extent) with a limb salvage of 60%-81%, and also in palliative settings it can help reduce symptoms(103,104). Some types of STS seem to respond well to ILP, e.g., high-grade pleomorphic sarcoma and angiosarcoma(105). Even though the results are promising, the evidence for prolonged overall survival following ILP is low(106). Further, the complex set-up with a heart-lung machine limits its broad clinical use.

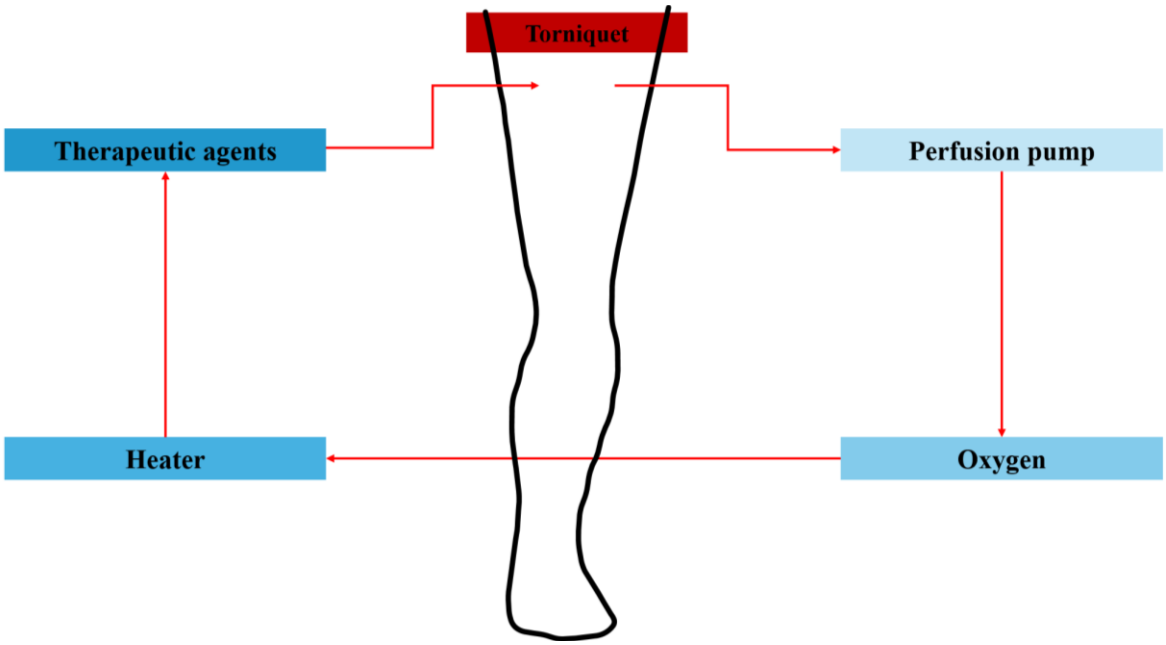

Figure 7: Isolated Limb Perfusion for Extremity Soft Tissue Sarcoma and Malignant Melanoma. Adapted from Russell et al. (102)

1.6 Local recurrence (LR) and distant metastasis (DM)

1.6.1 Treatment of LR

It is common that the LR is first detected by the patient, recognizing a lump in the previously treated region(60). With regards to treatment, it is important to use the same guidelines as for a newly diagnosed STS. Like primary STS, wide resections are crucial in LR but unfortunately positive margins are more common following resection of LR, occurring in up to 30%. This may be related to scar tissue impairing preparation, and multifocal recurrences(107,108).

It is mandatory to carry out a re-staging and define the histological subtype. Neoadjuvant or adjuvant RTX/CTX and/or ILP can be used in situations where the recurrence is too large or deep, resulting in a non-functional limb after wide resection, wherefore amputation is being considered. In addition, if the area has been previously irradiated, techniques such as intensity-modulated radiotherapy, proton therapy or brachytherapy should be taken into consideration(107).

Should no local treatment be possible, a systemic chemotherapy can be considered.

For most patients with a LR, limb salvage surgery provides a satisfying result with good local control. However, in tumors that invade arteries and/or nerves, it may

not be possible to spare the limb, and an amputation is the best overall choice(107).

1.6.2 Treatment of DM

Distant metastases most commonly develop in the lungs. Single metastases may be treated by metastasectomy. In STS, metastasectomy of pulmonary metastases has been associated with an improved outcome(109).
Alternatively, single or oligometastaess to the lungs may undergo stereotactic irradiation. In case of multiple metastases, a palliative CTX may be considered. However, CTX is of limited efficacy in patients with STS, and risks and benefits must thus be carefully weighted against each other.

1.6.3 Prognostic factors

LR after surgery for STS is a well-known complication with a frequency of 12% to 26%, depending on various factors. LR rates depend mainly on surgical margins (positive/negative), tumor grade, location, depth, histological subtype and age(60,110,111).
Deeply seated STS are usually considered more aggressive, and are at higher risk for LR. Metastases also seem to occur more often in larger sized, higher grade and deeply located STS. Grade 1 tumors for example only metastasize in 5 - 10%, but grade 3 STS in approximately 60%(60,111).
Risk factors for DM include histology, tumor size, patient age, grading, and location(112). While most STS set metastases to the lungs, myxoid liposarcomas are known to metastasize to uncommon anatomical areas as abdomen, bone, and other soft tissues(113).

1.7 Aim of the study

As mentioned above, LRs are relatively common complications in STS, especially if an unplanned excision has been performed. Between 12% and 26% of patients with STS develop LR over the course of the disease, and up to 30% develop DM(60,111).
Treatment of LR primarily involves surgical resection, alone or in combination with RTX (if not administered already), while in the case of DM, in addition to metastasectomy and local RTX, systemic therapy options are also employed.

Grading, as defined by the FNCLCC, indicates the degree of tumor dedifferentiation and thus its malignancy. STS are classified within this system as G1 (low-grade malignancy), G2 (moderate malignancy), and G3 (high-grade malignancy)(73,75,76). Notably, STS recurrences are not routinely graded. In case LR or DM occur, the question arises whether the tumor has become more aggressive over time - that is, whether a recurrence of a G1 STS is still histologically classified as G1, or whether it has further dedifferentiated (to G2 or G3). It also remains unclear whether such an upgrading is associated with a poorer prognosis for patients. It is assumed that upgrading is associated with a worse outcome, as it may be an indirect indicator of increasing tumor aggressiveness. The aim of this retrospective study is to investigate both the frequency and the prognostic relevance of "upgrading" in recurrence of STS. The findings may potentially close an important knowledge gap and give reason to routinely grade STS recurrences.

2 Materials and Methods

Between 1998 and 2016, 504 patients with primary localized STS surgically treated at the *Department of Orthopaedics and Trauma, Medical University of Graz* were retrospectively screened for development of LR, DM or both. Of these, 143 patients with a recurrence (either local or distant) during follow-up, i.e. between 1998 and up to 2022 were included. The ethics committee approval can be found in the appendix at the end of the thesis. Sex (male/female), age at surgery (calculated from date of birth to date of surgery), time to last follow-up (calculated from date of surgery to date of follow-up or death), as well as cause of death were documented as epidemiological data. Furthermore, information about the primary tumor and surgery was collected, including type of surgery, whether plastic reconstruction was used during definite surgery (and if so, what kind), use of endoprosthetic reconstruction, reconstruction of nerves and/or vessels, side (left/right) and detailed location of the tumor, depth relative to fascia, size in cm, histology, grading, surgical margins in mm according to the UICC classification, and whether primary lymph node metastases or DM were present. The data collected about recurrences (both LR and DM) included occurrence, date of 1st and 2nd recurrence, date of surgery, time from initial surgery to recurrence, total number of recurrences, treatment for recurrence, histology, grading and change of grading in relation to the primary tumor. In case of DM, the location of metastasis was also documented. Additionally, the duration and type of symptoms, date and type of postoperative complications and first and last date of RTX was also documented.

Each patient included into the analysis had either been primarily treated for STS at our institution or had been referred after an unplanned excision of the malignancy. Descriptive analysis was carried out including all 143 patients. In total, 59 of the 143 patients were excluded from further analyses (as shown in Figure 8), as no further information on change in grading was available.

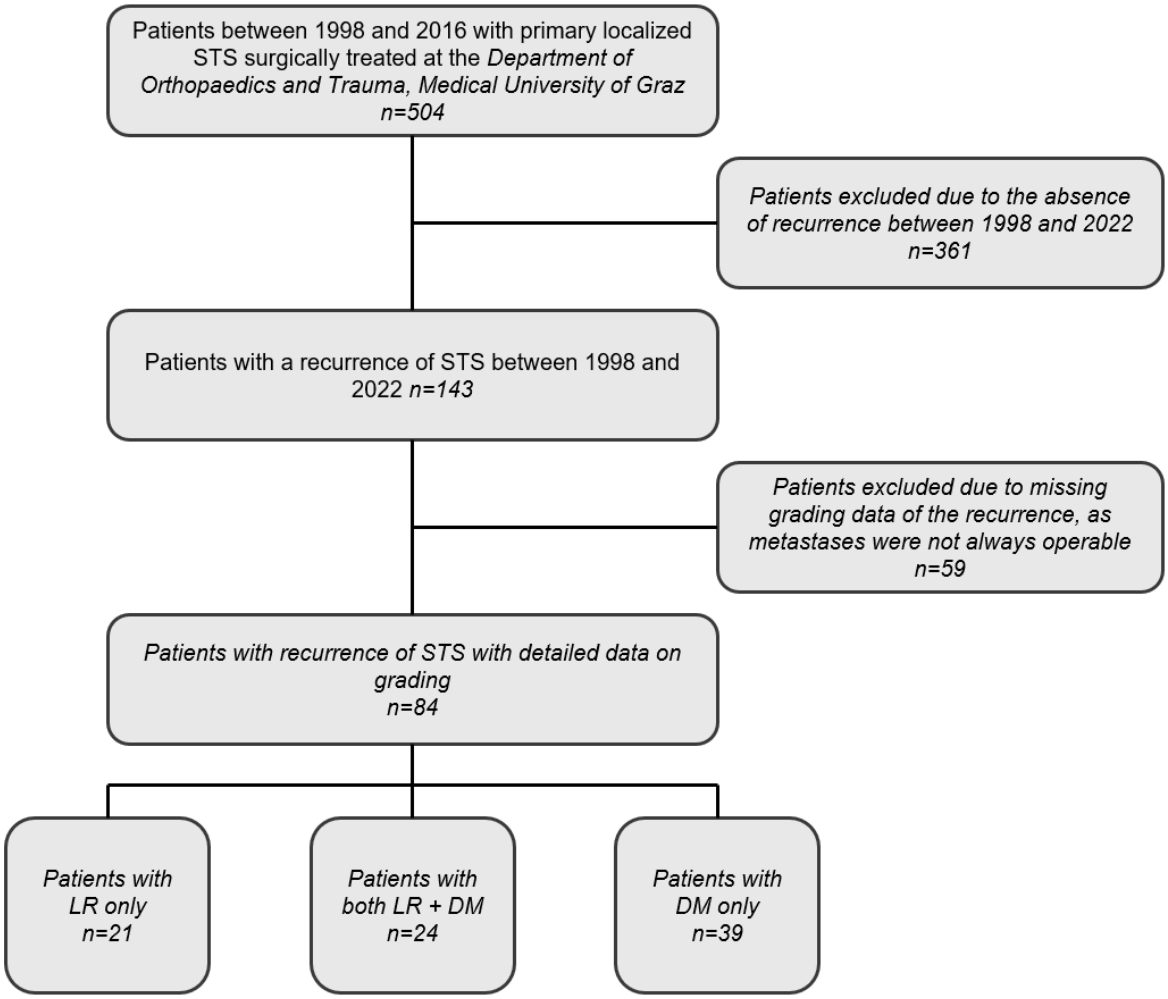

Figure 8: Flow diagram illustrating patient selection and inclusion process.

The data of the remaining 84 patients was also analyzed using descriptive methods as previously outlined; however, this subset underwent a more detailed examination focusing specifically on grading. This included the assessment of grading, identifying cases with no change, upgrading, or downgrading, as well as evaluating the frequency of these grading shifts and their potential prognostic significance in terms of overall survival (OS). All specimens were investigated at the same pathology department by experienced pathologists with profound knowledge in diagnosis of soft tissue tumors.

2.1 Statistical Analysis

Data collection and statistical analyses were conducted using Microsoft Excel for Windows (version 2506), IBM SPSS Statistics (version 30.0.0) and Stata (StataCorp Version 16.1 for Mac). A p-value of 0.05 or lower was considered statistically significant. Descriptive statistics were employed to determine the

frequency distribution of categorical variables, such as the proportion of low-, intermediate-, and high-grade tumors. For continuous variables (e.g. tumor size) exploratory data analysis was carried out to calculate the mean, median, interquartile range (IQR), standard deviation (SD), as well as minimum and maximum values. OS rates were estimated using Kaplan-Meier survival curves. Univariate Cox proportional hazards models were calculated to evaluate the association between change in grading on OS.

3 Results

3.1 Patient characteristics of the entire cohort (n=143)

Of the 143 patients included in the study, 78 were male (54.6%) and 65 were female (45.5%), with a mean age of 63.3 years (SD=5.89 years), ranging from 21 to 94.6 years. Surgery was performed in 142 patients, with limb salvage procedures accounting for the majority (131 patients, 92.3%) and amputations performed in 11 patients (7.8%). Most STS were located in the lower extremity (70.6%), followed by the upper limb (20.3%) and the trunk (9.1%). The median tumor size was 8cm (IQR: 5 - 13). The majority of patients presented with grade 3 primary tumors (n=107; 74.9%), followed by grade 2 STS (n=31; 21.7%), and only a small portion showed an initial grading of 1 (n=5; 3.5%). Histologically, MFS was the most common subtype with 46 cases (32.2%), followed by LMS (n=24; 16.8%), MFH/UPS (n=20; 14.0%), SS not otherwise specified (NOS)(n=9; 6.3%), MLS (n=9; 6.3%), SCS (n=5; 3.5%), and seldom diagnoses (n=6; 4.2%). All the other less common histological subtypes and patient characteristics are shown in Table 6.

Table 6: Patient characteristics and demographic data of the entire cohort (n=143)

Variable		Entire cohort (n=143)
Sex, n (%)	Male	78 (54.6)
	Female	65 (45.5)
Age at surgery (years)	mean ± SD	63.3 ± 15.89
	Min. to max.	21 – 94.66
Tumor size (cm)	Median (IQR)	8 (5 – 13)
	Min. to max.	0.2 - 27
Grading, n (%)	Grade 1	5 (3.5)
	Grade 2	31 (21.7)
	Grade 3	107 (74.8)
Performed surgery, n (%)	Limb salvage	131 (92.3)
	Amputation	11 (7.8)
Tumor localisation, n (%)	Lower limb	101 (70.6)
	Upper limb	29 (20.3)
	Trunk	13 (9.09)
Detailed histology, n (%)	**Angiosarcoma**	2 (1.4)
	MPNST	4 (2.8)
	Myxofibrosarcoma	46 (32.2)
	Synovial sarcoma	
	Synovial sarcoma, NOS	9 (6.3)
	Synovial sarcoma, spindle cell	0 (0)
	MFH/Undifferentiated pleomorphic sarc.	
	MFH/UPS	20 (14.0)
	Giant cell sarcoma	0 (0)
	Dermatofibrosarcoma, NOS	1 (0.7)
	Spindle cell sarcoma	5 (3.5)
	Liposarcoma	
	Myxoid liposarcoma	9 (6.3)
	Round cell liposarcoma	0 (0)
	Pleomorphic liposarcoma	1 (0.7)
	Mixed type liposarcoma	0 (0)
	Dedifferentiated liposarcoma	4 (2.8)
	Other	
	Embryonal rhabdomyosarcoma	4 (2.8)
	Clear cell sarcoma (NOS)	0 (0)
	Epitheloid sarcoma	1 (0.7)
	Fibrosarcoma, NOS	3 (2.1)

Fibromyxosarcoma	2 (1.4)
Leiomyosarcoma, NOS	24 (16.8)
Alveolar soft part sarcoma	2 (1.4)
Seldom diagnosis	6 (4.2)

3.2 Characteristics of patients with detailed information on grading available (n=84)

Information regarding whether a change of grading had occurred was available in 84 of the 143 patients. Thus, the other 59 patients (41.2%) were excluded from further analyses. Of these 84 patients, 48 were male (57.1%) and 36 were female (42.9%). The mean age was 63.7 years (SD=14.71 years), ranging from 21 to 94.6 years.

Table 7: Detailed patient characteristics and demographic data of patients with information on grading available (n=84)

Variable		**Patients with information on grading available (n=84)**
Sex, n (%)	Male	48 (57.1)
	Female	36 (42.9)
Age at surgery (years)	Mean ± SD	62.04 ± 14.71
	Min. to max.	21 – 94.70
General tumor localization, n (%)	Upper limb	16 (19.1)
	Lower limb	60 (71.4)
	Trunk	8 (9.5)
Detailed tumor localization, n (%)	**Upper limb**	
	Shoulder	5 (6.0)
	Axillary region	0 (0)
	Upper arm	4 (4.8)
	Elbow	0 (0)
	Lower arm	6 (7.1)
	Hand	1 (1.2)
	Lower limb	
	Gluteal region	3 (3.6)
	Inguinal region	4 (4.8)
	Thigh	37 (44.1)
	Knee	2 (2.4)
	Lower leg	13 (15.5)
	Foot	1 (1.2)
	Trunk	
	Head/Neck	3 (3.6)
	Thorax	4 (4.8)
	Abdomen	1 (1.2)

Tumor side, n (%)	Left	43 (51.8)
	Right	40 (48.2)
Tumor size (cm)	Median (IQR)	8 (5 – 13.15)
	Min. - max.	0.2 - 25
Tumor depth relative to fascia, n (%)	Superficial	23 (27.7)
	Deep	46 (55.4)
	Superficial + deep (combined)	14(16.9)
Grading of primary tumor, n (%)	Grade 1	4 (4.8)
	Grade 2	19 (22.6)
	Grade 3	61 (72.6)
Type of surgery, n (%)	Limb salvage	79 (94.1)
	Amputation	5 (6.0)
	Irresectable	0 (0)
Plastic reconstruction, n (%)	Yes	53 (63.1)
	No	31 (36.9)
Plastic reconstruction detail, n (%)	Muscular flap	4 (12.5)
	Skin graft/split skin	11 (34.4)
	Muscle + skin (combined)	14 (43.8)
	Mesh (e.g., prolene)	3 (9.4)
	Other	0 (0)
Endoprosthetic reconstruction, n (%)	Yes	9 (10.7)
	No	75 (89.3)
Reconstruction of nerves/vessels, n (%)	Yes	7 (8.3)
	No	77 (91.7)
Tumor margin (UICC) , n (%)	Wide > 2mm	67 (80.7)
	Marginal 0.1 – 2mm	14 (16.9)
	Intralesional	2 (2.4)
Neoadj. CTX, n (%)	Yes	3 (3.6)
	No	81 (96.4)
Adj. CTX, n (%)	Yes	16 (19.1)
	No	68 (81.0)
Neoadj. RTX, n (%)	Yes	1 (1.2)
	No	83 (98.8)
Adj. RTX, n (%)	Yes	54 (64.3)
	No	29 (34.5)
Time to LR, (month)	Median (IQR)	28 (8 – 53)
	Min. to max.	0 - 151

Time to DM, (month)	Median (IQR)	11 (4 – 22)
	Min. to max.	0 - 120
Time to any recurrence, (months)	Median (IQR)	12 (5 – 28)
	Min. to max.	0 - 120
Recurrences, n (%)	LR total	45 (53.6)
	DM total	63 (75)
	LR only	21 (25)
	DM only	39 (46.4)
	LR + DM	24 (28.6)
Time to loss of follow-up (month)	Median (IQR)	63 (24.5 – 100)
	Min. to max.	0 - 212
Survival, n (%)	Dead	46 (54.8)
	Alive	38 (45.3)
Detailed Histology, n (%)	**Angiosarcoma**	2 (2.4)
	MPNST	1 (1.2)
	Myxofibrosarcoma	26 (31.0)
	Synovial sarcoma	
	Synovial sarcoma, NOS	4 (4.8)
	Synovial sarcoma, spindle cell	0 (0)
	MFH/Undifferentiated pleomorphic sarc.	
	MFH/UPS	15 (17.9)
	Giant cell sarcoma	0 (0)
	Dermatofibrosarcoma, NOS	1 (1.2)
	Spindle cell sarcoma	3 (3.6)
	Liposarcoma	
	Myxoid liposarcoma	7 (8.3)
	Round cell liposarcoma	0 (0)
	Pleomorphic liposarcoma	0 (0)
	Mixed type liposarcoma	0 (0)
	Dedifferentiated liposarcoma	2 (2.4)
	Other	

Embryonal rhabdomyosarcoma	2 (2.4)
Clear cell sarcoma (NOS)	0 (0)
Epitheloid sarcoma	1 (1.2)
Fibrosarcoma, NOS	3 (3.6)
Fibromyxosarcoma	2 (2.4)
Leiomyosarcoma, NOS	11 (13.1)
Alveolar soft part sarcoma	1 (1.2)
Seldom diagnosis	3 (3.6)

3.3 Surgery and localisation

Out of the 84 patients, 79 (94.1%) underwent limb salvage surgery, while only 5 (6.0%) required amputation. None of the tumors was deemed irresectable. Plastic reconstruction was not necessary in 53 patients (63.1%), whereas 31 (36.9%) received plastic reconstruction during the initial surgery.

Among the 32 patients who underwent plastic surgery, 14 (43.8%) received reconstructions involving both muscular flaps and skin grafts or split skin, while 11 (34.4%) had only skin grafts/split skin. Four patients (12.5%) were treated with muscular flaps, and 3 (9.4%) received a mesh (e.g., prolene). In total, 9 of the 84 patients (10.7%) required endoprosthetic reconstruction, and 7 patients (8.3%) underwent reconstruction of nerves and/or vessels. The different types of surgery and its distribution can be seen in Figure 9. The distribution of tumor location by side was nearly even, with 43 tumors (51.8%) on the left side and 40 (48.2%) on the right. The vast majority of STS were located in the lower extremity (71.4%), followed by the upper limb (19.1%) and the trunk (9.5%). When examining detailed tumor localization, the thigh was the most common site, accounting for 37 out of 84 patients (44.1%), followed by the lower leg with 13 patients (15.5%) and the lower arm in 6 patients (7.1%). Other less common detailed localizations are provided in Table 7. During definitive primary surgery, a wide margin (> 2 mm distance according to UICC classification) was achieved in 67 patients (80.7%). A marginal distance between 0.1 and 2 mm was documented in 14 patients (16.9%), while in 2 patients (2.4%) the margin was intralesional. The median time from

surgery to LR was 28 months (IQR: 8 - 53), which is more than twice as long as the median time to DM, recorded at 11 months (IQR: 4 - 22). Overall, the median time to any recurrence was 12 months (IQR: 5 - 28).

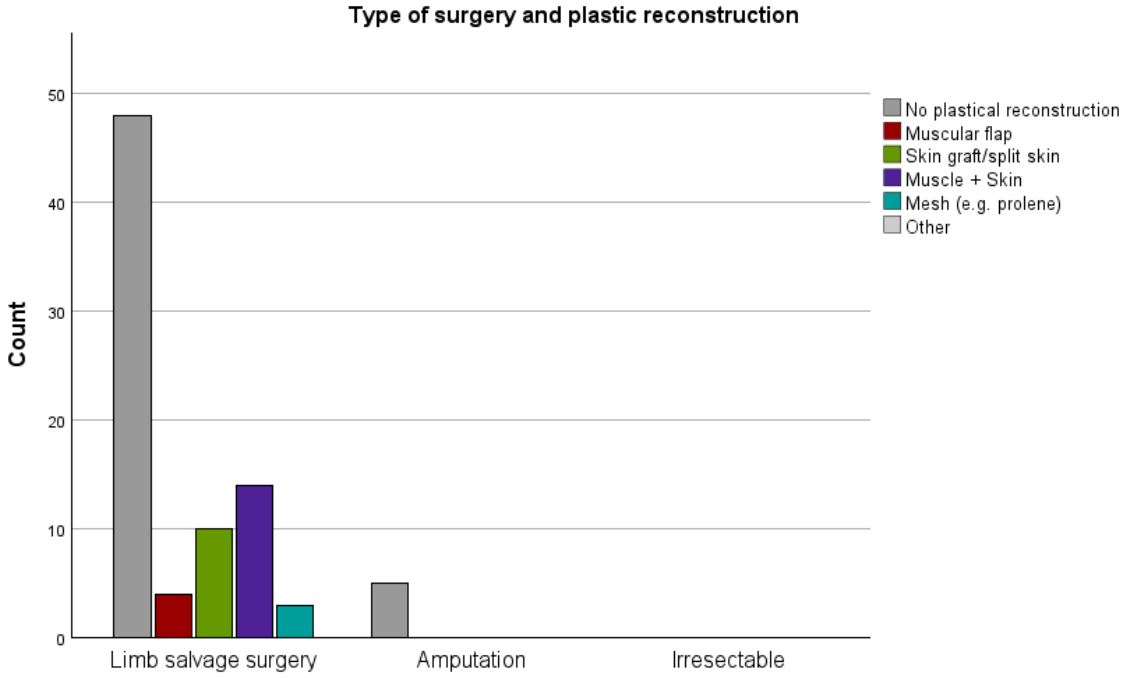

Figure 9: Bar graph showing frequency of plastic reconstructions separated by surgical approach (i.e., limb salvage, amputation, non-resectable).

3.4 Histology and grading

MFS was the most common histological subtype, observed in 26 patients (31%), followed by MFH/UPS (n=15; 17.86%), LMS (n=11; 13.1%), MLS (n=7; 8.3%), and SS-NOS (n=4; 4.8%). All other less frequent histological subtypes are listed in Table 7. In 15 recurrences, a histological change took place.

Most patients presented with a grade 3 tumor at the time of primary surgery (n=61; 72.6%), while 19 patients (22.6%) had grade 2 STS, and only 4 patients (4.8%) had a tumor initially diagnosed as grade 1.

In total, 45 patients (53.6%) developed a LR, and 63 patients (75%) experienced a DM. Specifically, 21 patients (25%) had only LR, 39 (46.4%) had only DM, and 24 patients (28.6%) developed both LR and DM. These findings are visualized in Figure 10.

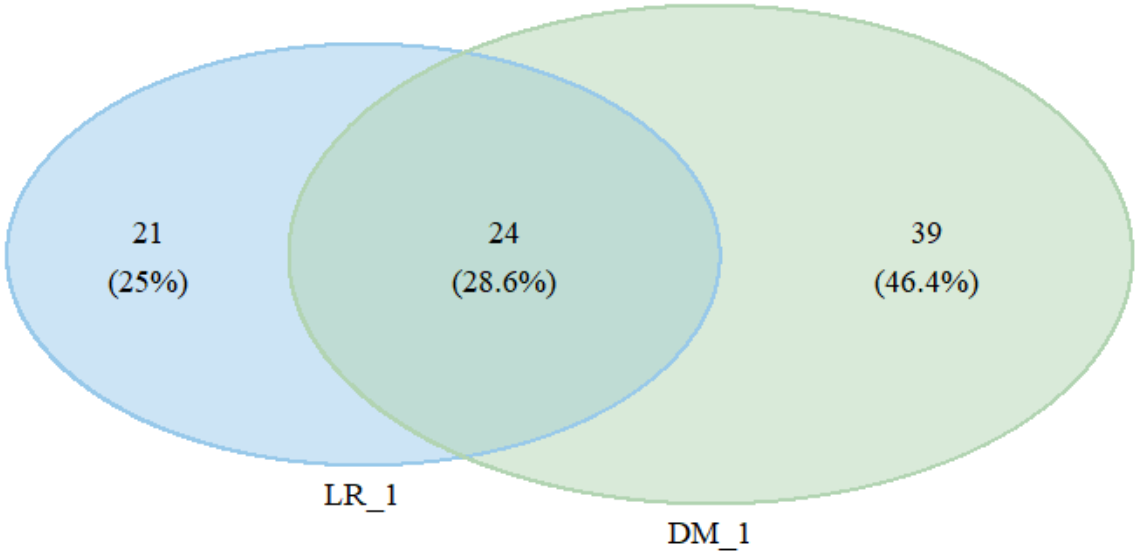

Figure 10: Venn diagram illustrating the distribution of LR and DM in patients with STS. A total of 21 patients (25%) experienced only LR, 39 patients (46.4%) had only DM, and 24 patients (28.6%) developed both LR and DM.

Grading information regarding the first LR was available for 42 patients (50%). Among them, 33 patients (78.6%) showed no change in grading compared to their primary STS. An upgrading was observed in 7 patients (16.7%), while a downgrading was documented in only 2 patients (4.8%).

A second LR with information on grading was seen in 4 patients. Upgrading occurred in 1 case (25%), while in the other 3 LRs (75%), no change in grading compared to the first tumor was found.

Grading information for the first DM was available in 56 patients, of whom 51 (91.1%) showed no change compared to the primary tumor. An upgrading was observed in 4 patients (7.1%), while 1 patient (1.8%) showed a downgrading.

A second DM with documented grading was recorded in 19 patients, with 14 (73.7%) showing no change, 4 (21.1%) exhibiting an upgrading, and 1 patient (5.3%) experiencing a downgrading. The frequency of grading changes among recurrences are shown in Figure 11.

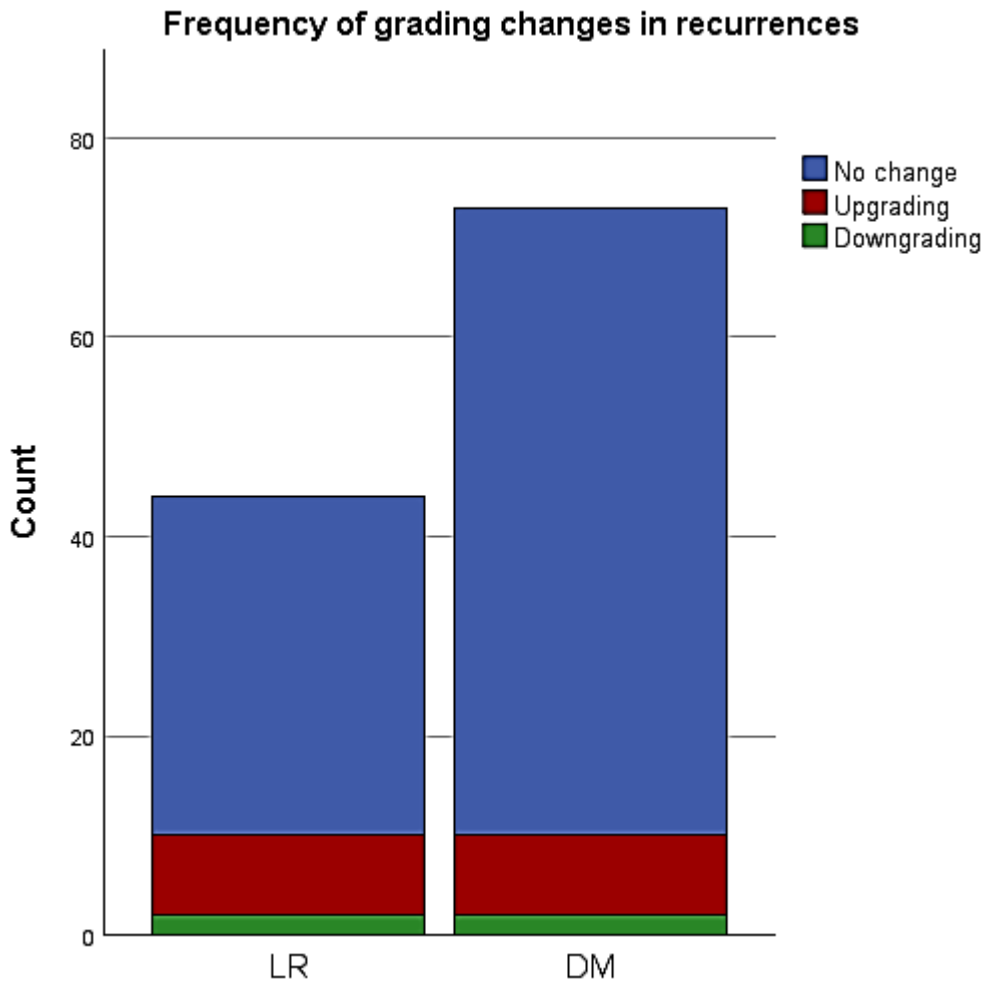

Figure 11: Frequency of grading changes in recurrences. LR: LR1 + LR2; DM: DM1 + DM2; Blue: No change in grading; Red: Upgrading; Green: Downgrading.

In summary, among the 84 patients with grading data available for LR and/or DM, 10 patients (11.9%) exhibited at least one instance of upgrading, including 4 patients (4.8%) who experienced two upgrading events. In total 4 patients (4.8%) experienced a single downgrading event.

When divided by histological subtypes, grading changes were only seen in a few patients. Upgrading occurred in MFS (3/26 patients; 11.5%), MLPS (2/7 patients; 28.6%), LMS (2/11 patients; 18.2%), MPNST (1/1 patient; 100%), SCS (1/3 patients; 33.3%), and FS (1/2 patients; 50%). Downgrading was observed only in MFS (1/26 patients; 3,86%), SS/NOS (1/4 patients; 20%), MLPS (1/7 patients; 14,3%), and LMS/NOS (1/11 patients; 9,1%), with one patient each. The distribution of grading changes across the various histological sarcoma subtypes

is visualized in Figure 12.

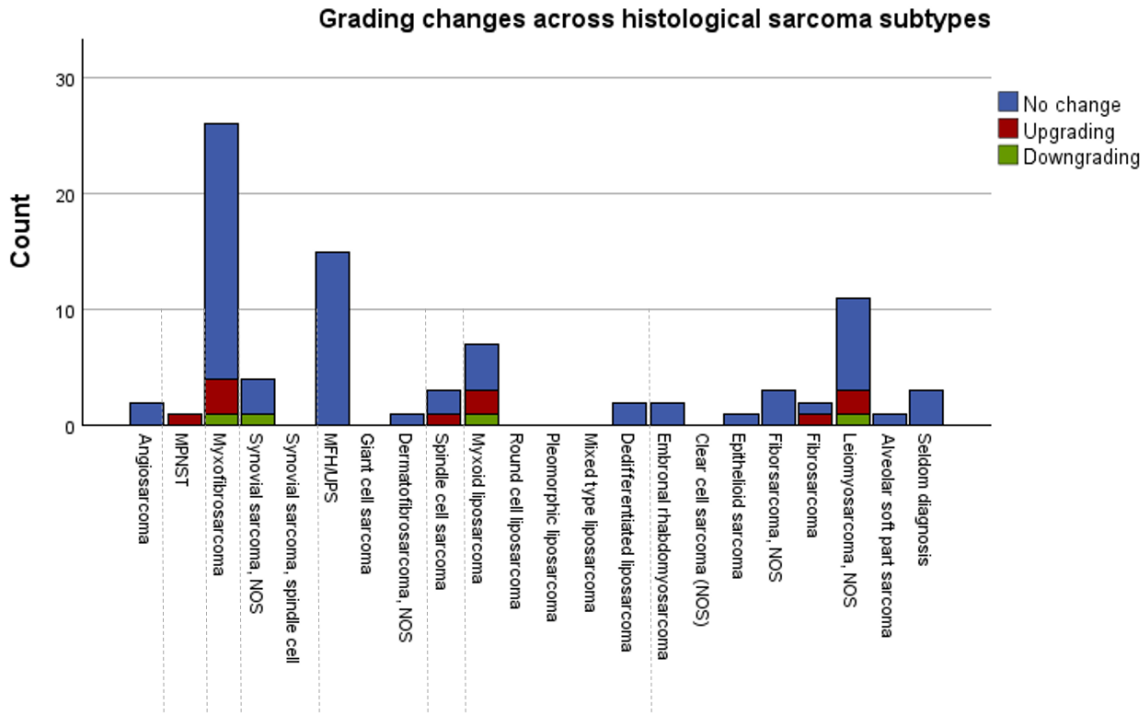

Figure 12: Bar graph showing grading changes across histological sarcoma subtypes. It illustrates the distribution of grading changes, categorized as no change (blue), upgrading (red), and downgrading (green), across different histological sarcoma subtypes.

3.5 Depth and size

Regarding the depth of the primary STS, 23 (27.7%) tumors were classified as superficial. In the majority of patients, however, the tumor was deeply located (n=46; 55.4%). In 14 patients (16.9%), the STS extended both superficially and deeply relative to the fascia. The median tumor size was 8 cm (IQR: 5 – 13.15). Tumor sizes ranged from a minimum of 0.2 cm to a maximum of 25 cm.

3.6 Primary metastasis

Primary lymph node metastases were rare, occurring in only 4 out of 84 patients (4.8%). No primary distant metastases were documented in this cohort as these patients had primarily been excluded from the study.

3.7 Neoadjuvant and adjuvant therapy

Neoadjuvant RTX was administered in just 1 case (1.2%), while adjuvant RTX was given to 54 patients (64.3%). A similar pattern was observed with CTX: 3 patients

(3.6%) received neoadjuvant CTX, whereas 16 patients (19.1%) were treated with adjuvant CTX.

3.8 Outcomes

The median timespan from the date of tumor surgery to the date of the last follow-up was 63 months (IQR: 24.5 – 100). Follow-up durations ranged from 0 to 212 months. By the end of the documentation period, 38 patients (45.2%) were still alive, while 46 patients (54.8%) had died.

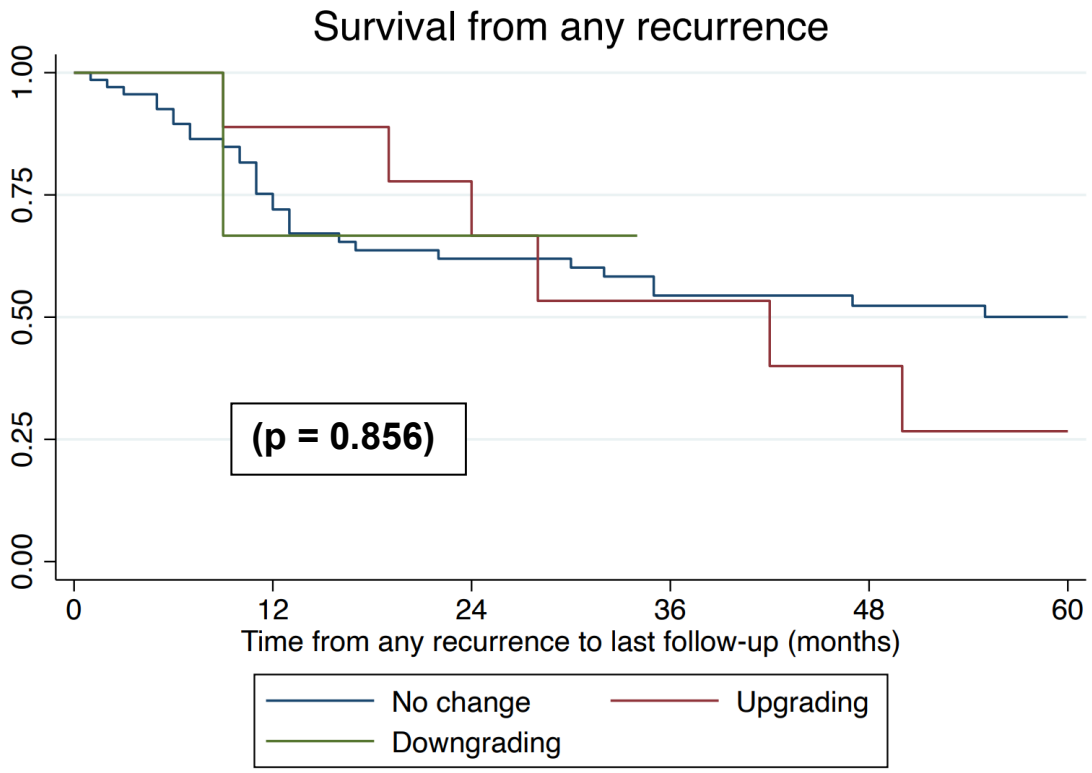

Figure 13: Kaplan-Meier-curve with information on survival of patients over time (in months) for any recurrence. No change (blue); Upgrading (red); Downgrading (green).

The Kaplan-Meier curve (Figure 13) shows post-recurrence survival in patients with STS, stratified by histological grade change at recurrence: no change (blue), upgrading (red), and downgrading (green). Due to the small number of patients in the downgrading group, the curve shows an abrupt drop toward the end, limiting its interpretability. Patients with upgrading and those with no change in tumor grade had comparable survival rates between months 36 and 40 at approximately 55%. However, by month 50, a divergence emerged: the survival rate in the

upgrading group dropped to 26%, while the no-change group maintained a survival rate of 50%. These differences did not reach statistical significance ($p = 0.856$).

4 Discussion

4.1 Answers to research questions

This retrospective study aimed to evaluate the frequency and prognostic relevance of histological upgrading in recurrent STS. Comparing the grading of the primary tumor and the recurrence of the evaluable cohort of 84 patients showed that 16.7% experienced a change in grading. Upgrading (11.9%) was more than twice as common as downgrading (4.8%). This finding underlines the importance of grading as a measure of monitoring since a grading change of a recurrence can be expected in one of 6-7 patients.

While most recurrences did not involve a change in grade, upgrading was not a rare phenomenon. A change in grading occurred in both LR and DM, albeit more commonly in LR. Importantly, grading changes were primarily observed in the first recurrence, and less frequently in subsequent ones, suggesting that the change in grading may occur early in the recurrence process.

Fletcher et. al noted that tumor upgrading may occur gradually over time, as the tumor becomes more necrotic, shows higher mitotic activity, and loses differentiation(114). This stepwise progression is most often observed in MFS, MLPS, MPNST, and LMS(114). In contrast, some tumors may experience an abrupt change in grading, referred to as dedifferentiation, where a low-grade tumor rapidly transforms into a high-grade sarcoma without intermediate stages. This pattern is most commonly seen in LPS(114,115). In all of the histological subtypes mentioned above, at least one upgrading was observed upon recurrence in the current study (Figure 12).

While downgrading was possible, it was rare and of uncertain clinical significance. Possible explanations for this phenomenon include the presence of a low-grade component within the high-grade tumor that leads to a lower grade recurrence. Or that a previously high-grade tumor component responded well to CTX, while the low grade component did not respond as well and later caused recurrence(114). Furthermore, differences in grading may arise from varying interpretations among pathologists with altering levels of experience, potentially leading to discrepancies. However, this was not the case in the present study, as all specimens were

assessed in the same pathology department by experienced pathologists with profound knowledge in the diagnosis of STS.
That said, these explanations are hypothesis-generating only.

With a limited sample size for grading changes (n=14), no significant difference (p=0,856) in survival depending on change in grading was observed.

Regarding the question ”frequency of upgrading in recurrences” the study provided a clear answer: it is happening! While most recurrences did not involve a change in grade, upgrading was not a rare phenomenon and could be found in 11,9% of recurrences. It occurred in both LR and DM, albeit more commonly in LR.

4.2 Comparative explanations

Currently, one published study is available that specifically examines the frequency of histological upgrading in recurrent STS and its prognostic impact(115). According to the Study “Change in histological grade in locally recurrent soft tissue sarcomas” by Peter C. Ferguson et al. a change in grading does not lead to a significant difference in the 5-year-survival rate of patients. The frequency of upgrading was 19%, while downgrading occurred in 8% of the patients(115). These numbers are a bit higher, but comparable with the outcomes of this study (no difference in 5-year-survival rate; 11.9% upgrading; 4.8% downgrading). Furthermore, according to previous studies MFS have a higher risk of upgrading (Figure 12) (114,115,117).

Nevertheless, most previous literature has focused either on grading at initial diagnosis or on broader prognostic factors, without systematically analyzing changes in grade over time(118–120). This highlights the relevance of this study. It provides initial evidence that histological upgrading alone might not be a reliable marker for increased tumor aggressiveness. Still, because the study is retrospective, grading systems have changed over time, and the number of events was limited, we cannot draw firm conclusions yet.

4.3 Conclusions

In conclusion, while the statistical evidence was limited by the small sample size, the study did not present a trend showing that histological upgrading in recurrent STS is associated with worse outcomes. Still, the results show, that upgrading is happening and suggest that grading changes in recurrence could be important and should not be overlooked. Future studies should focus on validating these results in larger, prospective cohorts, ideally through multicenter collaborations.

4.4 Limitations and critical reflexion

The first limitation of this study is that it was retrospective. Even though the cohort had a balanced sex distribution and a suitable age range, the quality of the data is influenced by accuracy and consistency of past documentation. Also, classification systems and treatment strategies for STS have changed a lot over the years, but these changes were not taken into account in the analysis(12). This is for example reflected by the low proportion of patients receiving neoadjuvant RTX, that is nowadays favored over adjuvant RTX in STS. In conclusion, differences in past documentation, shifting standards, and variations in treatment protocols may have caused limited comparability of the datapoints and could have affected the interpretation of the results.

Another important limitation is the relatively small sample size. Although 143 patients with recurrent STS were initially identified, detailed data on grading and histology was only available in 84 patients, because many recurrences are not addressed surgically (especially DM in the lungs) but are rather treated by systemic therapy or stereotactic radiotherapy. Of the 84 patients 14 showed a change in grading between primary and recurrent tumors (10 upgradings and 4 downgradings). The small number of patients with relevant data impairs the statistical strength of the analysis and makes it difficult to draw firm conclusions about the clinical or prognostic role of grading changes. Since complete data on grading of recurrences was not always available this may have caused a selection bias and impairs applicability of the results to a wider patient group.

Another limitation is the wide variety of STS subtypes included in the study. Over the years, more histological subtypes have been recognized, which allows for

more detailed classification(12). Since diverse subtypes can behave differently and respond to treatment in various ways, analyzing them separately could give more specific insights(121).
While Figure 12 shows differences grading changes between histological subtypes, these did not reach statistical significance because of the small sample size.

4.5 Implications for theory and practice

The findings of this study could have implications for both theoretical and clinical practice. On the theoretical side, they add to the understanding of how often grading changes occur between the primary tumor and recurrence, together with its prognostic value. This insight may help to improve existing models of tumor progression and the theoretical framework for risk management.

Despite all procedures being performed at the *Department of Orthopaedics and Trauma, Medical University of Graz*, a certified tumor center, detailed grading data in recurrences were missing in 41.3% of patients. This limitation reflects current clinical practice, in which metastases and recurrences are generally not subjected to formal grading.
In the future, pathologists may be encouraged to assess grading of recurrences to draw further conclusions on how eventual changes in grading affect patient outcomes.

Overall, these results underline the importance of reliable histopathological documentation at the time of recurrence and might support a more personalized approach to follow-up and treatment in the future. Still, further studies are needed to confirm these findings.

4.6 Outlook and suggestions for future research

In this study, we could not identify a potential association between upgrading of recurrences and worse prognosis in patients with STS. However, these results must be interpreted with caution, keeping several limitations in mind. Future research should try to address these issues by using data from prospective study

designs, as well as larger and more homogeneously stratified patient cohorts. Multicenter collaborations and registry-based studies could help reach higher patient numbers while providing up-to-date, high-quality data that reflect current diagnostic and treatment standards.

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The following tool was used to optimize the language of the text:

- Name: Chat GPT 3.5, 4 & 5
- Provider: Open AI
- Date: March 2024 – October 2025
- https://chatgpt.com

The following tool was used to optimize the language of the text:

- Name: Quillbot (v25.2.0)
- Provider: Learneo, Inc.
- Date: March 2024 – June 2025
- https://quillbot.com/

6 Appendix

Medizinische Universität Graz
Ethikkommission

Neue Stiftingtalstr. 6 - West, Q/04, A-8010 Graz
ethikkommission@medunigraz.at
Tel.: +43 / 316 / 385-13928

VOTUM

gültig bis 14.03.2024

EK-Nummer:	35-142 ex 22/23
Studientitel:	Local recurrence in soft tissue sarcoma. Frequency and prognostic relevance of "upgrading".- a retrospective study
Prüfer:	Univ.-Prof. Dr. Andreas Leithner Medizinische Universität Graz
Sponsor:	Medizinische Universität Graz
Ansprechpartner:	Dr.med.univ. Maria Anna Smolle, 8036 Graz, Auenbruggerplatz 5/6
CRO:	-
Antragsteller:	Medizinische Universität Graz
Ansprechpartner:	PD DDr.med.univ. Maria Anna Smolle, 8036 Graz, Auenbruggerplatz 5/6

Die o.a. Studie wurde von der Ethikkommission erstmals im 'expedited Review' am 03.01.2023 behandelt. Die Ethikkommission ist zu folgendem Schluss gekommen:

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

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

Zur Beurteilung vorliegende Dokumente:

Dokumente eingegangen am 14.12.2022, begutachtet im 'expedited Review' am 03.01.2023	
✓ Antragsformular undatiert/unsigniert	14.12.2022
Originalprotokoll Konzeptformular 01	02.10.2022
✓ CV SI Smolle undatiert/unsigniert	
✓ CV SI Golja unsigniert	18.07.2022
✓ Sonstiges: Ansuchen auf Erlass Bearbeitungsbeitrag undatiert	
Dokumente eingegangen am 09.01.2023 (in der nächsten Begutachtung mitbegutachtet)	
✓ Antragsformular Korrektur ohne Unterschrift	
Originalprotokoll Konzeptformular 01	02.10.2022
Dokumente eingegangen am 12.02.2023 (in der nächsten Begutachtung mitbegutachtet)	
✓ Originalprotokoll Konzeptformular 3.0	09.02.2023
Dokumente eingegangen am 17.02.2023, begutachtet im 'expedited Review' am 14.03.2023	
✓ Letter of Authorization MUG ohne Auflage	15.02.2023

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

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

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

- Abweichungen vom Protokoll aus Sicherheitsgründen oder Protokolländerungen

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

- Mutmaßliche unerwartete schwerwiegende Nebenwirkungen - SUSARs (AMG-Studien ab 1.5.2004; Directive 2001/20 EC), SADEs (Verordnung 74/2017 und 746/2107) oder schwerwiegende unerwünschte Ereignisse - SAEs (andere Studien)

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

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

Graz, 14. März 2023

Univ.Prof.DI Dr.Josef Haas
Vorsitzender

Univ.Prof.Dr.Hans Peter Dimai
Stv. Vorsitzender

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

Medizinische Universität Graz, Neue Stiftingtalstraße 6, A-8010 Graz. www.medunigraz.at
Rechtsform: Juristische Person öffentlichen Rechts gem. UG 2002. Information: Mitteilungsblatt der Universität. UID: ATU 575 111 79. Bankverbindung: Raiffeisen Landesbank Steiermark IBAN: AT443800000000049510, BIC: RZSTAT2G