Diplomarbeit

Unplanned excisions of soft tissue sarcoma: Influence on therapy and patients' survival

Tumour-related factors correlate with the rate of unplanned excisions.

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Preface

From the moment I did a clinical elective at the *Department for Orthopaedic Surgery* at the *Medical University of Graz* I was fascinated by this medical speciality. Not necessarily because of all the metal device used for fixing broken limbs or exchanging degenerated joints, but rather due to surgery performed for oncologic purposes. Looking back, I think this early fascination for orthopaedic onocology could be related to the fact that it was the first time during my studies that I realised how important a broadly based knowledge covering various medical specialities is.

This clinical elective was also the first one, where I felt being integrated into the therapeutic process by receiving explanations for the performed procedures. Moreover, even minor tasks as holding the suction or cutting stitches gave me the feeling of being needed.

Learning practical things is – at least to my opinion – not only about actively doing them, but also about observing professionals and comparing different techniques and approaches.

In the future, I do not only want to treat patients according to guidelines without using my own knowledge. Guidelines should be rather seen as guidances in order to help me as a junior doctor to find the right way to treat my patient. At least to my opinion thinking independently is one of the most important issues in medicine. Without discretely thinking doctors, there would be no research in medicine, no new discoveries and treatment approaches.

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My special thanks belong to all members of my family: Mom, dad, granny, grandpa, sister, elder brother and little brother. Especially I would like to thank them for never loosing patience with me in situations of overexertion and on the edge of despair caused by WLAN-breakdowns and other contretemps.

Contents

Glossary and Abbreviations

95%CI	95% Confidence Intervall
ACTH	Adrenocorticotrope hormone
AJCC	American Joint Committee on Cancer
CT	Computed tomography (scan)
CTX	Chemotherapy
CXR	Chest-X-ray
EBV	Ebstein-Barr-virus
FNA	Fine needle aspiration
FNCLCC	French Fédération Nationale des Centres de Lutte Contre le Cancer
GP	General practicioner
HR	Hazard ratio
IGF2	Insulin like growth factor 2
ILP	Isolated (hyperthermic) limb perfusion
LR	Local recurrence
MPNST	Malignant peripheral nerve sheath tumour
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHS	National Health Services
OS	Overall survival
PET	Positron emission tomography (scan)
RTX	Radiotherapy
STS	Soft tissue sarcoma
TNF-alpha	Tumour necrosis factor alpha
TNM	Tumour, Lymph node, Metastasis
UE	Unplanned excision
US	Ultrasound
WHO	World Heatlh Organisation

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Kurzfassung

Einführung: Ungeplante Exzisionen (UE) von Weichteilsarkomen (STS) stellen ein weit verbreitetes therapeutisches Dilemma dar. In onkologischer Therapie unerfahrene ChirurgInnen werden durch atypische Erscheinungsbilder und Fehlen von besorgniserregenden Symptomen zu Operationen verleitet. Das Ziel dieser Diplomarbeit ist es, den Einfluss von UE auf die Therapie und das Überleben von STS-Patienten zu eruieren.

PatientInnen und Methoden: Eingeschlossen wurden 427 seit 1998 an unserer Institution behandelte PatientInnen. Berechnungen wurden mit *SPSS Version 22.0* durchgeführt. PatientInnen-, tumour- und behandlungsassoziierte Faktoren wurden zwischen direkt zugewiesenen und ungeplant exzidierten PatientInnen verglichen. Überlebensanalysen wurden mit 376 Patienten berechnet, die weder primäre Metastasen noch Amputationen aufwiesen. Ein zweiseitiger p-Wert <0.05 wurde als statistisch signifikant angenommen.

Resultate: Von den 427 PatientInnen waren 215 männlich und 212 weiblich. UE wurden bei 165 PatientInnen vor einer Zuweisung an unsere Abteilung durchgeführt (38.6%). 392 PatientInnen konnten extremitätenschonend operiert werden, während bei 35 PatientInnen eine Amputation notwendig war. UE-PatientInnen hatten signifikant häufiger oberflächliche ($p<0.005$) sowie kleine Tumore ($p<0.005$) und benötigten häufiger plastische Deckungen ($p<0.005$) als direkt zugewiesene Patienten. Weder in univariater ($p=0.120$) noch multivariater ($p=0.147$) Cox-Regressions-Analyse zeigte sich eine veränderte Überlebensrate für UE-PatientInnen, allerdings war ein leichter Trend in Richtung einer besseren Prognose erkennbar. In beiden Gruppen erwiesen sich niedrig differenzierte Tumoren als negative prognostische Faktoren ($p<0.005$, HR: 3.827, 95%CI: 1.965-7.453 für direkt zugewiesene Patienten und $p=0.007$; HR: 4.791, 95%CI: 1.526-15.036 bei UE-Patienten). Allerdings stellte sich ein Alter über 60 als ein zusätzlicher negativer Faktor bei direkt zugewiesenen Patienten heraus ($p=0.009$, HR: 2.223; 95%CI: 1.217-4.063), während bei UE-Patienten eine Symptomdauer <6 Monate ($p=0.020$, HR: 0.347; 95%CI: 0.142-0.849) und ein Lokalrezidiv ($p=0.002$; HR: 4.867; 95%CI: 1.764-13.422) negative prognostische Faktoren waren.

Schlussfolgerung: Obwohl die Prognose von STS-Patienten nach einer UE nicht schlechter ist, brauchen sie öfter ausgedehnte Operationen und plastische Deckungen, wodurch die Lebensqualität vermindert werden könnte. Das Auftreten eines Lokalrezidivs nach vorangegangener UE ist ein besonders schlechter prognostischer Faktor. Alleine deshalb sollten UE bei STS vermieden werden.

Abstract

Introduction: Unplanned excisions (UE) of soft tissue sarcomas (STS) are a widely known therapeutic dilemma. The atypical presentation and absence of „worrying“ features may tempt inexperienced surgeons to perform surgery. The aim of this diploma thesis was to determine the influence of unplanned excisions on further therapy and patient's prognosis.

Patients and Methods: 427 patients referred since 1998 to our institution were included. Statistical analysis was carried out using *SPSS Version 22.0*. Tumour-, patient- and treatment-related parameters were compared between directly referred and inappropriately excised patients. Survival analysis was carried out excluding patients with primary metastasis and amputations, resulting in 376 patients eligible. A two-sided p-value < 0.05 was accepted as statistically significant.

Results: 212 patients were female and 215 male. 165 patients had undergone an UE (38.6%) prior to referral. 392 patients underwent limb-sparing surgery at our department, whereas in 35 patients, an amputation was necessary. UE-patients had significantly more often small ($p<0.005$) as well as superficial ($p<0.005$) tumours and required more often plastic reconstructions ($p<0.005$) than directly referred ones.

Neither univariate ($p=0.120$) nor multivariate ($p=0.147$) Cox-regression-analysis revealed an altered overall-survival for UE patients, though a trend towards a slightly better prognosis was visible. In both groups, multivariate analysis identified high-grade tumours as a significant negative prognostic factor ($p<0.005$; HR: 3.827, 95%CI: 1.965-7.453 in directly referred patients and $p=0.007$; HR: 4.791, 95%CI: 1.526-15.036 in UE patients). However, in the directly referred group only age over 60 was an additional significant parameter ($p=0.009$; HR:2.223, 95%CI: 1.217-4.063), whereas in the UE group duration of symptoms less than 6 months ($p=0.020$; HR: 0.347, 95%CI: 0.142-0.849) and local recurrence ($p=0.002$; HR: 4.867, 95%CI: 1.764-13.422) were additional negative prognostic factors.

Conclusion: Although the prognosis of STS-patients is not impaired after an UE, they require more often extensive surgery with plastic reconstruction, possibly impairing their quality of life. Additionally, local recurrence is a particularly poor prognostic factor when occurring after UE. For these reasons, UE of soft tissue sarcomas should be avoided.

Introduction

Soft tissue sarcomas (STS) constitute a very rare tumour entity, accounting for only 1% of all malignancies diagnosed per year. The incidence for STS is 4 per 100.000 per year, resulting in about 3.000 new cases within the United Kingdom per year (1). The incidence for STS in Austria is estimated at 4.4 per 100.000 in men and 2.7 per 100.000 in women (2). Only one out of 100 soft tissue tumours has a malignant histology. For the United Kingdom this means that a general practitioner (GP) would see one benign soft tissue tumour per year, but just one STS in 24 years of practice (3).

The exact aetiology of both benign and malignant STS is unknown, though some hereditary syndromes, viral infections (i.e. EBV and Kaposi's Sarcoma) and radiotherapy (applied in breast cancer- and retinoblastoma-treatment) are associated with the development of STS. Hereditary syndromes with specific genetic patterns predisposing to the development of STS will be discussed below.

Clinical Presentation

Although early detection and adequate treatment for STS is important, these malignancies do not necessarily facilitate their diagnosis. First of all, they can arise everywhere and in any age group, though the preferred sites are the lower limbs followed by upper limbs. Secondly, STS may cause no symptoms at all, just – and if even – constituting a "cosmetic" problem for patients. Moreover, the medical history related to the "lump in suspicion" is never explicit. Some patients may describe a trauma leading to the progress of a swelling, others will claim that the swelling has been present for several years and a group of patients may insist never having noticed a massive swelling bulging out of their thigh (Figure 1).

In several studies, the difficulties medical doctors have to face with when trying to distinguish between benign and malignant soft tissue masses have been discussed (4, 5).

An important indicator for malignancy is the location to the fascia: Superficially located tumours can be distinguished from tumours located in the deep by clinical examination. Tumours that are not attached to the muscular fascia are easily felt and moved in the subcutis, where they can be delimited from the surrounding tissue.

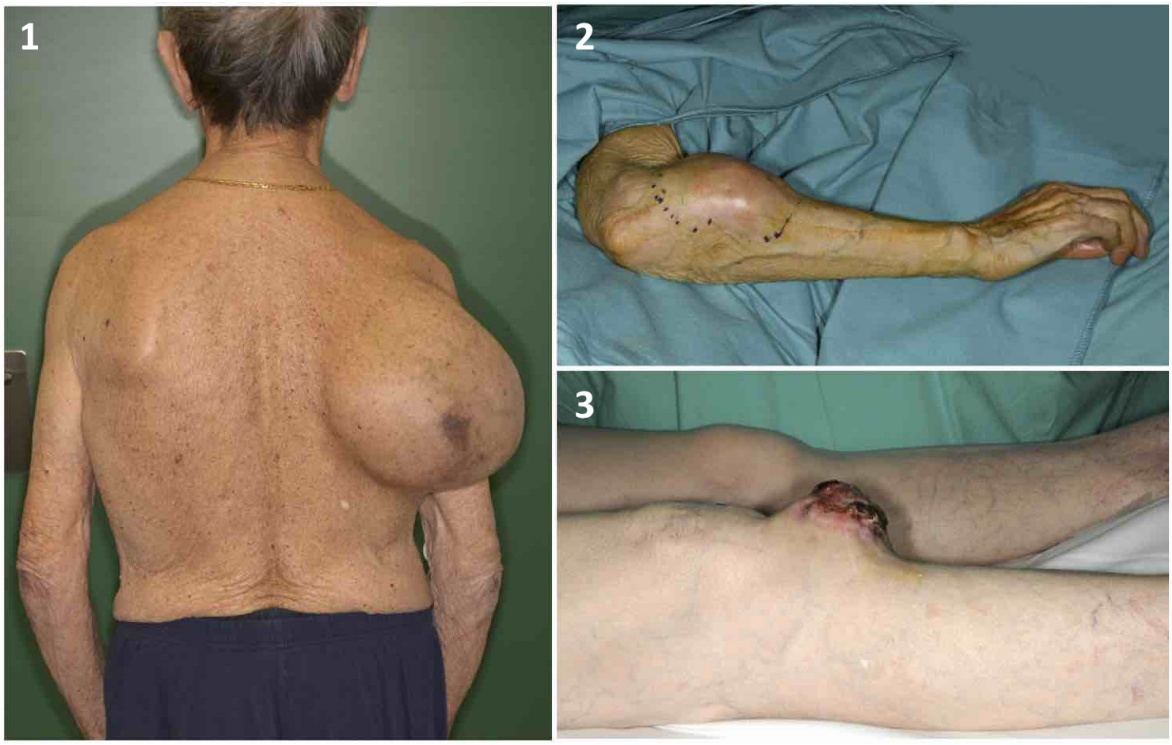

Figure 1 *Different clinical presentation of STS: Massive myxofibrosarcoma (G3) arising from the back of an 80 year old man (1). Myoxfibrosarcoma (G2) of the forearm in a woman aged 76 (2). Ulcerated myxofibrosarcoma (G3) on the right knee of a 70 year old woman (3).*

Tumours situated in the deep, however, seem to be fixed to the muscular fascia, cannot be moved within the subcutis and may present as non-definable swellings. The latter group is far more likely to actually represent a malignancy (6).

The most reliable factor for the differentiation between benign and malignant soft tissue swellings is the size. The larger the tumour, the more likely a malignant background is present. At the beginning, lumps larger than 5 cm were considered as being "worrying", meanwhile the limit has been lowered to 4 cm, based on large retrospective analyses (7).

Imaging

Imaging techniques are crucial in the diagnostic process and even more for planning the treatment of STS, as they constitute non-invasive methods. They give the doctor a clue about the actual location, size and possible invasion of adjacent structures. Sometimes, a distincition between different tumour entities is possible, though a histological confirmation only reinforces the tentative diagnosis. Ultrasound (US) may be used predominantly in a GP's practice, as it is cheap and easily available. The gold-standard, however, is *magneitc*

resoncance imaging (MRI) with contrast material, as this technique allows the distiction bewteen tumorous tissue and adjacent healthy structures. Moreover, together with *computed tomography scans* (CT-scans), MRI is used for tumour staging. The tumour's stage has an influence on further therapeutical management and eventually gives a hint on a patient's prognosis.

Depending on the presentation in T1- and T2-weighted sequences, some subgroups of STS may be identified. Fibrosarcomas, for example, have a medium signal intensity on T1 weighted images and a high signal intensity with intermittent low signal areas on T2 weighted sequences. On the other hand, larger synovial sarcomas are homogeneously low on T1 and heterogeneous on T2 weighed images (8).

The radiologic differentiation between lipoma, atypical lipomatous tumour (ALT) and lipsarcoma requires some experience. Whilst lipomas contain nearly a 100% fatty tissue, ALTs often contain an area without any fat. Moreover, ALTs may present with "pencil-like" septa within the mass. On the other hand, a feature typical for liposarcoma would be a lobulated fatty mass enchasing a dedifferentiated area. This area subsequently undergoes CT-guided biopsy, often revealing an underlying pleomorphic sarcoma.

Positron Emission Tomography (PET)-Scans allow the assessment of the tumour's bioactivity and therefore help to differentiate between benign and malignant lesions (9). Moreover, *PET-Scans* help to identify distant tumour foci, though especially in the lungs, conventional *CT-Scans* are still considered as gold-standard.

Preoperative imaging with *MRI* and/or *CT-Scans* of the lesion is also necessary in order to define possible vascular or neural involvement, resulting in altered surgial approaches.

Biopsy

After imaging, biospies constitute a crucial step in the managment of suspicious soft tissue lesions. A biopsy is best taken with incisions oriented along the skin tension lines overlying the suspected lesion, as this causes minimal contamination of the prospective operation field. The best approach is an incisional biopsy attempting minimal extension into adjacent tissue planes, whilst keeping in mind the need for appropriate tissue samples. Even if lesions are very small, have a long-lasting history and do not cause any pain, excisional biopsies should best be avoided (10). Although fine needle aspirations (FNAs) and needle biopsies

have the advantage of minimal contamination, the amount of tissue sample is limited and special diagnostic techniques as cytogenetics cannot be performed.
Biopsies can also be taken under *Ultrasound-, CT-* and *MRI*-guidance, especially in cases, where the lesion is located in the deep.

Grading and Staging

Grading

There are two grading systems mainly used for STS, namely the *NCI-system* by the United States National Cancer Institute and the *FNCLCC-system* provided by the French Fédération Nationale des Centres de Lutte Contre le Cancer (11, 12). The *NCI-system* uses a combination of histological subtype, pleomorphism, cellularity and mitotic rate (Ki69-index) to distinguish between grade 1 and 3. The distinction between grade 2 and 3 is dependent on the rate of necrosis. More than 15% of necrosis indicate a high cell turnover as well as an aggressive behaviour, wherefore these tumours are classified as grade 3 (11).
The *FNCLCC-system* combines three histological features, being the mitotic rate (Ki67-index), tumour differentiation and amount of necrosis. As the tumour differentiation is strongly associated with the histological subtype, the *FNCLCC-system* relinquishes the STS subtypes for their grading system. A score is calculated for each parameter by multivariate analysis. By addition of these three scores, the grade can be determined (12).

Staging

The *TNM-system* is useful to determine the extent of various malignancies. In case of STS, the T-variable is slighly different from other malignancies, at it describes the local spread of the tumour (i.e. size, superficial or deep location). The N- and M-variables are similar in case of STS and other malignant neoplasms. Table 1 outlines the *TNM-system* applicable to STS.
According to the *American Joint Committee on Cancer* (AJCC), the classification for STS combines information about tumour size, nodal status, metastasis and grade (13).

Primary Tumour (T)	
TX	Primary tumour not assessable
T0	No primary tumour evident
T1	Tumour < 5 cm
T1a	Superficial tumour < 5 cm
T1b	Deep tumour < 5 cm
T2	Tumour > 5 cm
T2a	Superficial tumour > 5 cm
T2b	Deep tumour > 5 cm
Regional lymph nodes (N)	
NX	Regional LN not assessable
NO	No regional LN metastasis present
N1	Regional LN metastasis
Distant Metastasis (M)	
M0	Absence of distant metastasis
M1	Distant metastasis

Table 1 TNM-system used to describe the local extent of soft tissue sarcomas.

With this classification, STS can be assorted into different anatomic stages and prognostic groups (13). There are 4 main stages (I – IV) and stage I as well as stage II are subdivided into IA, IB, IIA and IIB (see Table 2).

Stage	Primary Tumour	Regional LN	Metastasis	Grade
IA	1a	0	0	1, X
	1b	0	0	1, X
IB	2a	0	0	1, X
	2b	0	0	1, X
IIA	1a	0	0	2, 3
	1b	0	0	2, 3
IIB	2a	0	0	2
	2b	0	0	2
III	2a, 2b	0	0	3
	any	1	0	any
IV	any	any	M1	any

Table 2 Staging for soft tissue sarcomas according to the AJCC-classification.

Therapy

STS should be treated in a multidisciplinary approach, including orthopaedic as well as plastic surgeons, radiologists, pathologists, oncologists, radiotherapists and physiotherapists. Whichever approach might be chosen, the involvement of all disciplines is mandatory to archive the best outcome for each patient. Due to the fact that STS are a rare tumour entity, referrals to specialist centres should be encouraged. Several studies have demonstrated that the patient's prognosis is better when they are treated at hospitals with high case numbers, be it prostate cancer, bronchial carcinoma or STS (14, 15). A referral scheme for possible STS is depicted in Figure 2. Initially, a small lump may be best assessed by careful clinical examination and ultrasound. Instant *MRI* would constitute the imaging technique of choice for highly suspicous, large and/or ulcerated soft tissue masses. However, a possible delay until patients get an appointment for *MRI* should be taken into account (16).

In case of unsuspicious imaging and inconspicuous clinical appearance, the patient should be encouraged to observe the lump carefully and regular check-ups should be scheduled. As soon as imaging and/or clinical examination give any reason for concern, *MRI* with contrast agent has to be performed urgently, as the tumour's external appearance does not necessarily depict the actual size and extent. Soft tissue masses that are larger than 4 cm or located deep to the fascia should be referred directly to the specialist centre following *MRI*, as these tumours are rather malignant than benign (7). In case a tumour is smaller than 2 cm on *MRI* or ultrasound, an excision biopsy can be performed. An incision biopsy is appropriate in case a tumour is smaller than 4 cm – but already larger than 2 cm – on *MRI or ultrasound*. In the best case, the operation was curative and in the worst case, the procedure would count as a diagnostic biopsy of a STS.

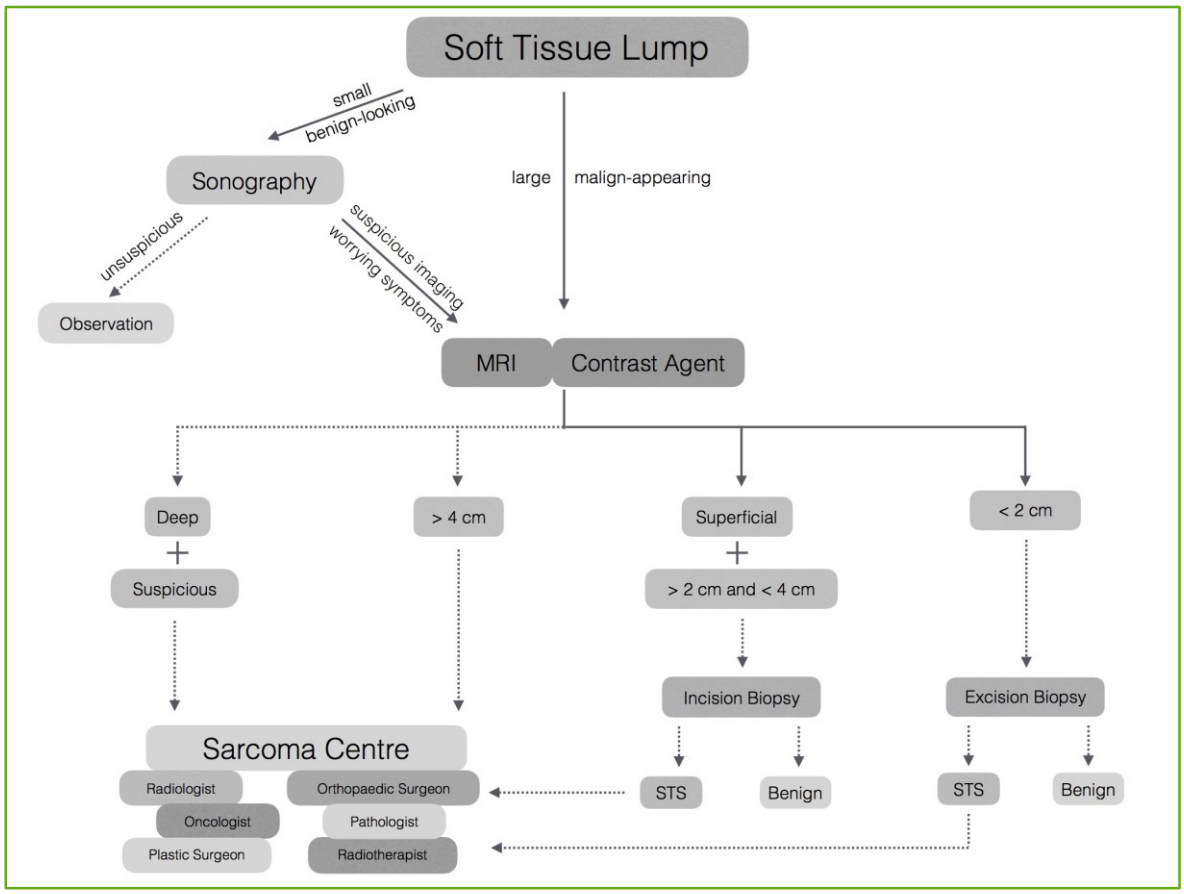

Figure 2 *Referral algorithm for worrying soft tissue lumps and bumps. Adapted from* Leithner et al. *(17).*

Surgery

By starting a journey into the past, the role of surgery in STS may be explained best. In the 1940s, local recurrences (LR) occurred in up to two thirds of patients treated for STS, whereas amputations resulted in a better prognosis (18). The conclusion was drawn that LRs develop depending on the type of surgery and, as a consequence, the more radical the procedure, the better the outcome. In the 1970s, Enneking and Simon realised the connection between clear surgical margins and LR. They developed a surgical approach comprising removal of a whole compartment once the tumour was located within the muscular layer. With their technique the rates of LR could be lowered to 15% – 20% (19). However, development of metastases and outcome could not be reduced significantly, as factors influencing LR and the development of metastases are different.

Nowadays, curative treatment models aim for R0 resections. Depending on the type of classification for resection margins, R0 resection margins are more or less close to the

histological tumour borders. R1 resections describe microscopically contaminated resection margins and in R2 resections, macroscopic bare tumour areas are present (20). Resections with wide surgical margins involve removal of the biopsy- and drain-tract as well as en-block resection of the tumour (Figure 3).

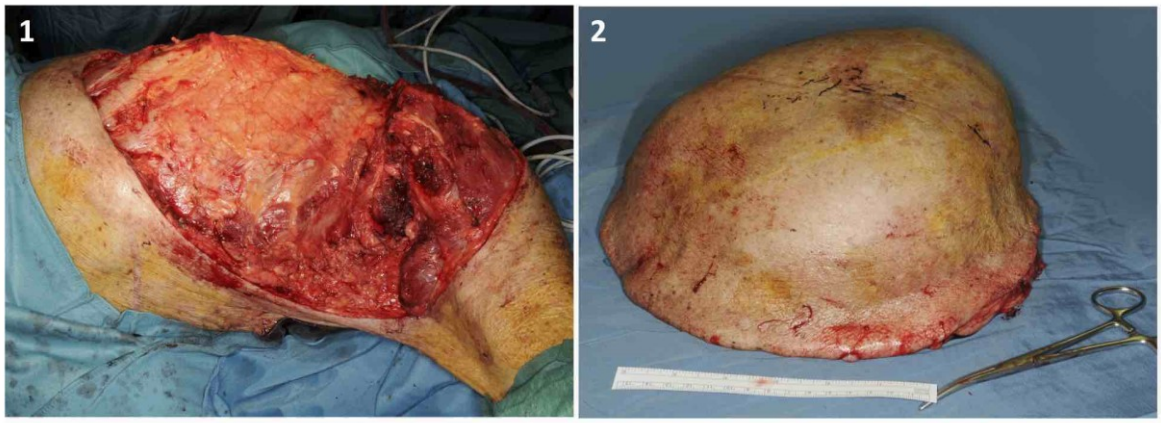

Figure 3 Operating field going down to the ribs and M. serratus anterior after tumour resection of a G3 myxofibrosarcoma in an 80 year old man (1). En-block resected specimen measuring about 21 cm (2).

In cases where STS are located within the compartment, functional compartmental resections are performed; muscles are not resected from insertion to origin, albeit preserving wide surgical margins. The remaining muscles result in a better functionality, thus improving the patient's quality of life (20). Once tumours invade the whole compartment, the muscles have to be resected from insertion to origin. Though compartmental resection is associated with worse functionality of the affected limb, it is the safest method provided the extremity can be preserved. Extracompartmental STS are resected together with a surrounding capsule of healthy tissue, e.g. periosteum or muscular fascia.

Wide resection including the skin sometimes renders primary wound closure impossible. In these cases, plastic reconstruction with skin grafts or muscular flaps may be necessary, as adequate wound closure is mandatory in order to avoid wound healing deficits and infections (Figure 4).

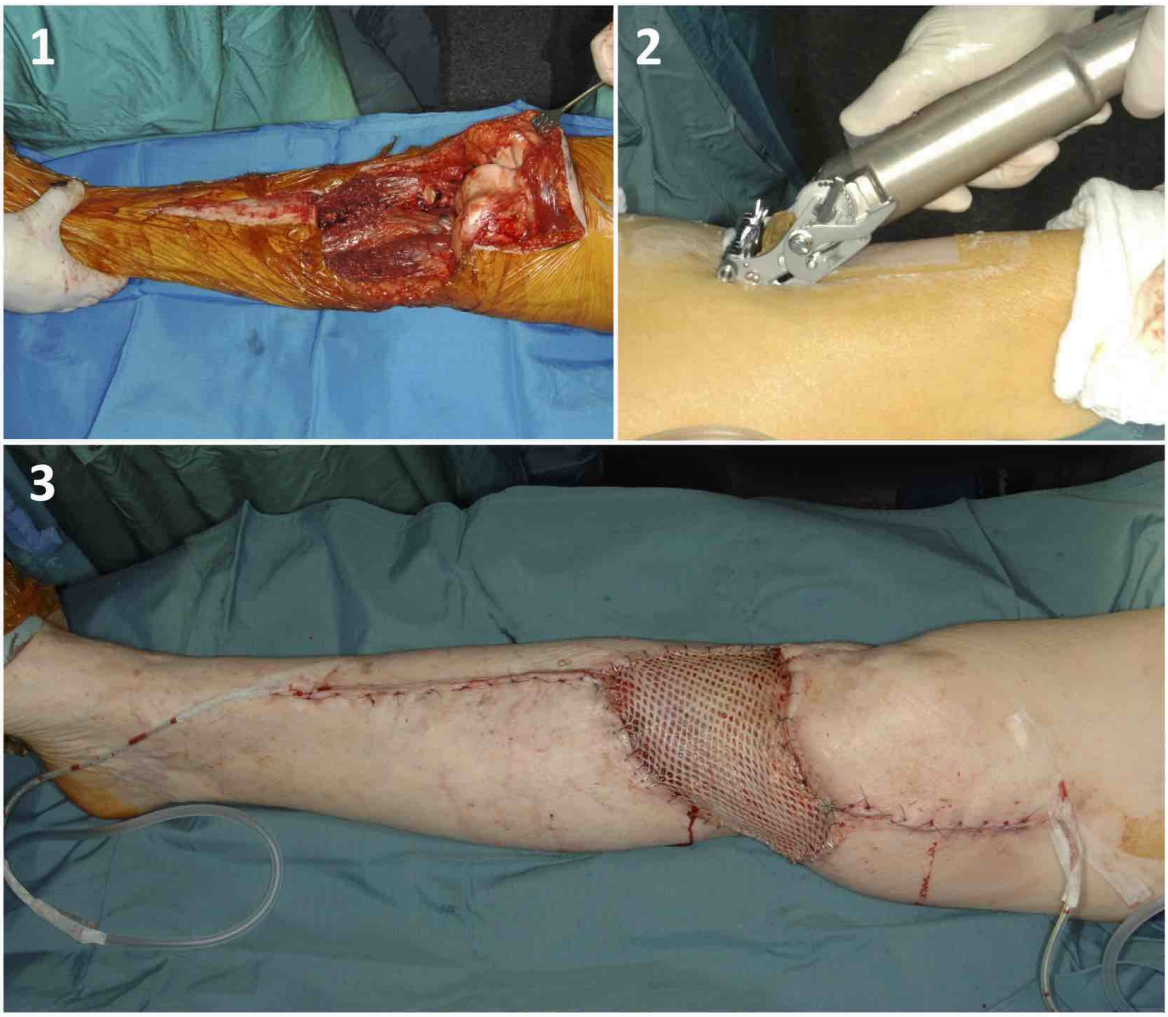

Figure 4 *Wide resection of a myxofibrosarcoma (G3) around the knee joint. Removal of proximal tibia and reconstruction with GMRS® Distal Femoral Replacement (1). Harvesting of skin graft from patient's left thigh (2). Wound defect covered with meshed skin graft before application of a VAC-System® (3).*

Amputations may be choosen in curative or palliative settings. The former is the case if wide surgical margins, even with neoadjuvant therapies, cannot be archived or in case the surgery would result in desperate limb function. The latter may be carried out in order to improve the patients' quality of life, stop severe bleedings or to prevent upcoming sepsis due to tumour necrosis (20).

Radiotherapy

The use of radiotherapy (RTX) in patients with STS is well established, as LR decreases dramatically when neoadjuvant or adjuvant RTX is used (21). Interestingly, several studies

have shown that the timing (i.e. neoadjuvant, adjuvant) as well as the technique (i.e. intraoperative RTX, external beam RTX, brachytherapy) have no significant influence on the patients' prognosis (21). This could be owing to the fact that local RTX will not have an effect in patients with micro-metastases. Whilst administration of adjuvant RTX following complete resection in low-grade tumours does not significantly decrease LR rates, a benefit is present when applied in high-grade STS (22). Thus, adjuvant RTX in patients with a G1 liposarcoma (now classified as „atypical lipomatous tumour") is not required.

Discussions whether RTX should be applied pre- or postoperatively are endless. Some centres prefer neoadjuvant RTX, as tumour shrinking fascilitates limb-sparing surgery and may be associated with lower rates of LR (23). However, postoperative complications as wound healing deficits may develop, due to damage of surrounding tissue by radiation. On the other hand, the administration of adjuvant RTX premises advanced tumour grades and unplanned excision margins, wherefore the LR rates may be higher in this group. Local dosage is lower in adjuvant RTX, as the irradiated field is significantly smaller in comparison to target volumes comprising the whole tumour (20). Moreover, the necessary delay between neoadjuvant RTX and definite surgery may potentially allow further tumour spread. Nevertheless, complications following either pre- or postoperatively administred RTX include nerve damage, fractures (especially femoral fractures in patients with STS of the thigh), tissue fibrosis and – in the worst case – induction of a secondary malignancy, as fibrosarcoma (24).

In patients where a limb salvage surgery is not feasible due to the large tumour extent, neoadjuvant RTX would lead to fibrosis of the mass – thus restraining the tumour cells' ability to proliferate – but would not cause any significant shrinkage.

Proton Beam Therapy

The advantage of proton beam therapy in comparison to conventional photon therapy is the possibility to exactly define the area where the maximal radiation will impinge. The point where ionised particles are most effective is called the *Bragg peak* (Figure 5).

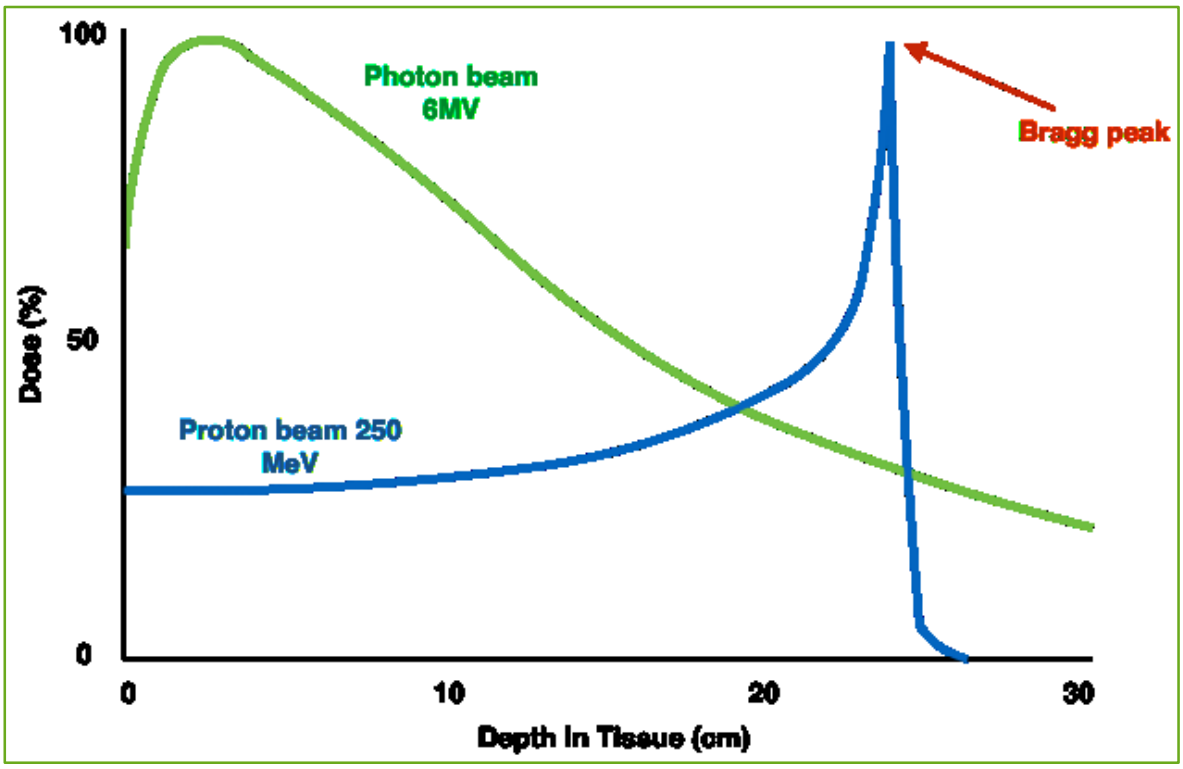

Figure 5 *Comparison of conventional photon beam therapy and proton beam therapy.*

Beneath this location, nearly no radiation is measurable (25).

As protons are relatively large massed particles, the lateral scattering is low. Protons with low energy penetrate just superficial layers, whereas high-energy protons can target masses located in the deep (25).

The *MedAustron* in Lower Austria will provide 3 treatment rooms and one for non-clinical research. Each room delivers RTX based on protons and carbon ions for patients with various malignancies, including brain tumours, chordomas, rhabdomyosarcomas and Ewing sarcomas.

Chemotherapy

Systemic chemotherapy (CTX) can be applied in neoadjuvant, adjuvant and palliative settings. In children and young adolescents, the use of adjuvant CTX is well established, whilst the utilisation in adult patients remains controversial (26). The literature is inconsistent regarding possible effects of adjuvant CTX on adult patient's prognosis. According to the *ESMO Clinical Practice Guidelines*, adjuvant CTX should be offered to patients with deeply located, high-grade tumours that are larger than 5 cm or patients participating in clinical trials (27).

Tumour response to neoadjuvant CTX is examined by studying specimens acquired during definite surgery histologically and by comparing images taken prior and after neoadjuvant CTX. The poor effect of adjuvant CTX on OS in STS patients may be again related to the fact that aggressive tumours have already dropped micro-metastases showing minor response to systemic CTX (20).

Chemotherapeutic drugs available for the palliative treatment of STS are listed in Table 3. Table 4 depicts special chemotherapeutic agents used depending on the histological subtype. Established combinations are shown in Table 5.

Single Dose							
Drug	Doxorubicin	Ifosfamide	Gemcitabine	Trabectedin	Epirubicin	Dacarbazine	Pazopanib
Dose	60 mg/m2	2000-3000 mg/m2	1200 mg/m2	1.5 mg/m2	69-90 mg/m2	250 mg/m2	800 mg
Administration	IV	IV (+ Mesna)	IV	IV	IV	IV	PO
Time	Over 1 – 3 days	Over 24 h or 5 days	Day 1 and 8	Over 24 h	Bolus	For 5 days	Continuously
Courses	Every 3 weeks	Every 3 weeks	Every 3 weeks	Every 3 weeks	Every 3 weeks	Every 3 weeks	

Table 3 Chemotherapeutic drugs used for treatment of soft tissue sarcomas (28).

Adjuvant CTX is mainly offered to patients with STS of the limbs, as they have the greatest benefit. However, the value of adjuvant CTX is not established for STS in the extremities (27).

Combinations				
Scheme	**AIM**	**AD**	**MAID**	
Drugs	Doxorubicin	Doxorubicin	Doxorubicin	Gemcitabine
	Ifosfamide	Dacarbazine	Ifosfamide	Docetaxel
	(+ Mesna)		Dacarbazine	(+ Growth Factors)
			(+ Mesna)	

Table 4 Chemotherapeutic agents preferred for treatment of distinct histological subtypes (28).

Limited metastatic disease only involves one organ, wherefore metastectomy may be taken into consideration. In cases with disseminated metastases, either an observational or palliative therapeutic approach may be chosen, including RTX, CTX and surgery. Standard CTX in metastatic disease consists of anthracyclines (e.g. Doxorubicin). The combination of several chemotherapeutic agents seems to have no significant effect on OS rates. In selected cases with a distinct histology, however, multiagent CTX may prove beneficial (see **Table 5**) (27).

By Histological Subtype					
Subtype	**Leiomyosarcoma**		**Angiosarcoma**		**Synovial Sarcoma**
Drugs	Gemcitabine	Temozolomide	Paclitaxel	Sorafenib	Ifosfamide
	Doxetaxel				Doxorubicin

Table 5 *Combinations of chemotherapeutic drugs used for soft tissue sarcoma treatment (28).*

Whilst the administration of concurrent RTX during a cycle of *Doxorubicin* is feasible, the combination of RTX and *Ifosfamide* is associated with severe toxicity (29). Better tumour-response can be archived by combining CTX-regimes (e.g. MAID) and RTX. However, side effects are common, wherefore experienced centers only should use these therapeutic models (29).

Hyperthermic Limb Perfusion

Isolated hyperthermic limb perfusion (ILP) can be useful in patients with locally advanced STS. TNF-alpha and melphalan are administered into the vessels feeding the tumour region in a high concentration. Nevertheless, the systemic effect is minor (20). Following ILP, in up to 85% of patients ablative procedures can be avoided and limb-salvage surgeries are possible due to excellent tumour response (30). There is no evidence that ILP alone prolongs OS. However, significantly better tumour response rates and local progression-free survival rates have been observed, especially when ILP and systemic CTX were used simultaneously (31).

Tumour Entities

In the "*Pathology and Genetics of Tumours of Soft Tissue and Bone*", the *World Health Organisation* (*WHO*) distinguishes between more than 50 different histological subtypes of

STS. Not only the histological picture, but also the biological behaviour among the various subtypes is different: Varieties concerning preferred age group, site of occurence, clincial presentation, treatment modalities and aggressivity are commonly found. This huge histologic variability is a major task also for experienced pathologists, as they have to use an array of diagnostic methods to distinguish between those entities.

Regarding the molecular genetics of STS, two main groups can be distinguished from each other. The first group comprises tumours with specific genetic aberrations and simple karyotypes, including translocations, mutations and numerical changes. The second group includes those tumours with unbalanced karyotypes and non-specific genetic alterations.

Table 6 gives an overview over the different types of benign and malignant soft tissue neoplasms defined by the *World Health Organisation (WHO)* in 2013. The next section will describe briefly the most common types of STS.

1. Adipocytic tumours	**Intermediate (rarely metastasising)**
Benign	Plexiform fibrohistiocytic tumour
Lipoma	Giant cell tumour of soft tissues
Lipomatosis	**Malignant**
Lipomatosis of nerve	Undifferentiated pleomorphic sarcoma
Lipoblastoma/Lipoblastomatosis	Undifferentiated pleomorphic sarcoma with giant cells
Angiolipoma	Undifferentiated pleomorphic sarcoma with prominent inflammation
Myolipoma	**4. Smooth muscle tumours**
Chondroid lipoma	Angioleiomyoma
Extrarenal angiomyolipoma	Deep leiomyoma
Extra-adrenal myelolipoma	Genital leiomyoma
Spindle cell/pleomorphic lipoma	Leiomyosarcoma
Hibernoma	**5. Pericytic (perivascular) tumours**
Intermediate (locally aggressive)	Glomus tumour
Atypical lipomatous tumour/Well differentiated liposarcoma	Myopericytoma
Malignant	**6. Skeletal muscle tumours**
Dedifferentiated liposarcoma	**Benign**
Myxoid liposarcoma	Rhabdomyoma (adult/fetal/genital type)
Round cell liposarcoma	**Malignant**
Pleomorphic liposarcoma	Embryonal rhabdomyosarcoma
Mixed-type liposarcoma	Alveolar rhabdomyosarcoma
Liposarcoma, not otherwise specified	Pleomorphic rhabdomyosarcoma
2. Fibroblastic/Myofibroblastic tumours	**7. Vascular tumours**
Benign	**Benign**
Nodular fasciitis	Haemangiomas
Proliferative fasciitis	Epithelioid haemangioma
Proliferative myositis	Angiomatosis
Myositis ossificans	Lymphangioma

Ischaemic fasciitis	**Intermediate (locally aggressive)**
Elastofibroma	Kaposiform haemangioendothelioma
Fibrous hamartoma of infancy	**Intermediate (rarely metastasising)**
Myofibroma/Myofibromatosis	Retiform haemangioendothelioma
Fibromatosis colli	Papillary intralymphatic angioendothelioma
Juvenile hyaline fibromatosis	Composite haemangioendothelioma
Inclusion body fibromatosis	Kaposi sarcoma
Fibroma of tendon sheath	**Malignant**
Desmoplastic fibroblastoma	Epithelioid haemangioendothelioma
Mammary-type myofibroblastoma	Angiosarcoma of soft tissue
Calcifying aponeurotic fibroma	**8. Chondro-osseous tumours**
Angiomyofibroblastoma	Soft tissue chondroma
Cellular angiofibroma	Mesenchymal chondrosarcoma
Nuchal-type fibroma	Extraskeletal osteosarcoma
Gardner fibroma	**9. Tumours of uncertain differentiation**
Calcifying fibrous tumour	**Benign**
Giant cell angiofibroma	Intramuscular myxoma
Intermediate (locally aggressive)	Juxta-articular myxoma
Superficial fibromatoses (Dupuytren disease, Mb. Ledderhose)	Deep ("aggressive") angiomyxoma
Desmoid-type fibromatoses	Pleomorphic hyalinising angiectatic tumour
Lipofibromatosis	Ectopic hamartomatous thymoma
Intermediate (rarely metastasising)	**Intermediate (rarely metastasising)**
Solitary fibrous tumour and haemangiopericytoma	Angiomatoid fibrous histiocytoma
Inflammatory myofibroblastic tumour	Ossifying fibromyxoid tumour
Low grade myofibroblastic sarcoma	Mixed tumour/Myoepithelioma/Parachordoma
Myxoinflammatory fibroblastic sarcoma	**Malignant**
Infantile fibrosarcoma	Synovial sarcoma
Malignant	Epithelioid sarcoma
Adult fibrosarcoma	Alveolar soft part sarcoma
Myxofibrosarcoma	Clear cell sarcoma of soft tissue
Low grade fibromyxoid sarcoma	Extraskeletal maxoid chondrosarcoma
Sclerosing epithelioid fibrosarcoma	PNET/Extraskeletal Ewing tumours
3. So-called fibrohistiocytic tumours	Desmoplastic small round cell tumour
Benign	Extra-renal rhabdoid tumour
Giant cell tumour of tendon sheath	Malignant mesenchymoma
Diffuse-type giant cell tumour	Neoplasms with perivascular epithelioid cell differentiation (PEComa)
Deep benign fibrous histiocytoma	Intimal sarcoma

Table 6 Histological classification of soft tissue sarcomas as defined by the World Health Organisation (WHO) in 2013.

Angiosarcoma

Angiosarcomas within the soft tissues, also known as malignant haemangioendothelioma or lymphangiosarcoma, have a peak incidence in the 7th decade of life. In children, this type of STS is extremely rare (32). The preferred location is the thigh, followed by upper extrimities, trunk, head and neck. In one third of patients, accompanying symptoms may be present, as anaemia, persistent haematoma or coagulopathy (32). Associations with *Mb. Recklinghausen* (Neurofibromatosis Type I) have been described, when angiosarcomas developed within malignant and even benign nerve sheath tumours (32). Moreover, angiosarcomas can occur as secondary malignancies following local radiotherapy for other tumours.

Histologically, angiosarcomas have a broad variety in presentation, making the diagnosis difficult, when based barely on microscopic appearance. Generally, angiosarcomas contain both spindle cell and epithelioid areas. In case of angiosarcoma, epithelioid cells tend to form rudmentary vascular channels with an irregular shape and infiltrative components (33). The prognosis for angiosarcomas is relatively poor, as they are highly aggressive tumours. LR develop in 20% of patients and due to metastatic spread, nearly 50% of the patients are expected to die within one year after initial diagnosis (32).

Epithelioid Sarcoma

In males, epithelioid sarcomas develop 2-times more often as compared with females (34). Patients are usually teenagers or young adults at time of diagnosis. The site of involvement includes fingers, hand, wrist, forearm, knee, lower leg, upper arm, ankle, foot and toes, with decreasing frequency (34). Under the microscope, epithelioid sarcomas are composed of spindle cells as well as eosinophilic epithelioid cells and often contain a pseudogranulomatous centre due to necrosis. Therefore, these sarcomas can be misdiagnosed as a benign lesion with granulomatous processes, like rheumatoid nodules (34).

Epithelioid sarcomas tend to spread alongside adjacent fascial planes, tendon- and nerve-sheaths, wherefore radical surgery with wide surgical margins is inevitable in order to archieve local tumour control (35). Up to 80% of patients will have developed a local recurrence after 10 years of initial diagnosis (36). About 40% of patients develop metastases, often following multiple local recurrences (36). In these cases, the prognosis is rather poor.

OS rates range between 50% and 80%, depending on other factors as tumour size, location and advanced age at diagnosis (34).

Fibrosarcomas

The diagnosis of a true adult fibrosarcomas should be made carefully, as several distinct subtypes resemble this tumour type. They occur in the adult population and are preferentially located in deep soft tissues of extremities, head and neck (37). Histologically, a typical herringbone architecture is visible (38). Adult fibrosarcomas metastasise mainly to the lungs and the axial skeleton, whereas lymph node metastases are rarely seen (39).

The synonym for myxofibrosarcoma is myxoid malignant fibrous histiocytoma. These tumours are typically found in the lower limbs, followed by the upper limbs. Myxofibrosarcomas of the hand, head/neck region, feet and trunk constitute a rarity (40, 41). Although the histological pattern is variable, some features are common for all myxofibrosarcomas, including a multinodular growth, fibrous septa and myxoid stroma. They often recur locally irrespective of tumour grade or location. However, the development of metastases – again predominantly to the lungs (Figure 6) – and low disease-specific survival rates are associated with high-grade tumours and a deep location (42, 43).

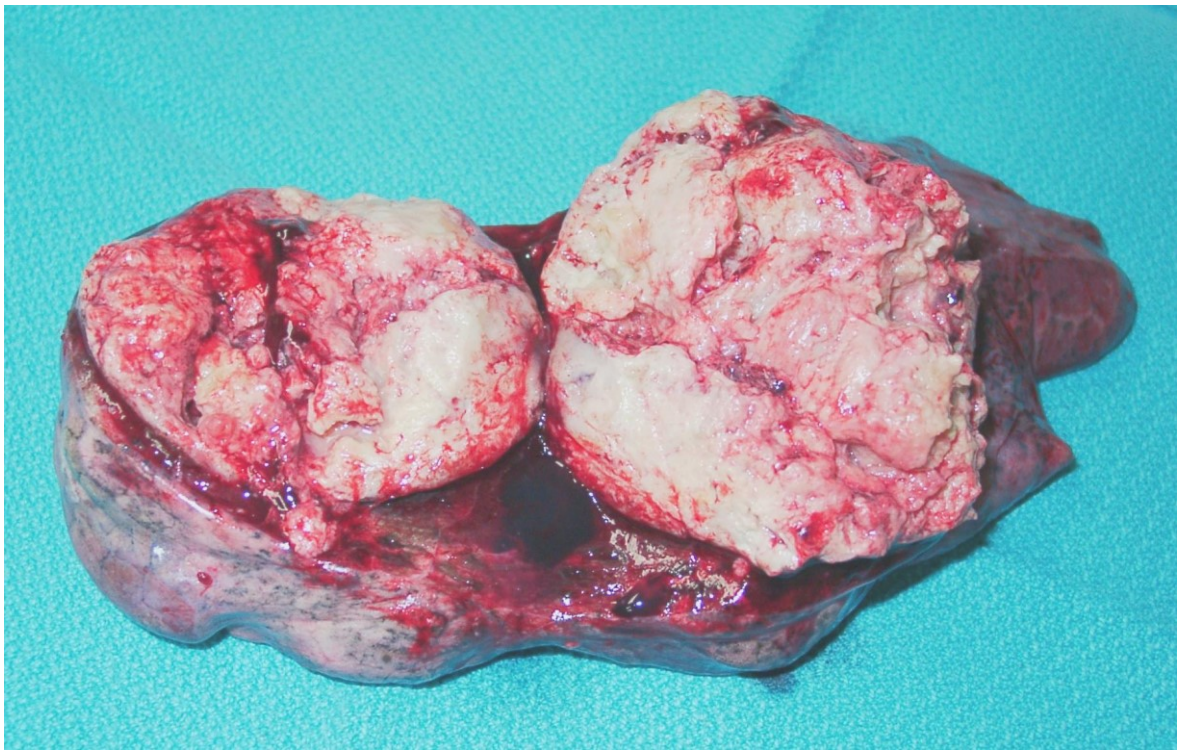

Figure 6 Sliced specimen for macropathological examination of a lung metastasis from a myxofibrosarcoma (G3).

Leiomyosarcoma

Leiomyosarcomas account for less than 15% of all limb soft tissue sarcomas, albeit representing the majority of retroperitoneal sarcomas. The preferred age groups are adults and older patients (44). Female patients predominate in retroperitoneal and pelvic locations, whereas for other sites both sexes are affected equally.

There are three distinct subgroups of leiomyosarcomas: The first one has been described above, where leiomyosarcomas occur within the retroperitoneum and pelvis. The second subgroup tends to originate from the *tunica muscularis* of big vessles (i.e. inferior vena cava, large veins of the lower limbs), whilst arteries are seldomly affected. The third group comprises leiomyosarcomas occuring in the limbs without any connection to the *tunica muscularis* (e.g. subcutaneous, intramuscular) (45).

Microscopically, leiomyosarcomas have a distinict pattern, with spindle cells crossing at about 90°. In large tumours, hypocellular, hyalinised and necrotic areas may be present (46).

The prognosis depends on the tumour size and site of involvement. Retroperitoneal sarcomas have a poor prognosis, as a complete resection is not feasible in most cases (47). Consequently, local recurrences and distant metastases occur early on. The prognosis in leimoyosarcomas of the extremites is better, yet depending on the extent of vascular involvement (48).

Liposarcomas

“Liposarcoma” in general circumscribes a variety of malignant tumours of adipocytic origin, like pleomorphic, myxoid and dedifferentiated liposarcoma.

Dedifferentiated liposarcomas are 3 times more likely to arise in the retroperitoneal space than in the extremities. Well-differentiated liposarcomas show a tendency to dedifferentiate, especially when located within the muscles or in the retroperitoneum (3). However, 90% of dedifferentiated liposarcomas arise “de novo”. It is supposed that the predominance of deeply and retroperitoneally located dedifferentiated liposarcomas is caused by late diagnosis of the tumours due to lack of symptoms. During this “delay”, well-differentiated liposarcomas might have the chance to dedifferentiate without being detected (3). The prognosis depends on the resectability of the tumour, with tumours located in the retroperitoneum having the worst prognosis. About 40% of dedifferentiated liposarcomas recur locally, whereas metastases are seen in 15-20% of cases (49).

A myxoid liposarcoma contains both non-lipogenic mesenchymal cells and small cells containing a big fatty vacuole with a marginalised nucleus (so-called signet-ring cells). The typical histopathological feature is an arborising vasculature, with vascular branches resembling crowfeet. Myxoid liposarcomas tend to arise in younger age groups than other malignant adipocytic tumours. Distant metastases occur in about 30% of patients, though the metastatic site is often atypical; even before spreading to the lungs, metastases in the retroperitoneum, the opposite limb and bones are commonly found (50).

Pleomorphic liposarcomas are predominantly located in the lower limbs, followed by the upper limbs. They are typically located within the muscular layers. This type of liposarcoma is rarely diagnosed in the retroperitoneal space, contrary to dedifferentiated liposarcoma. Histologically, the tumour consists of pleomorphic spindle-shaped tumour cells, pleomorphic lipoblast and a generally „colourful" tumour stroma (51).

Pleomorphic Sarcoma

In the past, pleomorphic sarcomas were termed as „malignant fibrous histiocytomas" together with other subtypes (52). This definition lead to some confusion, as pleomorphic sarcomas show no real histiocytic differentiation (53). Therefore, pleomorphic sarcomas constitute an exclusion diagnosis, in case supplementary diagnostic techniques have not lead to a clear result. Regarding clinical presentation, pleomorphic sarcomas behave like „typical" sarcomas. Predominantly, they are located in the extremities, arise in the deep and the incidence increases with age (54). Histologically, pleomorphic sarcomas have no distinct pattern, yet containing spindle-, giant- and round histiocyte-like cells (55). The prognosis is rather poor, with a 5-year OS rate of 50-60%. Moreover, about 5% of patients will present with distant metastases at initial diagnosis (54).

Rhabdomyosarcomas

There are three subtypes of rhabdomyosarcoma, namely the embryonal, alveolar and pleomorphic type.

Embryonal rhabdomyosarcomas are the commonest STS in children and adolescents. Tumours predominantly occur in the head and neck region (oropharynx, orbital cavity) and genitourinary system (prostate, bladder), whereas the extremities are affected in only 9% of cases (56). Symptoms are various, depending on the site of involvement. In general, complaints arise due to obstruction by the enlarging tumour. Under the microscope,

primitive mesenchymal cells differentiating into myocytes are present forming aggregates within loose myxoid mesodermal tissue (57). The prognosis depends on site and size of the tumour, histological grade and the patient's age, with a favourable outcome for younger patients (58).

The second subtype, termed alveolar rhabdomyosarcoma, may occur at any age and is preferentially located in the upper and lower limbs (59). Clinically, these tumours present as rapidly enlarging soft tissue masses and are often high-grade at time of diagnosis. Though alveolar rhabdomyosarcomas can be subdivided into further entitites depending on the histological impression, the baseline feature is round cells with myoblastic differentiation (60). Alveolar rhabdomyosarcomas are generally more aggressive than their embryonal counterpart (58). Younger age is again a positive prognostic factor (61).

Pleomorphic rhabdomyosarcomas arise almost exclusively in adults over 60, with a male predominance (62). Most tumours are located in the lower limbs and deep to the fascia, though – as for most STS – any site of presentation is possible. Histologically, pleomorphic rhabdomyosarcomas are composed of undifferentiated round to spindle-like shaped cells. The combination of highly aggressive and invasive tumours and advanced patient's age leads to an extremely poor prognosis (63).

Synovial Sarcoma

The translocation t(X;18) (p11;q11) is pathognomic for synovial sarcomas (64). Historically, the term "synovial sarcoma" was introduced based on the observation that some STS with indistinct histology were located adjacent to the joints. However, synovial sarcomas neither originate from synovial epithelium nor do they resemble synovium under the microscope (65). They account for about 10% of all STS and show a slight predominance in men (66). Most synovial sarcomas arise between 15 and 35 years of age, though every age group might be affected (66). Patients often describe a long-lasting history of complaints with varying symptoms.

Synovial sarcomas are predominantly found in the lower limbs, followed by upper limbs and trunk as well as the head and neck region. Especially the latter group has an extremely poor prognosis as compared to synovial sarcoma located in the extremities (67).

Monophasic, biphasic and dedifferentiated types of synovial sarcoma can be distinguished histopathologically (68). The biphasic type contains epithelial and spindle cells in changing

proportions, whereas the monophasic type is exclusively built up with spindle cells (68). In dedifferentiated synovial sarcomas, the picture is dominated by a high proportion of cells, many mitoses and necroses due to massive cell turnover (69).

Poor prognosis in synovial sarcoma is associated with advanced age, large tumour size, progressive disease at time of diagnosis and a high Ki67-index. Nearly half of patients will develop a local recurrence, most commonly after 2 years. About 40% of synovial sarcomas will metastasise, predominantly to the lungs, but also bones and lymph nodes (**Figure 7**). The 5-year survival-rate ranges between 36% and 76%, depending on the factors mentioned above (53).

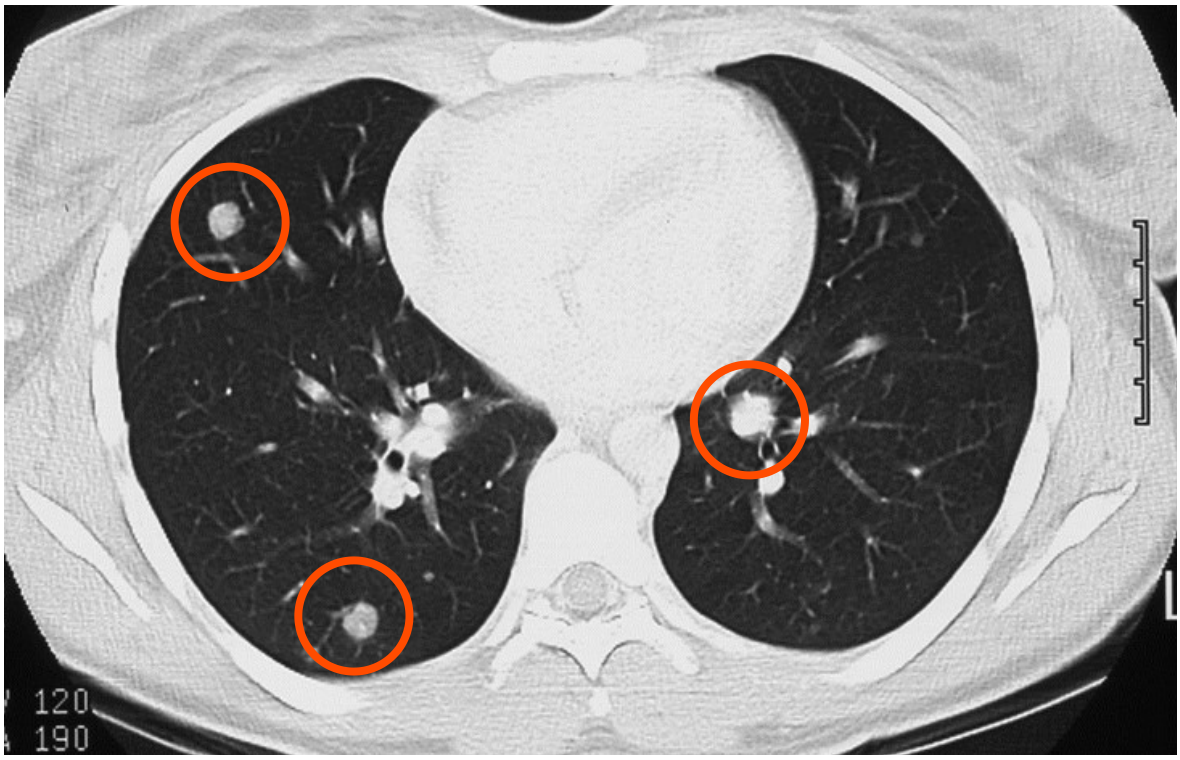

Figure 7 *CT-scan of the chest with 3 pulmonary metastases from a synovial sarcoma.*

Hereditary Tumour Syndromes

Though each hereditary tumour syndrome has a relatively low incidence, the presence of one of the following syndromes should be considered in some patients. They may develop tumours at an early age, initially present with cutaneus anomalies or develop several malignancies within their lifetime. Specific germline mutations are responsible for a pathognomic phenotype constituting an increased risk of developing STS. **Table 7** gives an

overview of various genes involved in the molecular pathogenesis of STS. Unsurprisingly, some of them are the main cause of the tumour syndromes mentioned below.

Protein	Clear Cell Sarcoma	Ewing's Tumour	Intimal Sarcoma	Intramuscular Myxoma	Leiomyosarcoma	Liposaroma	MFH	MPNST	Rhabdomyo-sarcoma	Spindle Cell Sarcoma	Synovial Sarcoma	Protein
AURKA					High							**AURKA**
c-Myc	High				High						High	**c-Myc**
Cyclin D1		High										**Cyclin D1**
Cyclin D2									High			**Cyclin D2**
Cyclin D3									High			**Cyclin D3**
CDK4			High			High			High	High		**CDK4**
p16	Low				Low							**p16**
FGFR1	High		High									**FGFR1**
FGFR4									High			**FGFR4**
Gs-alpha				Low								**Gs-alpha**
hMLH1					Low		Low	Low		Low		**hMLH1**
MEK4					High		High		High			**MEK4**
MCL1									High		High	**MCL1**
MDM2			High		High	High			High	High		**MDM2**
NF1								Low	Low			**NF1**
PTEN			Low		Low							**PTEN**
pRB					Low	Low						**pRB**
SRC					High						High	**SRC**
STAT6						High				High		**STAT6**
p53					Low							**p53**

Table 7 Overexpression (=high) and underexpression (=low) of proteins involved in the pathogenesis of STS (70).

Beckwith-Wiedemann Syndrome

The *Beckwith-Wiedemann syndrome* is caused by a mutation in the *insulin like growth factor 2* (IGF2) gene and is important mainly in childhood (71). Affected children are strikingly tall (i.e. >90th percentile) and present with macroglossia. Patients are at high risk of developing certain tumours, especially Wilm's tumour, hepatoblastoma and embryonal rhabdomyosarcoma (72). Therefore, careful screening is mandatory in order to diagnose possible malignancies at early stages.

Carney Complex

An inactivating mutation in the type 1-alpha regulatory subunit of the *PRKAR1A* gene causes the *Carney complex*. *PRKAR1A* encodes for the protein kinase A (73). The predominant symptom is an ACTH-independet Cushing's syndrome. Patients are at high risk of developing cardial myxomas as well as osteochondromyxomas (74).

Li-Fraumeni syndrome

The *Li-Fraumeni syndrome* is one of the best known hereditary tumour syndromes. An inactivating mutation in the *TP53* gene leads to impaired DNA repair mechanisms in the cell cycle (75). Due to malfunctioning p53 proteins, patients are at high risk of developing any type of cancer, from leukaemia over melanoma to bone- and soft tissue sarcoma (76). Familial clustering of malignant diseases should arouse attention and prompt genetic testing for *TP53* mutations.

Maffucci Syndrome

Unlike *Ollier's disease*, patients with *Maffucci syndrome* develop both intramedullary cartilagineous tumours and haemangiomas. The latter is missing in patients affected by *Ollier's disease* (77). The subcutaneously located haemangiomas are either present at birth or develop in early childhood. Though the vascular lesions have no metastatic potential, the histological subtype named spindle cell haemangioma has a high tendency to recur locally (78). In comparison to patients with *Ollier's disease*, individuals affected by *Maffucci syndrome* are at even higher risks of developing chondrosarcomas originating from one the innumerous chondromas (79).

Neurofibromatosis Type I

The *NF1* gene encodes for Neurofibromin 1 which is a negative regulator of the RAS/MAPK-pathway, an important cellular signalling track (80). Cutaneous abnormalities as neurofibromas and café-au-lait spots can help to confirm the diagnosis of *Neurofibromatosis type I*. Patients have a high risk of developing specific types of STS, as rhabdomyosarcomas, malignant peripheral nerve sheath tumours and undifferentiated pleomorphic sarcomas (81).

Retinoblastoma Syndrome

The *Retinoblastoma syndrome* almost inevitably leads to the development of binocular retinoblastoma, a malignant tumour arising from the embryonic neural retina. It is caused by an inactivating mutation of the *RB1* gene, encoding for the tumour surpressor protein RB (82). Fortunately, today most patients can be cured from their retinoblastoma predominantly by radiotherapeutic techniques. Secondary malignancies, however, are common in patients affected by this syndrome and include fiborsarcoma, Ewing's sarcoma, lymphoma, melanoma and leukaemia. These tumours may be located in and around the irradiated area (i.e. orbital cavity) or arise in completely different sites (83).

Aim of the Study

As mentioned above, STS constitute a rare tumour entity and have a broad spectrum of clinical presentation. The differentiation between benign and malignant soft tissue swellings is difficult and even with imaging techniques, a distinction may not be possible. Moreover, due to their invasiveness and high metastatic potential, surgery requires some experience and should only be performed at specialist centres. However, sometimes patients are referred to our institution after unplanned excision of the suspected mass. This inappropriate treatment is also called „whoops"-procedure, as surgeons may be a little bit startled when they receive the pathologist's report containing the diagnosis of STS (84).
Re-resections at special units are necessary, as there is an increased likelihood of local as well as systemic recurrence for intralesionally resected STS.
In the United Kingdom, a special campaign has been launched in order to raise the awareness of general practicioners (GPs) regarding benign and malignant soft tissue neoplasms. The „golf-ball"-project should remind every GP that soft tissue swellings exceeding 4.1 cm in size have an increased likelihood of being malignant and should therefore be referred to a specialist centre as soon as possible (7). In combination with the „Two-week-wait referral system", patients can be referred to a dedicated special unit no later than fourteen days after their first appointment at the GP's clinic. For the *National Health Services* (NHS) of the United Kingdom, this is an important way of referring patients as quickly as possible to a medical specialist, as there are usually intervals of about 6 months between the GP-visit and the first hospital appointment (4).

The Austrian health care system is much different, offering direct appointments with any type of medical doctor, including GPs, non specialised hospitals and specialist consultants, along with all positive and negative effects. In Austria, however, unplanned excisions are not less of an issue than in the United Kingdom (85).

Although unplanned excisions require re-resections and are believed to influence the patient's prognosis in a negative way, long-term studies have discovered something completely different: Patients with inadequate treatment prior to referral had a significantly better prognosis as compared with patients initially treated at specialist centers (86, 87). The reason for this apparent contradiction is discussed controversially in literature, but no satisfactory explanation has been found yet (87, 88).

One aim of this study is to determine which tumour-related features tempt physicians to perform an unplanned excision of a malignant soft tissue neoplasm. Furthermore, it will be evaluated in which way unplanned excisions influence the patient-specific treatment and prognosis.

Materials and Methods

427 patients with a soft tissue sarcoma treated between 1995 and 2015 at the *Department of Orthopaedic Surgery, University Hospital Graz, Austria* were included into the retrospective analysis. Gender, date of birth, date of last follow-up or death and cause of death and residential area were documented as epidemiologic parameters. Furthermore, the date of an unplanned excision ("whoops" procedure), where it had been performed, the time until definite surgery, duration of sypmtoms and presence of pain were documented. Tumour specific factors as superficial or deep location, size, histological grade, anatomical site, histological subtype and AJCC-classification were collected as well. Regarding treatment, detailed notes of the definite surgery were taken, including information about plastic or vascular reconstruction, amputation or implantation of reconstructive devices and resection margins. Type and date of the first postoperative complication requiring intervention were ascertained. Information about neoadjuvant, adjuvant and palliative chemotherapy (CTX) was collected together as were the names of the chemotherapeutics. Likewise, utilisation of neoadjuvant, intraoperative, adjuvant and palliative radiotherapy (RTX) was documented.

The follow-up schedule at our institution provides local *MRI scans* as well as abdominal ultrasound every 3 months for the first 3 years. Afterwards, appointments are scheduled every 6 months for the next 2 years. From that moment on, *MRI* scans and abdominal sonographies are carried out annually. At each appointment, either *chest X-rays* (*CXRs*) or *CT scans* of the thorax are performed.

The presence and date of diagnosis of lymph-node metastasis, local recurrence, primary metastasis and secondary metastasis were documented. Date of last follow-up or death and information about the cause of death were ascertained by reviewing patient records and the register of death updated by the *Department of Clinical Oncology* as well as by contacting patients or relatives by telephone.

Inclusion/exclusion criteria

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 and X^2-tests were calculated by including all 427 patients. Tumours were grouped

into the 3 categories according to their size: 0 – 5 cm, 5 – 10 cm and > 10 cm, corresponding with international standards.

Patients in whom a limb-salvage surgery had not been possible (n=35) and patients with metastatic spread at time of diagnosis (n=16) were excluded from the survival analysis, as their inclusion would have caused a bias.

Therefore, univariate and multivariate survival analyses were performed for 376 patients as well as separately for patients with (n=154) and without unplanned excisions (n=221).

Statistical Analysis

Microsoft Excel for Mac 2015, Version 15.17 and *IBM SPSS Statistics, Version 22.0* were used for data collection and statistical analysis. Results were accepted as significant with a p-value of 0.05 or below. The frequency of categorial variables was ascertained with descriptive analysis (e.g. rate of low-, intermediate and high-grade tumours). Explorative analysis was used to determine the mean, 95% confidence interval (CI), median, variance, standard deviation (SD), minimum and maximum of a continuous variable (e.g. size of the tumour). *Pearson's chi squared test* was used to evaluate the relationship between two categorial variables (e.g. gender vs. increase in size). OS rates were calculated with *Kaplan-Meier-Survivorship Curves*. Parameters were compared by using the *Log-Rank (Mantel-Cox) test* and again, results with a p-value less than 0.05 were accepted as significant.

The *Cox proportional hazard model* was used for univariate and multivariate analysis in order to determine the influence of different parameters on OS (e.g. impact of unplanned excisions on OS). The method used in multivariate analyis was *enter*, meaning that all variables were forced into the the equation in one step.

Results

Patient Characteristics

Of the 427 patients, 212 were females (49.6%) and 215 males (50.4%). The mean age was 59 years at time of definite surgery (range: 16 – 96 years).

58.5% of STS were located in the lower limbs (n=250), followed by upper limbs in 22.7% (n=97) and trunk in 15.7% of cases (n=67). Retro- and intraabdominal as well as head-and-neck tumours added up to 3% of all STS in our cohort (**Figure 8**).

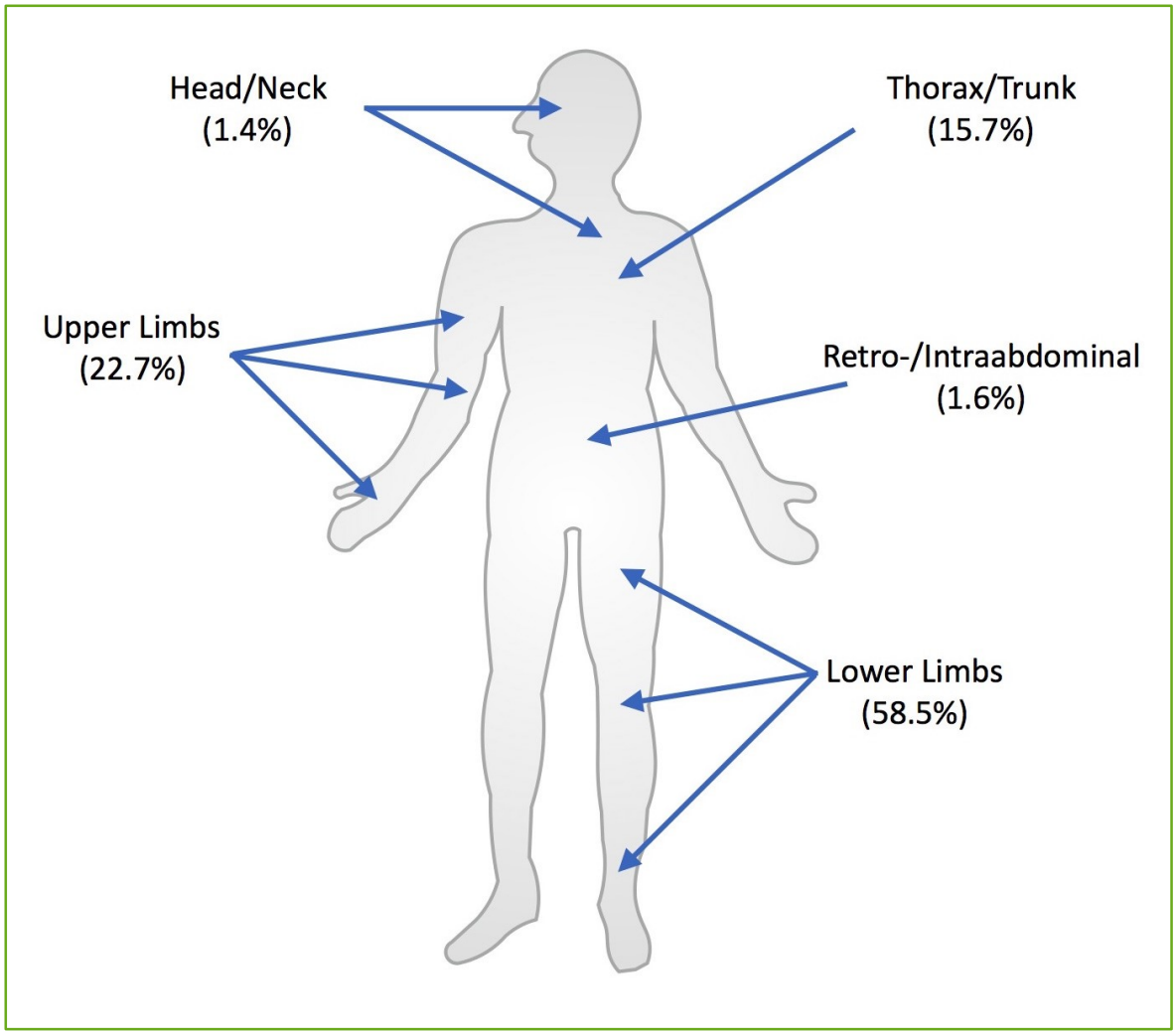

Figure 8 *Frequency of malignancies depending on anatomical region.*

In 77% of patients (n=325), a detailed history of complaint could be ascertained. The mean duration of symptoms prior to referral was 19.4 months (range: 1 – 360 months; 95%CI: 14.9 – 23.8 months). 64.3% of patients reported a recent increase in size of the tumour, whereas

the lesion had not changed in size in the remaining 116 patients (35.7%). In the majority of cases the tumour was non-tender to touch (65%), whilst 35% of patients presented with a painful swelling.

No significant difference for the duration of symptoms was present regarding gender (p=0.853, X^2-Test). Though statistically nonsignificant, patients over 60 presented with a considerably shorter mean duration of symptoms in comparison to younger patients (15.4 months vs. 23.9 months; p=0.073, X^2-Test). **Figure 9** depicts the mean duration of symptoms varying with increasing age of patients.

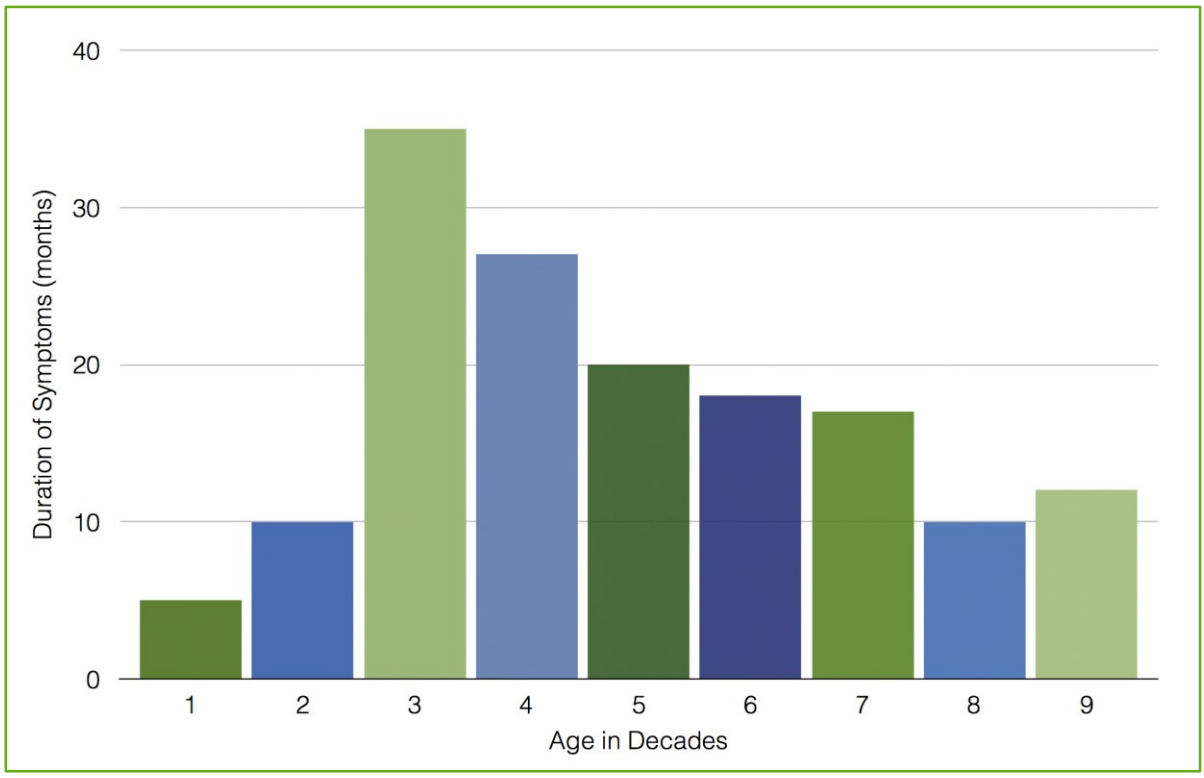

Figure 9 *Mean duration of symptoms changing with decades.*

Tumour Characteristics

The most common histological diagnosis was myxofibrosarcoma in 28,6% of cases (n=122), followed by liposarcoma in 24.6% (n=105), leiomyosarcoma in 11.5% (n=49), synovial sarcoma in 7.5% (n=32), malignant peripheral nerve sheath tumour in 3.3% (n=14) and fibrosarcoma in 0.7% of patients (n=3). The remaining 102 cases comprised miscellaneous subtypes, wherefore they were grouped into an „others“ category (23.9%).

260 patients presented with a high-grade tumour (G3) at time of diagnosis (60.9%), 88 patients with a low-grade tumour (G1; 20.6%) and 79 patients had an intermediate-grade tumour (G2; 18.5%).

Based on the AJCC-classification, 163 tumours were stage III (38.2%), 124 tumours stage IIA (29%) and 58 tumours stage IB (13.6%) at time of diagnosis. Furthermore, 43 patients initially presented with stage IIB tumours (10.1%), 21 had tumours staged IA (4.9%) and in 12 patients, tumours were stage IV (2.8%).

Exactly two thirds of STS were located deep to the muscular fascia (n=283) and one third of tumours superficially (n=144).

The average tumour size was 9.9 cm (range: 1 – 47 cm). When grouped into 3 categories, 120 tumours were smaller than 5 cm (28.1%), 169 STS were sized between 5.1 and 10 cm (39.6%) and 138 malignancies exeeded 10 cm in size (32.3%).

The size of the lesions significantly differed depending on the tumour site ($p<0.005$, X^2-Test). STS of the head and neck region were generally the smallest with an average size of 7.1 cm (SD +/- 4.1 cm), followed by lesions in the upper limbs with 7.3 cm (SD +/- 5 cm). Tumours of the thorax and trunk measured 7.8 cm (SD +/- 5.9 cm) on average, those located in the lower extremities 10 cm (SD +/- 6.6 cm) and retro- or intraabdominal STS were sized about 19.6 cm (SD +/- 13.3 cm; see Figure 10).

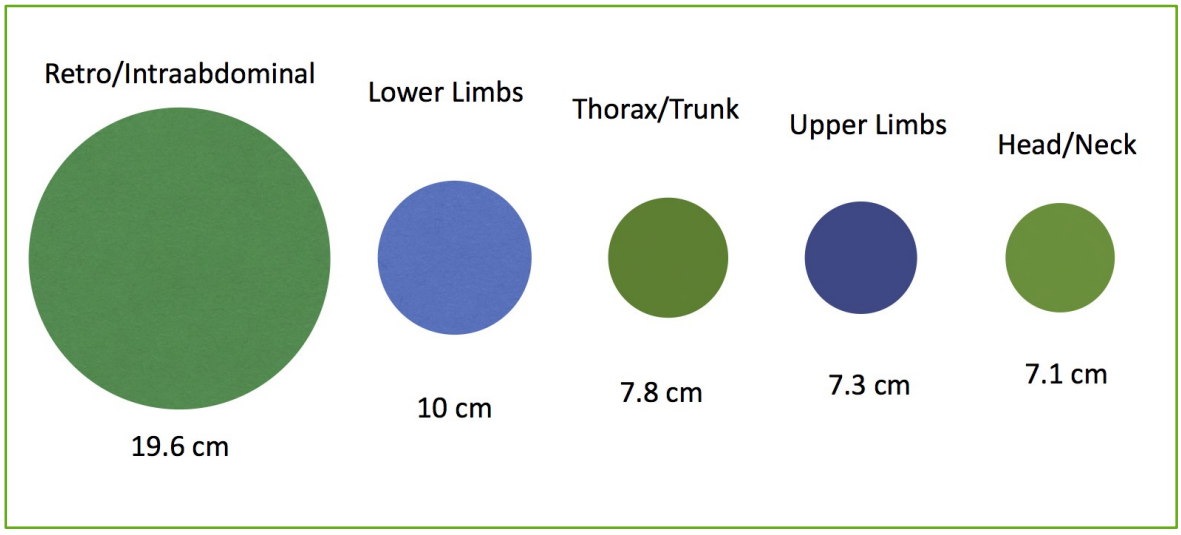

Figure 10 Tumour size varying with anatomical location.

Treatment Characteristics

Radiotherapy and Chemotherapy

The mean follow-up was 4.2 years, ranging from 0 to 16.9 years.

Radiotherapy (RTX) in general was used in 273 patients (63.9%). 4 patients received RTX in a neoadjuvant setting (1.5%), 5 patients underwent RTX intraoperatively (1.5%) and in 9 patients, RTX was applied with a palliative intent (3.3%). In the majority of patients, RTX was administred following surgical resection (n=255; 93.4%).

86 patients received some sort of chemotherapy (31.5%). Neoadjuvant CTX was used in 17 patients (19.8%), adjuvant CTX in 43 patients (50%) and palliative CTX in 12 patients (14%). 7 patients received both neoadjuvant and adjuvant CTX (8.1%) and 5 patients adjuvant and palliative CTX (5.8%). In additional 2 patients, chemotherapy was administred in neoadjuvant, adjuvant and palliative settings (2.3%). Details about the therapy are depicted in Figure 11.

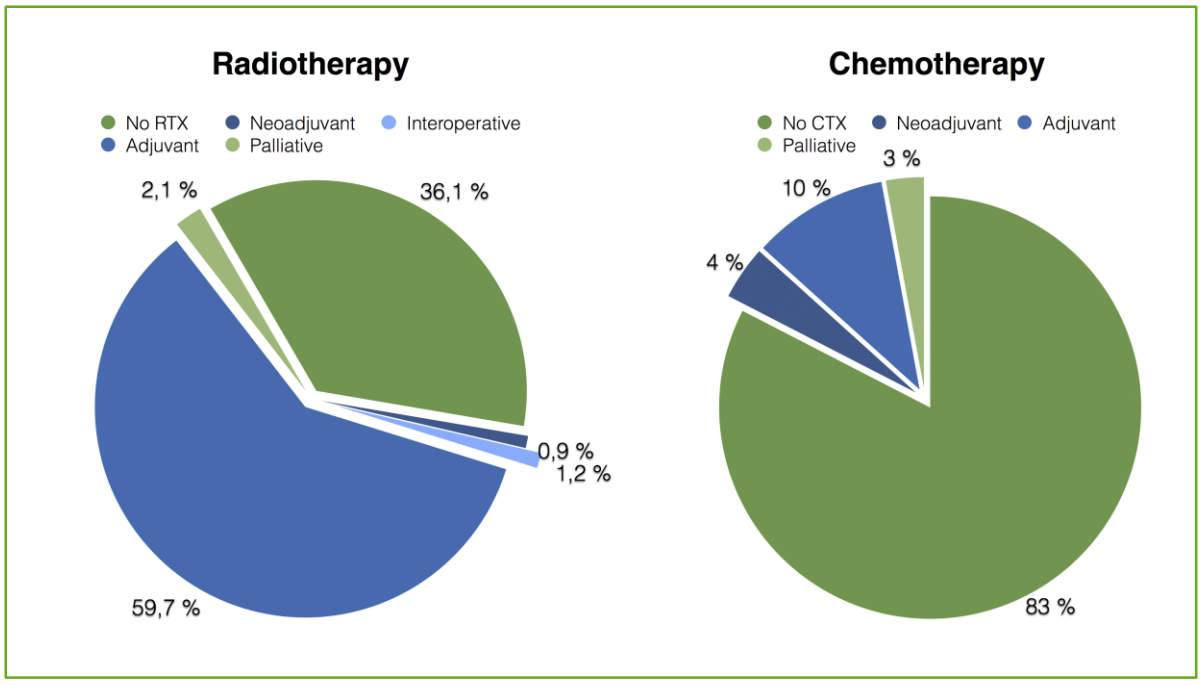

Figure 11 Piecharts depicting the administration of radiotherapy and chemotherapy.

Definite Surgery

261 patients were directly referred to our institution for definite surgery (61.3%), whereas in 165 patients, an unplanned excision had been performed prior to admission (38.7%). With

surgery at our institution, in 389 patients R0 resections could be archived (91.1%) whilst R1 resections occured in 38 patients (8.9%).

In 41.2% of patients (n=166), one or more plastic reconstructions became necessary, as split skin grafts and muscular flaps (Table 8).

Type	Percentage	Count
Biceps femoris flap	0,5%	1
Biological mesh (abdominal wall)	1,0%	2
Extensor digitorum flap	0,5%	1
Fascia latae strip	1,5%	3
Gastrognemic flap	3,6%	7
Gluteus flap	1,5%	3
Gracilis flap	2,0%	4
Latissimus dorsi flap	11,7%	23
M. sartorius transfer	3,1%	6
M. supraspinatus transfer	0,5%	1
Muscular flap	2,0%	4
Planta pedis flap	0,5%	1
Prolene mesh (abdominal wall)	4,6%	9
Prolene mesh (thoracic wall)	2,6%	5
Radialis flap	1,0%	2
Rectus abdominis flap	5,1%	10
Scapula flap	2,6%	5
Soleus flap	1,5%	3
Split skin	39,8%	78
Tibialis posterior flap	0,5%	1
Upper arm flap	2,6%	5
Vastus medialis flap	1,0%	2

Table 8 Frequency and type of plastic reconstruction performed during definite surgery.

In 24 patients, vascular reconstructions due to extensive tumour growth had to be carried out during definite surgery (5.7%).

In the vast majority of cases, a limb salvage surgery was feasible (n=389; 91.7%), whereas in 35 patients, an amputation had to be performed (8.3%).

In 9.7% of patients, reconstructive devices ranging from plates for bone stabilisation to complex tumour prostheses were used (n=41). Table 9 depicts the devices used for reconstruction. During follow-up, postoperative complications emerged in 22% of patients (n=94), including wound healing deficits, haematomas and flap necrosis.

Device	Count	Percentage
Total hip replacement	1	2,4%
Femoral plate	6	14,6%
Femoral allograft	1	2,4%
Femoral prosthesis	6	14,6%
Tibial plate	3	7,3%
Tibial prosthesis	1	2,4%
Humeral prosthesis	2	4,9%
Radial plate	1	2,4%
Radial allograft	1	2,4%
Ligament reconstruction	19	46,3%
Total	41	100,0%

Table 9 *Description of reconstructive devices used during definite surgery.*

Unplanned Excisions

In 38.7% of patients, unplanned excisions (or "whoops" procedures) had been performed prior to admission (n=165). The rate of unplanned excisions referred to our unit over the years among all patients treated for STS ranged between 26.8% and 56.3% (**Figure 12**).

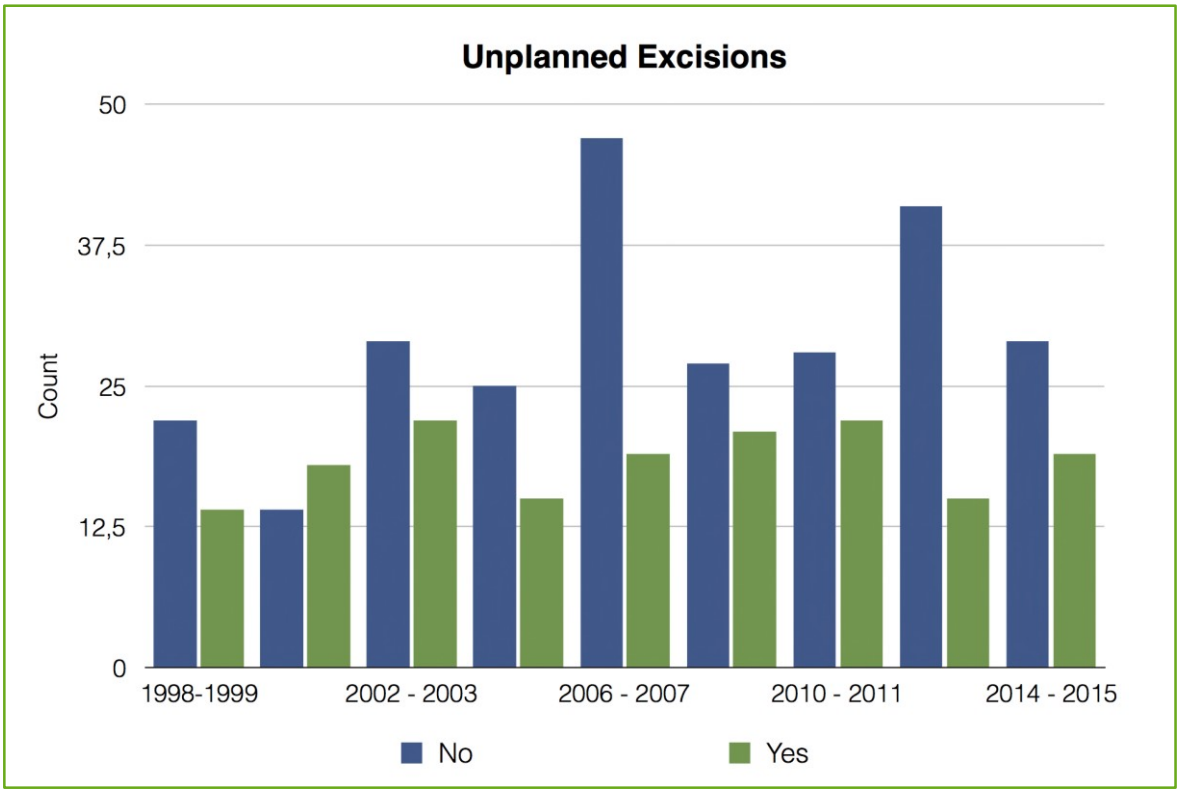

Figure 12 *Rate of unplanned excisions referred to our institution over the years.*

Unplanned excisions later referred to our institution had been performed in several counties of Austria (see Figure 13). The mean intervall between the unplanned excision and definite surgery at our department was 13.8 weeks (range: 0 – 384 weeks; 95%CI: 8.2 – 19.4 weeks; median 7.0 weeks).

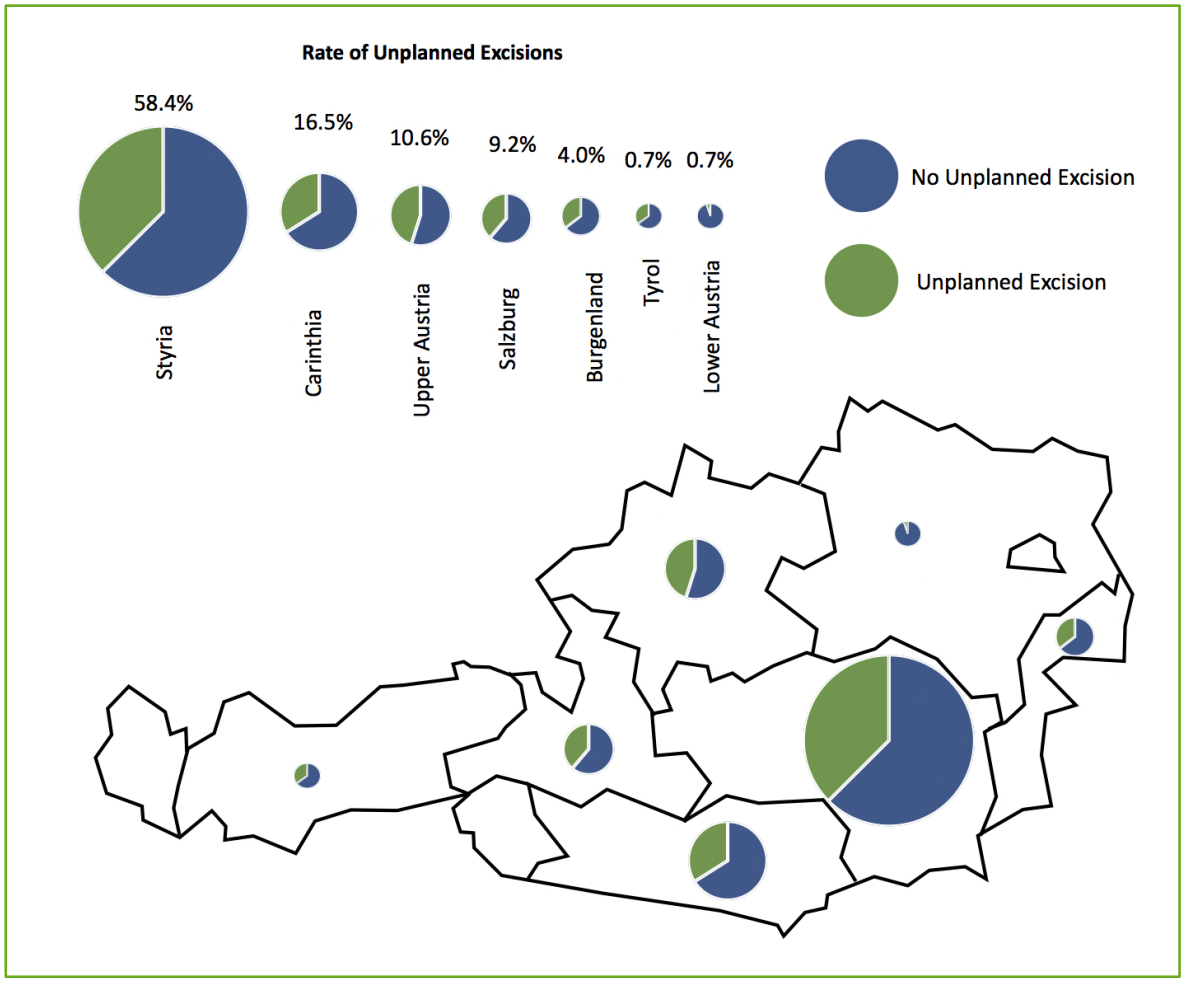

Figure 13 Distribution of unplanned excisions in Austria that had been referred to our institution afterwards.

Table 10 depicts patient-, tumour- and treatment-related characteristics depending on the presence of unplanned excisions.

		Unplanned Excision						p-value
		No	Percent	Yes	Percent	Total	Missing	
Patient Characteristics								
Gender	*Female*	137	64.6%	75	35.4%	212	1	0.157
	Male	124	57.9%	90	42.1%	214		
Age	*< 50 years*	67	54.5%	56	45.5%	123	1	0.067
	> 50 years	194	64%	109	36%	303		
Duration of Symptoms	*< 6.1 months*	134	73.2%	49	26.8%	183	106	**0.037**
	> 6.1 months	86	62.3%	52	37.7%	138		
Increase in size	*No*	80	69%	36	31%	116	102	0.797
	Yes	147	70.3%	62	29.7%	209		
Pain	*No*	145	67.8%	69	32.2%	214	98	0.246
	Yes	85	73.9%	30	26.1%	115		
Tumour Characteristics								
Histological Subtype	*Fibrosarcoma*	1	33.3%	2	66.7%	3	1	0.054
	Liposarcoma	76	72.4%	29	27.6%	105		
	Myxofibrosarcoma	76	62.8%	45	37.2%	121		
	Leiomyosarcoma	29	59.2%	20	40.8%	49		
	Synovial Sarcoma	14	43.8%	18	56.3%	32		
	MPNST	7	50%	7	50%	14		
	Others	58	56.9%	44	43.1%	102		
Location	*Head/Neck*	3	50%	3	50%	6	1	**0.003**
	Lower Limbs	172	69.1%	77	30.9%	249		
	Retro/Intraabdominal	4	57.1%	3	42.9%	7		
	Thorax/Trunk	36	53.7%	31	46.3%	67		
	Upper Limbs	46	47.4%	51	52.6%	97		
Depth	*Superficial*	62	43.1%	82	56.9%	144	1	**0.000**
	Deep	199	70.6%	83	29.4%	282		
Tumour Size	*< 5 cm*	41	34.2%	79	65.8%	120	1	**0.000**
	5.1 - 10 cm	109	64.9%	59	35.1%	168		
	> 10.1 cm	111	80.4%	27	19.6%	138		
Primary Metastasis	*No*	243	60.1%	162	39.9%	404	3	**0.018**
	Yes	18	81.8%	3	18.2%	22		
Grading	*G1*	61	69.3%	27	30.7%	88	1	0.198
	G2	45	57%	34	43%	79		
	G3	155	59.8%	104	40.2%	259		
AJCC-Classification	*IA*	14	51.9%	13	48.1%	27	1	**0.000**
	IB	46	79.3%	12	20.7%	58		
	IIA	41	33.3%	82	66.7%	123		
	IIB	28	65.1%	15	34.9%	43		
	III	121	74.2%	42	25.8%	163		
	IV	11	91.7%	1	8.3%	12		

		Unplanned Excision						p-value
		No	Percent	Yes	Percent	Total	Missing	
Treatment Characteristics								
Resection Margins	*R0*	229	59%	159	41%	388	1	**0.002**
	R1	32	84.2%	6	15.8%	38		
Prosthetic Devices	*No*	228	59.4%	156	40.6%	384	3	**0.009**
	Yes	33	82.5%	7	17.5%	40		
Amputation	*No*	234	60.2%	155	39.8%	389	3	**0.048**
	Yes	27	77.1%	8	22.9%	35		
Vascular Reconstruction	*No*	245	61.3%	155	38.8%	400	3	0.596
	Yes	16	66.7%	8	33.3%	24		
Plastic Reconstruction	*No*	187	72.5%	71	27.5%	258	3	**0.000**
	Yes	74	44.6%	92	55.4%	166		
Radiotherapy (general)	*No*	104	67.5%	50	32.5%	154	1	**0.046**
	Yes	157	57.7%	115	42.3%	272		
Adjuvant Radiotherapy	*No*	113	68.5%	52	31.5%	165	1	**0.015**
	Yes	148	56.7%	113	43.3%	261		
Chemotherapy (general)	*No*	202	59.4%	138	40.6%	340	1	0.118
	Yes	59	68.6%	27	31.4%	86		
Adjuvant Chemotherapy	*No*	225	61%	144	39%	369	1	0.753
	Yes	36	63.2%	21	36.8%	57		
Postoperative Complications	*No*	202	61.2%	128	38.8%	330	4	0.480
	Yes	58	62.4%	35	37.6	93		
Local Recurrence	*No*	235	61.5%	147	38.5%	382	1	0.754
	Yes	26	59.1%	18	40.9%	44		

Table 10 Patient-, tumour- and treatment-related parameters split by presence of unplanned excisions (n=427)

37.7% of patients with symptoms lasting for more than 6 months were treated inappropriately as compared to only 26.8% of patients with a shorter duration of symptoms (p=0.037, X^2-Test).

No significant results regarding the rate of unplanned excisions were either present for histological subtype (p=0.053, X^2-Test), grading (p=0.198, X^2-Test), tumours increasing in size (p=0.802, X^2-Test), painful masses (p=0.259, X^2-Test), gender (p=0.157, X^2-Test) or age over 50 years (p=0.067, X^2-Test).

Depending on the location, some patients were at higher risk of undergoing a "whoops" procedure than others (p=0.003, X^2-Test). More than half of patients with tumours located in the upper limbs had an unplanned excision (n=51 out of 97; 52.6%) and nearly half of

patients with STS of the thorax and trunk were treated inadequately (n=31 out of 67; 46.3%). From 6 patients with tumours in the head and neck region, 3 underwent a “whoops“ procedure (50%) and from 7 patients with retro- or intraabdominal STS, 3 were treated inappropriately (42.9%).

Of 249 patients with tumours located in the lower limbs, only 77 underwent an unplanned excision (30.9%).

STS located superficially were significantly more often treated inappropriately (n=82 out of 144; 56.9%) as compared with tumours situated beneath the muscular fascia (n=83 out of 282; 29.4%; p<0.005, X^2-Test).

The tumour stage according to the AJCC-classification was significantly associated with the likelihood of unplanned excision. Patients with early tumour stages (IA, IIA) underwent significantly more often unplanned excisions in comparison to patients with advanced disease (III, IV; p<0.005, X^2-Test).

Tumours smaller than 5 cm were significantly more often excised inappropriately (n=79 out of 120; 65.8%) than tumours sized between 5.1 and 10 cm (n=59 out of 168; 35.1%) or STS exceeding 10.1 cm (27 out of 138; 19.6%; p<0.005, X^2-Test). Moreover, patients with metastasis at time of diagnosis (n=3 out of 21; 14.3%) had been treated inadequately significantly less often in comparison to patients without metastatic spread (n=162 out of 405; 40%; p=0.018, X^2-Test).

56.4% of patients needed plastic reconstruction during definite surgery if they had undergone a “whoops“ procedure, in comparison to 28.4% of patients treated directly at our institution (p<0.005, X^2-Test). Limb-sparing surgery was not feasible in 10.3% of directly referred patients in comparison to 4.9% of patients who had undergone a “whoops“ procedure (p=0.048, X^2-Test). Moreover, prosthetic devices were significantly less often used in patients with an unplanned excision in comparison to patients, where initial treatment was carried out at our institution (4.9% vs. 12.6%; p=0.009, X^2-Test).

Patients with an unplanned excision were significantly more often treated with RTX (p=0.046, X^2-Test). From 165 patients with a „whoops“ procedure, RTX was used in 69.7% (n=115), in comparison to 59.6% of patients with direct referrals (n=157 out of 261).

Vascular reconstruction was not significantly more often necessary in patients treated inadequately prior to referral (p=0.596, X^2-Test). Interestingly, the rate of postoperative complications was not significantly increased in patients with a „whoops“ procedure as

compared to directly referred patients (22.3% vs. 21.5%; p=0.480, X^2-Test). Additionally, there was no difference whether patients had been primarily resected or had undergone re-resection regarding the interval until development of a postoperative complication (p=0.788; Log-Rank test).

Prognosis

The 5-year overall survival rate for all patients was 74.8% and the 10-year OS rate 59%. Of directly referred patients, 72.3% and 56.6% were alive after 5 and 10 years, in comparison to 78.8% and 62.6% of patients with a prior unplanned excision (p=0.118, Log-Rank test). Depending on the histological subtype, patients had a significantly altered prognosis according to the Log-Rank test. The best results emerged for patients with liposarcoma, whereas patients with MPNST and leiomyosarcoma had a relatively poor outcome (p=0.001, Log-Rank test; see **Figure 14**).

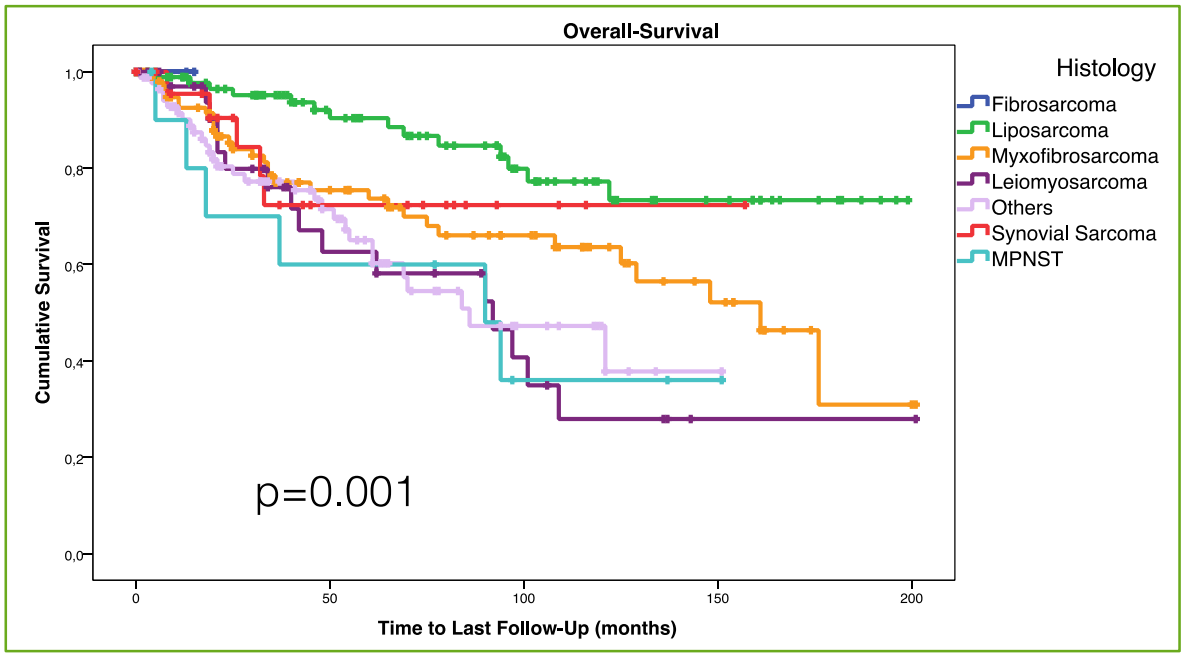

Figure 14 *Kaplan-Meier survivorship curve showing difference in overall survival depending on the histological subtype (n=376).*

85.6% and 72.6% of patients with G1- and G2-tumours were alive after 5 and 10 years, as compared with only 66.6% and 47% of patients with G3 tumours (p<0.005, Log-Rank test). Nonsurprisingly, the 5- and 10-year survival-rates for patients with early tumour stages was significantly better as compared with late AJCC-stages (p<0.005, Log-Rank Test; see **Figure 15**).

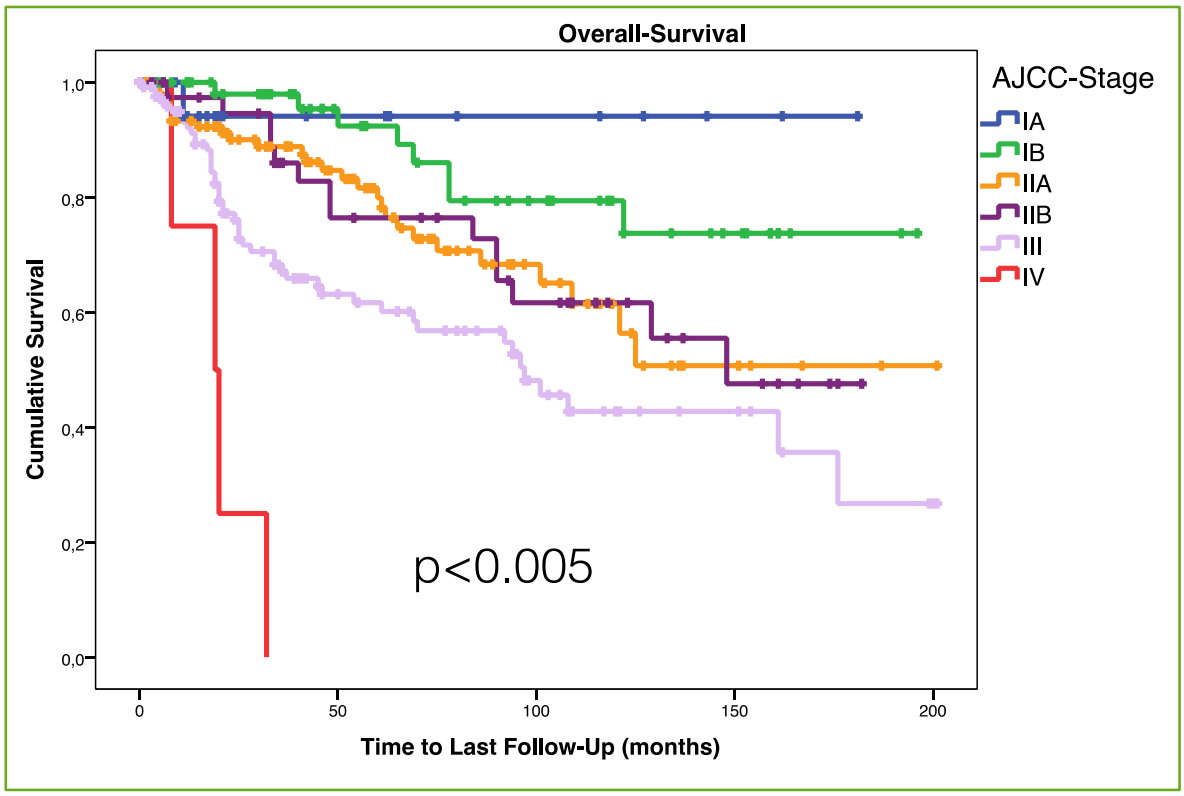

Figure 15 *Kaplan-Meier survivorship curve depicting the influence of the AJCC-stage on overall-survival (n=376).*

Patients who had been administered adjuvant CTX had a significantly poorer OS in comparison to patients without CTX (p=0.023, Log-Rank test). The 5- and 10-year OS rates for patients with adjuvant CTX were 60.3% and 37.9%, respectively. On the other hand, 77.6% and 62.7% of patients without any adjuvant CTX were alive 5 and 10 years after surgery (**Figure 16**).

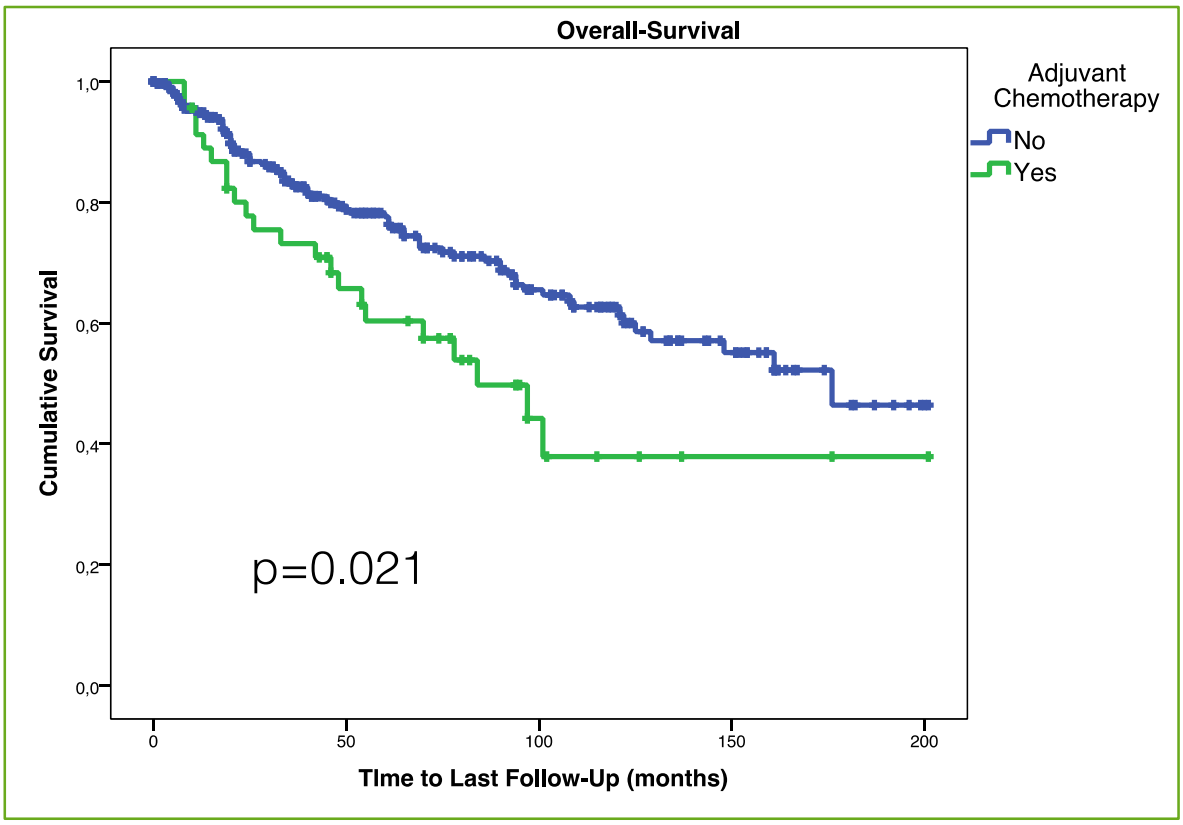

Figure 16 *Kaplan-Meier survivorship curve displaying patient's overall survival depeding on administration of adjuvant chemotherapy (n=376).*

Patients with a duration of symptoms less than 6 months had a significantly poorer prognosis in comparison to patients with symptoms exceeding 6.1 months according to the Log-Rank test (p=0.003). Whilst patients reporting a long duration of symptoms presented with a 5- and 10-year OS rate of 85.3% and 69.8%, only 65.9% and 51.8% of patients with a short history of complaint were alive at the same time points (**Figure 17**).

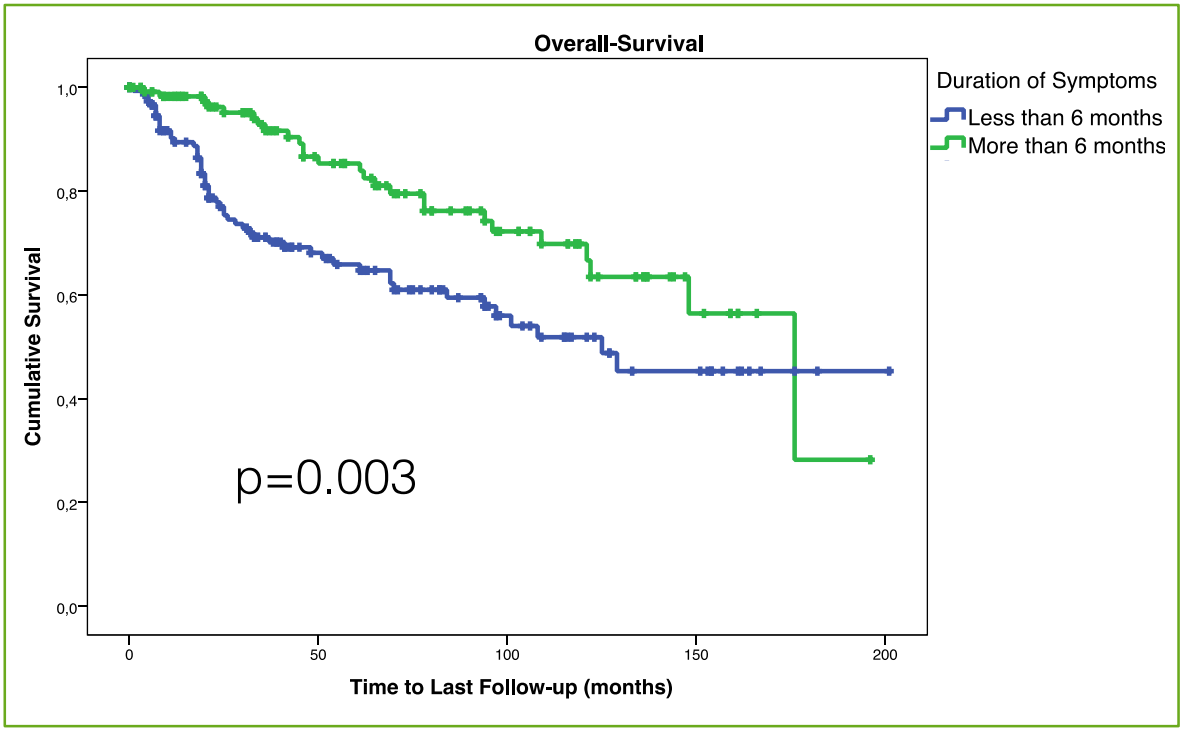

Figure 17 *Kaplan-Meier survivorship-curve showing the improved overall survival for patients with a duration of symptoms exceeding 6 months (n=282).*

Local recurrence occured in 10.1% of patients during follow-up (n=38 out of 376). There was no significant difference between the time-period until development of a LR and whether a prior unplanned excision had been performed or the patient had been directly referred (Student's T-test; p=0.732). Directly referred patients developed LR on average 32 months following surgery, in comparison to 37 months for patients with prior UE.

No significant results regarding OS were obtained using the Log-Rank test for the tumour site (p=0.508), administration of RTX (p=0.168), male or female sex (p=0.334), whether an unplanned excision had been performed (p=0.118; see **Figure 18**), local recurrence (p=0.456) and tumour size (p=0.175).

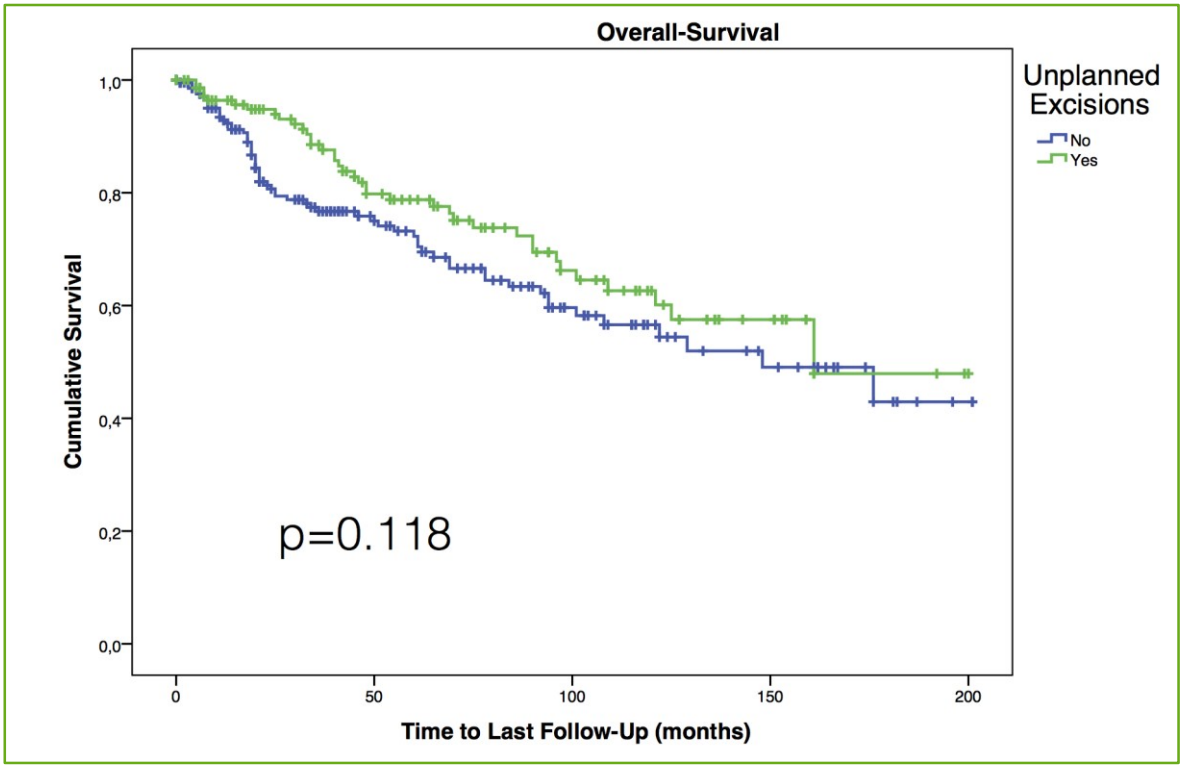

Figure 18 Kaplan-Meier Survivorship Curve depicting the tendency towards a better overall survival for patients with prior unplanned excision (n=376).

Univariate Analysis

Factors negatively influencing the patient's prognosis in univariate Cox-regression analysis were identified as age over 60 (p=0.003), short duration of symptoms (p=0.004), G3 tumours (p<0.005), administration of adjuvant chemotherapy (p=0.023) and local recurrence (p=0.020).

The detailed hazard ratios (HRs) and 95% confidence intervals (CIs) for all patients are depicted in Table 11.

Due to the fact that unplanned excision prior to referral showed a tendency towards better OS in univariate analysis, we decided to recalculate the univariate analysis separately for patients with (Table 12) and without unplanned excisions (Table 13).

		All Patients (n=376)			
		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Patient Characteristics					
Gender	*Female*	1			0.336
	Male	1,212	0,820	1,792	
Age	*< 60 years*	1			**0.003**
	> 60 years	1,885	1,247	2,850	
Duration of Symptoms	*< 6.1 months*	1			**0.004**
	> 6.1 months	0,499	0,312	0,798	
Increase in size	*No*	1			0.217
	Yes	1,343	0,841	2,160	
Pain	*No*	1			0.177
	Yes	0,723	0,451	1,158	
Tumour Characteristics					
Depth	*Superficial*	1			0.568
	Deep	0,887	0,588	1,338	
Tumour Size	*< 5 cm*	1			0.182
	5.1 - 10 cm	1,529	0,900	2,598	
	> 10.1 cm	1,635	0,950	2,815	
Grading	*G1/2*	1			**0.000**
	G3	2,431	1,582	3,734	
Treatment Characteristics					
Unplanned Excision	*No*	1			0.120
	Yes	0,727	0,486	1,087	
Resection Margins	*RO*	1			0.968
	R1	0,985	0,478	2,029	
Reconstructive Devices	*No*	1			0.580
	Yes	0,824	0,415	1,635	
Vascular Reconstruction	*No*	1			0.249
	Yes	0,589	0,239	1,450	
Plastic Reconstruction	*No*	1			0.458
	Yes	1,159	0,785	1,712	
Adjuvant Radiotherapy	*No*	1			0.171
	Yes	1,366	0,874	2,134	
Adjuvant Chemotherapy	*No*	1			**0.023**
	Yes	1,731	1,078	2,779	
Postoperative Complications	*No*	1			0.647
	Yes	0,898	0,567	1,422	
Local Recurrence	*No*	1			**0.020**
	Yes	1,756	1,095	2,816	

Table 11 *Univariate Cox-regression analysis depicting the influence of tumour-, patient- and treatment-specific features on overall survival of all patients (n=376).*

		Unplanned Excision (n=154)			
		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Patient Characteristics					
Gender	*Female*	1			0,381
	Male	1,349	0,69	2,64	
Age	*< 60 years*	1			0.229
	> 60 years	1,492	0,778	2,861	
Duration of Symptoms	*< 6.1 months*	1			**0.009**
	> 6.1 months	0,328	0,142	0,756	
Increase in size	*No*	1			0.547
	Yes	0,789	0,366	1,704	
Pain	*No*	1			0.264
	Yes	0,596	0,24	1,478	
Tumour Characteristics					
Depth	*Superficial*	1			0.498
	Deep	0,801	0,422	1,522	
Grading	*G1*	1			0.096
	G2/3	1,853	0,896	3,835	
Tumour Size	*< 5 cm*	1			0.348
	5.1 - 10 cm	1,271	0,590	2,734	
	> 10.1 cm	1,838	0,804	4,203	
Treatment Characteristics					
Resection Margins	*R0*	1			0.855
	R1	1,204	0,165	8,815	
Reconstructive Devices	*No*	1			0.370
	Yes	0,403	0,055	2,946	
Vascular Reconstruction	*No*	1			0.663
	Yes	0,728	0,175	3,033	
Plastic Reconstruction	*No*	1			0.820
	Yes	1,08	0,558	2,089	
Adjuvant Radiotherapy	*No*	1			0.064
	Yes	2,287	0,952	5,491	
Adjuvant Chemotherapy	*No*	1			0.078
	Yes	1,98	0,927	4,228	
Postoperative Complications	*No*	1			0.747
	Yes	0,884	0,417	1,874	
Local Recurrence	*No*	1			**0.012**
	Yes	2,474	1,225	4,998	

Table 12 *Univariate Cox-regression analysis for patients with unplanned excisions (n=154) regarding to overall-survival.*

		No Unplanned Excision (n=221)			
		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Patient Characteristics					
Gender	*Female*	1			0.396
	Male	1,237	0,757	2,023	
Age	*< 60 years*	1			**0.007**
	> 60 years	2,115	1,22	3,628	
Duration of Symptoms	*< 6.1 months*	1			0.141
	> 6.1 months	0,653	0,371	1,151	
Increase in size	*No*	1			0.060
	Yes	1,787	0,976	3,27	
Pain	*No*	1			0.376
	Yes	0,778	0,446	1,357	
Tumour Characteristics					
Depth	*Superficial*	1			0.541
	Deep	0,835	0,468	1,489	
Grading	*G1/2*	1			**0.000**
	G3	3,172	1,855	5,425	
Tumour Size	*< 5 cm*	1			0.612
	5.1 - 10 cm	1,483	0,677	3,247	
	> 10.1 cm	1,325	0,601	2,919	
Treatment Characteristics					
Resection Margins	*R0*	1			0.690
	R1	0,852	0,388	1,87	
Reconstructive Devices	*No*	1			0.794
	Yes	0,906	0,431	1,905	
Vascular Reconstruction	*No*	1			0.243
	Yes	0,5	0,156	1,601	
Plastic Reconstruction	*No*	1			0.164
	Yes	0,431	0,863	2,373	
Adjuvant Radiotherapy	*No*	1			0.573
	Yes	1,165	0,685	1,983	
Adjuvant Chemotherapy	*No*	1			0.112
	Yes	1,64	0,891	3,019	
Postoperative Complications	*No*	1			0.772
	Yes	0,918	0,513	1,641	
Local Recurrence	*No*	1			0.389
	Yes	1,331	0,695	2,549	

Table 13 *Univariate Cox-regression analysis depicting the infuence of various parameters on overall-survival of directly referred patients (n=221).*

For patients with an unplanned excision, univariate Cox-regression analysis revealed a short duration of symptoms (p=0.009) and local recurrences (p=0.012) as negative prognostic factors. Nonsignificant factors turned out to be tumour size (p=0.348), depth (0.498), G3 tumours (p=0.096), adjuvant CTX (p=0.078), adjuvant RTX (p=0.064), pain (p=0.264), increase in size (p=0.547), postoperative complications (p=0.747), location of the tumour (p=0.337), resection margins (p=0.855), plastic reconstruction (p=0.820) and gender (p=0.381).

The prognosis of patients referred directly to our institution was significantly influenced by age > 60 (p=0.007) and G3 tumours (p<0.005) according to univariate Cox-regression analysis. Neither gender (p=0.396), plastic reconstruction (p=0.164), resection margins (p=0.690), postoperative complications (p=0.772), a short duration of symptoms (p=0.141), increase in size (p=0.060), pain (p=0.376), adjuvant RTX (p=0.573), adjuvant CTX (p=0.112), depth (p=0.541), local recurrence (p=0.389) nor tumour size (p=0.612) had a significant influence on the patient's prognosis.

Multivariate Analysis

The same approach as for univariate analysis was also chosen for multivariate analyses (i.e. calculations including all patients, as well as separate calculation for inadequately treated patients and direct referrals).

Short duration of symptoms (p=0.011), G3 tumours (p<0.005) and age over 60 years (p=0.038) significantly influenced the prognosis of all patients in multivariate Cox-regression analysis in a negative way (see Table 14).

		All patients (n=376)			
		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Age	*< 60 years*	1			**0.038**
	> 60 years	1,634	1,026	2,601	
Duration of Symptoms	*< 6.1 months*	1			**0.011**
	> 6.1 months	0,53	0,324	0,867	
Tumour Size	*< 5 cm*	1			0.671
	5.1 - 10 cm	0,806	0,432	1,503	
	> 10.1 cm	1,062	0,644	1,753	
Grade	*G1/2*	1			**0.000**
	G3	3,174	1,872	5,383	
Unplanned Excision	*No*	1			0.147
	Yes	0,691	0,419	1,139	
Postoperative Complications	*No*	1			0.058
	Yes	0,585	0,337	1,018	
Adjuvant Radiotherapy	*No*	1			0.682
	Yes	0,899	0,542	1,493	
Local Recurrence	*No*	1			0.085
	Yes	1,633	0,935	2,852	

Table 14 *Multivariate Cox-regression analysis concerning overall-survival for all patients (n=376).*

For patients with an unplanned excision, a short duration of symptoms (p=0.020), G3 tumours (p=0.007) and development of local recurrences (p=0.002) turned out as significant factors in multivariate Cox-regression analysis (**Table 15**). For the remaining 221 patients treated adequately, G3 tumours (p<0.005) and age over 60 years (p=0.009) were associated with a poor outcome (see **Table 16**).

		Unplanned Excision (n=154)			
		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Age	*< 60 years*	1			0.532
	> 60 years	1,299	0,572	2,951	
Duration of Symptoms	*< 6.1 months*	1			**0.020**
	> 6.1 months	0,347	0,142	0,849	
Tumour Size	*< 5 cm*	1			0.865
	5.1 - 10 cm	0,746	0,253	2,2	
	> 10.1 cm	0,791	0,257	2,436	
Grade	*G1/2*	1			**0.007**
	G3	4,791	1,526	15,036	
	Yes				
Postoperative Complications	*No*	1			0.497
	Yes	0,689	0,235	2,017	
Adjuvant Radiotherapy	*No*	1			0.121
	Yes	2,244	0,809	6,225	
Local Recurrence	*No*	1			**0.002**
	Yes	4,867	1,764	13,422	

Table 15 *Multivariate Cox-regression analysis for patients with unplanned excisions (n=154) regarding overall-survival.*

		No Unplanned Excision (n=221)			
		HR	95%CI		p-value
			Lower Limit	Upper Limit	
Age	*< 60 years*	1			**0.009**
	> 60 years	2,223	1,217	4,063	
Duration of Symptoms	*< 6.1 months*	1			0.247
	> 6.1 months	0,706	0,392	1,273	
Tumour Size	*< 5 cm*	1			0.498
	5.1 - 10 cm	0,659	0,277	1,568	
	> 10.1 cm	1,12	0,627	2,001	
Grade	*G1/2*	1			**0.000**
	G3	3,827	1,965	7,453	
	Yes				
Postoperative Complications	*No*	1			0.122
	Yes	0,591	0,303	1,151	
Adjuvant Radiotherapy	*No*	1			0.094
	Yes	0,575	0,301	1,099	
Local Recurrence	*No*	1			0.950
	Yes	1,025	0,475	2,21	

Table 16 *Multivariate Cox-regression analysis with regard to overall-survival of patients who had been directly referred (n=221).*

Discussion

Soft tissue sarcomas constitute a rare tumour entity and comprise over 50 different histological subtypes. Each subtype has a more or less varying biological behaviour, thus affecting the patient's prognosis. Wide surgical margins are mandatory in order to obtain local – and as a consequence – systemic control of the disease. Depending on the local tumour extent and its anatomical location, the surgical approach may be difficult and necessitates vascular, plastic and anatomical reconstruction. In this context, surgeons should have a broadly based knowledge in surgical oncology, orthopaedics and reconstructive surgery. Moreover, STS should best be treated in a multidisciplinary approach, including radiologists, orthopaedic surgeons, oncologists, pathologists, radiotherapists and physiotherapists. Only dedicated sarcoma centers should treat soft tissue sarcomas – and patients should be directly referred to these units either by their GP or the local hospital.

Patient Characteristics

Patients usually make an appointment if they are worried about their health condition. In case of soft tissue swellings, symptoms may include long-lasting indolent bumps, painful swollen areas or rapidly enlarging lumps (7).

The first problem that emerges, however, is that a differentiation between benign and malignant soft tissue swellings can be very tricky. Taking into account that only 1 out of 100 soft tissue tumours is actually a sarcoma does not simplify this circumstance (89). Symptoms being associated with the presence of a STS include rapid increase of the swelling as well as painful masses. However, recent results indicate that the presence of a painful swelling is a poor discriminator for STS (90). According to our results, the majority of patients reported painless masses (65%), whilst a recent increase in size of the tumour was stated by 64.3% of patients. However, also the patient's individual concerns have to be taken into account and it is necessary to listen carefully: Patients often try to be more confident in front of a doctor than they actually are. They would rather say "this swelling is a cosmetical problem for me..." than "this ugly little lump now really bothers me... ". In consequence, some doctors may believe their patients blindly and attempt promt surgical excision of the bothering object rather than initiating imaging and referral to an experienced unit.

The rapid increase in size may be the most likely cause for patients to consult a physician, especially if lesions have been stable in size for a long time and suddenly started to enlarge. In our study, the mean duration of symptoms was 19.4 months, being considerably long, as compared with other malignancies such as breast cancer with a mean history of complaint of about 6 months (91). This so-called "patient delay" may be caused by absence of "worrying" symptoms such as bleeding or pain in association with the lump. More importantly, psychological factors may play a role, as patients either ignore the symptoms for a long time or feel ashamed because of blemishing swellings. We did not discover a significant difference between both sexes regarding duration of symptoms. Younger patients, however, presented with a mean history of symptoms lasting for 23.9 months, whilst in patients aged over 60 the mean duration of symptoms was 8.5 months shorter (15.4 months; p=0.073). Interestingly, the mean duration of symptoms was low in the 1st and 2nd and cumulated in the 3rd and 4th decade of life, before continuously declining again (**Figure 9**). This peak in 30 to 40 year olds could be caused by psychosocial reasons mentioned above, with patients ignoring symptoms due to specific aspects concerning their social environment (i.e. family, children, work). According to *Urakawa and colleagues*, a symptom duration less than 6 months is significantly associated with poor outcome in a group of 152 STS patients (92). This is concordant to our results, revealing a 2-year reduction of the mean survival time for patients with symptoms lasting less than 6 months (9.4 years vs. 11.4 years).

Tumour Characteristics

In a study by *Italiano and colleagues* based on 3255 patients with STS a significant influence on metastatic-free survival could be demonstrated depeding on the histological subtype (93). In our cohort, more than half of patients either presented with a myxofibrosarcoma (28.6%) or a liposarcoma (24.6%), being associated with a relatively good prognosis. On the other hand, the outcome for patients with MPNST or leiomyosarcoma was rather poor (p=0.001).

The mean tumour size was 9.9 cm, with 28.1% of tumours being smaller than 5 cm, 32.2% larger than 10.1 cm and the rest measuring between 5.1 and 10 cm (39.6%). This is concordant to previous observations, additionally indicating the independent prognostic

effect of the tumour-size on the patient's outcome (7). The association between large tumour size and poor outcome may be related to several factors: In order to gain volume, a satisfactory energy supply is required for each tumour. Thus, the tumour sooner or later needs to tap blood vessels and starts invading adjacent structures. As a consequence, surgery becomes more difficult and the probability for intralesional resections increases. The combination of insufficient local control and systemically circulating tumour cells due to tapping of vessels could explain the increased mortality in patients initially presenting with large tumours.

Though we could not demonstrate a significant effect of large tumour size on OS rates in univariate Cox-regression analysis, a trend was visible (p=0.182). This may be related to the fact that patients with predominantly large tumours and a poor prognosis (i.e. those with primary metastasis and amputations) had been excluded from survival analysis.

Treatment Characteristics

The positive effect of RTX on the rate of LR, administered either pre- or postoperatively, is generally accepted. Nevertheless, no significant influence on OS could be demonstrated so far (21, 94). This is concordant to our results, showing no difference in OS for patients with or without adjuvant RTX. However, the decision for or against adjuvant RTX depends on various factors, including histological subtype, tumour grade, local tumour extent, resection margins, anatomic location and also the (personal) experience of the multidisciplinary team. Unfortunately, generally valid recommendations when to apply adjuvant RTX are missing (20). Nevertheless, at least in G3 tumours, the combination of surgery and adjuvant RTX is beneficial regarding local tumour control (95).

The administration of adjuvant CTX in patients with STS is a controversial topic. In children and adolescents, adjuvant CTX definitely has a positive influence on OS (26). In adulthood, though, the beneficial effects of adjuvant CTX are not that evident. However, by using the MAID-regimen in a neoadjuvant setting for high-risk patients with very large tumours (i.e. > 8 cm), response rates between 30% and 43% may be achieved (96, 97). Nevertheless, results of studies looking at possible effects of adjuvant CTX on the patient's prognosis are diverse, due to different selection criteria and treatment strategies (98, 99). In our study, the administration of adjuvant CTX was significantly associated with poorer OS (p=0.023). Since the cohort observed in this study received adjuvant CTX based on clinical risk factors (i.e.

histological subtype, grade, stage), the results are rather non-surprising. Interestingly, a retrospective study involving 674 patients treated for extremity STS both at the *MD Anderson Cancer Center* and *Memorial Sloan-Kettering Cancer Center* within a 14-year period revealed a slight benefit for patients treated with neoadjuvant or adjuvant Doxorubicin-based CTX during the first year of follow-up (100). After one year, however, this advantage disappeared. Thereofore, the authors conclude that randomized clinical trials with a short-term follow-up should be seen more critical (100).

Unplanned excisions

Unplanned excisions of STS are not only a problem in Austria, as they are rather observed all over the world (86, 90, 101, 102). Inadequate surgeries may occur for 3 main reasons: First, the surgeon is profoundly convinced of a benign lesion based on his or her personal experience and clinical examination. Second, the surgeon is confident that the lesion is benign due to inconspicuous sonography or X-ray. Third, the surgeon feels confident to correctly treat a soft tissue swelling despite highly suspicious imaging and clinical findings.

Concerning the first reason, clinical examination alone is more or less useless for definite diagnosis of a malignant soft tissue tumour. Regarding the second cause, the distinction between a benign soft tissue swelling and STS using imaging techniques requires a lot of experience and is rarely foolproof. As to the third reason, surgical treatment of STS demands a lot of experience gained with multiple surgeries and sometimes requires the surgeon's realisation that the tumour might be better off in more experienced hands.

38.7% of patients referred to our department since 1998 had undergone an unplanned excision prior to admission (n=165). This is sligthly less than the rate registered by the *Vienna Bone and Soft Tissue Tumour Registry*, comprising 752 patients with a STS of whom 310 had undergone an inappropriate resection (41.2%) (85). Over the years, the rate of inappropriately resected STS among all STS treated at our unit ranged between 26.8% in years 2012 and 2013 and 56.3% in years 2000 and 2001 (**Figure 12**).

Following unplanned excisions, the median delay until patients could be treated appropriatelly at our institution was 1.6 months. This "doctor's delay" is half the time period observed by other institutions, reporting a median delay of 3.2 months (4). However, the British study did not distinguish between inappropriately treated and directly referred patients, as they incuded all patients who had first been seen by their GP. Moreover, the

health care systems of Austria and the United Kingdom are not absolutely identical and referral to a specialist centre is more difficult in the latter, which could explain the discrepancy in doctor's delay.

Our findings suggest that tumour-related symptoms did not significantly influence the rate of unplanned excisions, although 63.3% of patients with a "whoops"-procedure reported an increase of the lesion and 30.3% complained about painful masses.

Patients with tumours located in the upper limbs were treated inappropriately in 52.6% of cases, in comparison to only 30.9% of patients with tumours of the lower limbs (p=0.003). This could be partly related to the fact that the upper limbs constitute easily accessable regions for minor surgery. Moreover, tumours in this region were sized 7.3 cm on average, as compared to 10 cm for STS located in the lower limbs. It is beyond all question that smaller tumours appear harmless and lower the surgeon's threshold of performing surgery.

It is generally accepted that soft tissue tumours appearing fixed to the muscle during clinical examination are highly suspicious of sarcoma (103). However, this does not necessarily mean that all superficially located tumours are benign. In our cohort, one third of STS were actually located superficially. Unsurprisingly, 56.9% of patients with tumours located superficially underwent an unplanned excision, in comparison to 29.4% of patients with deep STS. This is consistent with results obtained by other groups (86).

We could demonstrate a significant correlation between AJCC-stage and the presence of an unplanned excision. Of patients with an unplanned excision, 64.8% had early stage tumours (i.e. IA, IB or IIA), in comparison to 38.7% of directly referred ones. Patients with tumours exceeding 5 cm in size without any additional "risk factor" (i.e. stage IB) were treated inappropriately in 20.7% only, in comparison to small but intermediate- to high-grade tumours (i.e. stage IIA) in 66.7%. It seems obvious that small tumours lower the threshold of surgeons to give surgery a go prior to an adequate investigation.

However, unplanned excisions of STS necessitate re-resections in almost all cases, as the risk of residual tumour is esteemed with 59% (104). According to our results, 56.4% of patients with unplanned excisions required plastic reconstruction during definite surgery, in comparison to only 28.4% of patients with primary resection. Moreover, in only 4.3% of inappropriately resected patients prosthetic devices were needed in definite surgery, whereas in 12.6% of patients with primary resection endoprostheses were used. This

discrepancy could be explained by the fact that inappropriately excised tumours were generally early-stage lesions, decreasing the necessity for biological reconstruction.

Although the rates for plastic reconstruction and use of endoprotheses were slightly higher in our cohort, the results are concordant with those obtained by *Funovics and colleagues* as well as *Morii and colleagues* indicating an increased necessity of skin grafts and muscular flaps in patients with foregone unplanned excisions (85, 86). Moreover, they both reported a decreased need for reconstructive devices. In our cohort, amputations were carried out significantly more often during primary surgery, whereas the data provided by the *Vienna Bone and Soft Tissue Tumour Registry* could not reveal a significant difference (85). This may again be related to the fact that patients with unplanned excisions were more likely to present with superficial, small and early-stage tumours.

A 5.7% rate of vascular reconstruction was present for all patients, without significant alterations between directly referred and re-excised patients, again being concordant with the results obtained by *Funovics and colleagues* (85).

In this study, adjuvant RTX was applied significantly more often in 69.7% of patients treated inappropriately prior to referral in comparison to 59.6% of patients following primary surgery (0.046, X^2-Test). This may be related to the fact that most unplanned excisions resulted in gross contamination of the operation field, wherefore a decision in favour of postoperative RTX was reached.

Although re-resected patients required significantly more often plastic reconstruction and adjuvant RTX, the postoperative complication rate was similar in both groups. 22.3% of patients treated inappropriately prior to referral developed complications postoperatively, in comparison to 21.5% of patients with primary surgery. The more frequent use of RTX following re-resection did not result in a higher rate of wound dehiscence. One could argue that patients may develop complications earlier following second surgery in comparison to primary resected cases. According to our results, there was no difference between the onset of complications and the amount of preceding surgeries.

Prognosis

Advanced age is a negative prognostic factor in different human diseases. Naturally, cells in elderly patients are prone to damage and do not have the capacity of regenerating as readily as in young ones. Moreover, the risk of DNA-damage is increased in older cells, resulting in

accumulation of damaged DNA. As a consequence, preventive apoptosis or maldevelopment (i.e. cancerous growth) emerge (105). In univariate analysis for all patients and those originally treated adequately, patients aged under 60 had a significantly better prognosis as compared to older patients. Likewise, *Italiano and colleagues* reported a significant association between advanced age and local recurrence-free as well as metastasis-free survival, though they used a cut-off of 55 years (93).

In our cohort, a trend towards a better prognosis emerged for patients with primarily inadequately resected STS. This observation has been described previously (86, 87). Therefore, we decided to look at the possible risk factors separately for patients with an unplanned excision and those without.

Patients with a considerably short duration of symptoms had a worse prognosis both in the univariate as well as in the multivariate setting. Separate analysis for primarily adequately treated patients revealed no association between a short duration of symptoms and poor outcome. However, this factor turned out to be independently associated with a worse prognosis for patients who had undergone an unplanned excision.

A short history of complaint may rather be present in patients with rapidly growing, aggressive and G3 STS. On the other hand, patients reporting symptoms for several months may present with small and low-grade tumours with little metastatic potential. However, neither rapidly increasing nor painful tumours were associated with a worse prognosis in univariate analysis (90).

Patients with G3 tumours had a significantly worse OS in comparison to patients with G1 and G2 STS in multivariate analysis. There was no difference between inappropriately resected and directly referred patients. Our results are concordant to previous studies indicating a prognostic influence of the tumour grade on the prognosis (106, 107).

By recalling the histological features influencing grading as defined by the FNCLCC (i.e. tumour differentiation, amount of necrosis and mitotic rate), it is evident that the biological aggressiveness is depicted by grading. Though grading is a strong prognostic factor for metastasis and survival in STS patients, it seems to have little influence on LR rates (11, 108).

Indications for ablative surgery include large tumours with gross infiltration of adjacent tissue, both factors increasing the risk of (micro-)metastatic spread. Moreover, the attempt of wide resection in order to preserve the extremity will sometimes result in an impaired

limb function requiring extensive plastic reconstruction and time-consuming rehabilitation. Thus, an amputation should be considered in particular cases (109).

In our cohort, the prognosis was significantly poorer in cases where an amputation had to be done in comparison to limb-sparing procedures in the univariate setting. Therefore, all further analysis was carried out excluding patients with ablative procedures. The unfavourable prognosis in patients with an amputation may be related to the circumstance that our multidisciplinary team aims for limb-sparing procedures whenever possible. Thus, ablative procedures are the last alternative for the very patients with extremely large and/or extensively invading tumours.

The presence of postoperative complications (e.g. haematoma, wound healing deficit, muscular flap necrosis) was not significantly associated with an altered outcome. At first glance, this result is like a contradiction, as complications could put patients in jeopardy due to need for another surgery. Interestingly, *Jeys and colleagues* actually observed a better outcome for osteosarcoma-patients who developed postoperative infections (110). The „beneficial“ effect of postoperative infections on the patient's prognosis has also been described for bronchial and laryngeal carcinoma (111, 112). It is assumed that infections of the operating field are followed by a systemic inflammatory response with activation of *TNFalpha*, natural killer cells, makrophages and T-cells (113). The cytokine *TNFalpha* induces tumour lysis, whilst the cellular components do not only target microbial pathogens, but also have the ability to kill tumour cells (114). This may explain the previously observed increased outcome for patients with postoperative infections. However, we could not demonstrate a better prognosis for patients with postoperative complications in our cohort, although a trend was visible in multivariate analysis (p=0.058).

Plastic reconstruction in the primary resection group is usually carefully planned and only necessary in patients with big tumours resulting in large tissue defects following adequate surgery. Larger tumours are more likely to invade adjacent tissues and tap blood vessels, thus facilitating the systemic migration of tumour cells. Therefore, these patients are already at higher risk of developing distant metastases (7). Nevertheless, the need for plastic reconstruction had no negative effect on the patient's prognosis in our cohort.

The decision for plastic reconstruction in the re-resection group is not necessarily related to the original size or local invasion of the tumour, but is rather associated with the extent of prior inappropriate surgery. In consequence, more than half of inappropriately resected

patients in our cohort required a plastic reconstruction, in comparison to one fourth of patients with primary resection.

The beneficial role of adjuvant RTX in heterogenous patient populations has been desribed before, albeit only significantly reducing the risk for local recurrence (21, 94, 115). Other studies obtained a significantly better outcome for patients with G3 tumours and adjuvant RTX (95, 116). Our multidisciplinary team follows current guidelines when to apply adjuvant treatment modalities.

Adjuvant RTX had no significant influence on OS including all patients, neither in univariate nor multivariate analysis.

Interestingly, in the multivariate setting for directly referred patients, administration of adjuvant RTX showed a trend towards improved survival. On the other hand, a trend towards impaired survival was present for patients with prior unplanned excision receiving adjuvant RTX.

Taking into account that postoperative RTX in prior inappropriately excised patients is only administered in those rare cases with a poor prognosis (i.e. residual tumour, G3 tumours, large size), the results are consistent.

Follow-up schedules aim at three main targets: First, surveillance of the patient's quality of life. Second, early diagnosis of local tumour relapse. Third, detection of metastatic disease. Therefore, an accurate local examination is necessary at every appointment during follow-up in order to identify local complications and recurrence. According to a systematic review by *Stoeckle and colleagues*, LR rates are 21% in patients treated with surgery alone, 22% in cases where adjuvant local RTX was applied and 16% if adjuvant RTX was used systemically (106).

The LR rate for our entire cohort was 10.1% and was almost similar for inappropriately resected and directly referred patients (10.9% vs. 10%). Though being confusing at first glance, the almost equal LR rates in the directly referred and inappropriately excised cohort are caused by the fact that re-resection was performed before a LR could develop in the latter group.

Unsurprisingly, other studies could demonstrate a significantly lower LR rate in patients treated by sarcoma specialists in comparison to comparably inexperienced surgeons in peripheral hospitals (102, 117). In case STS would be left untreated after an inappropriate excision, it is obvious that patients would develop LR early with the consequence of a very

poor prognosis. Fortunately, patients usually undergo adequate surgery following unplanned excisions, thus reducing the peril of residual tumour.

According to a retrospective analysis by *Ueda and colleagues* including 143 patients, the development of LR was associated with an impaired survival in univariate analysis (p=0.006). However, in multivariate analysis combining LR either present at initial presentation or after definite surgery, histological grade, tumour size, depth and surgical margin status, LR did not significantly decrease OS (118).

We obtained nearly the same results for our patients, with a significantly decreased OS for patients who had developed LR in univariate analysis (p=0.022). In the multivariate setting, development of a LR was not significantly associated with an impaired prognosis, though (p=0.085).

By calculating Cox-regression analyses separately for patients with and without unplanned excisions, both univariate and multivariate analysis revealed an interesting conjuncture: LR was neither significant in univariate (p=0.389) nor multivariate analysis (p=0.950) for directly referred patients. However, patients with prior unplanned excisions with a LR during follow-up had a significantly impaired prognosis both in univariate (p=0.012) and multivariate analysis (p=0.002).

In a study by *Novais and colleagues*, the negative prognostic influence of resection margins could be shown. Patients with a tumour-free surgical margin less than 2 mm had a significantly worse prognosis as compared to patients with a surgical margin between 2 mm and 2 cm or a wide margin exceeding 2 cm (119). However, they had excluded G3 tumours, metastatic disease, patients who had been treated at other institutions (unplanned excision not indicated) as well as superficially located STS. In a study by *Lewis and colleagues* including 116 patients with LR out of 911 STS patients, a significantly negative influence of LR on disease-specific survival in G3 and/or tumours larger than 5 cm could be demonstrated (120).

One could claim that our results are not reliable because the likelihood of a LR is higher in G3 tumours and we did not exclude low-grade STS. However, the LR rate was almost equal, ranging between 10.2% for G1 and G2 tumours and 10% for G3 STS.

Limitations

One limitation of the study is its retrospective design. Especially the patients' medical history (i.e. duration of symptoms, pain, increase in size) prior to definite treatment was dependent on the quality and exhaustiveness of medical records. Therefore, this information could not be ascertained in every case. Moreover, treatment protocols for STS have slightly changed over the years, wherefore patients might have been treated differently back in the 1990s in comparison to patients referred to our institution in 2010.

Another limitation is the heterogeneity of STS subtypes in our cohort, as each entity has a distinct biological behaviour and treatment approaches vary slightly.

One could argue that the retrospective analysis itself may impair prognostic value of our data. However, we do not know of any prospectively designed study evaluating the effect of unplanned excisions on the outcome of patients.

Conclusion

The heterogeneous presentation of STS impedes correct diagnosis and treatment. Whilst doctors consider as short history of complaint as “worrying”, they often feel on “safe-side“ when symptoms had been present for several years. Moreover, in case a tumour is located in the upper limbs and rather small, doctors are even more tempted to perform a surgical resection.

Although tumours undergoing UE are usually small and located superficially, plastic reconstruction is significantly more often required at re-resection. In combination with the increased need for adjuvant RTX following UE, the hazard of healing by second may be augmented. This fact by itself demonstrates how unfavourable UE are for patients. However, we did not observe any difference in postoperative complications between UE-patients and directly referred ones.

In our cohort, patients with UE had no improved OS in comparison to directly referred ones, although a trend was still visible. Despite development of LR is not associated with an impaired prognosis for all patients, patients with prior unplanned excisions had a fatal prognosis when developing LRs.

Considering all these facts, we assume that the inevitable second-look surgery aiming at wide tumour margins in combination with doctors’ lowered inhibition levels regarding administration of adjuvant RTX lead to a favourable patient’s outcome following UE. Nonetheless, unplanned excisions should be avoided at any rate. Inappropriate resections not only unsettle and may even shock patients after being informed about a malignant histology, but also require additional – and often more extensive – surgeries.

Doctors of whichever profession should be aware that any benign-appearing soft tissue lump may actually be malignant. Thus, every surgeon ought to think twice whether to remove the bump immediatelly or better refer the patient for adequate examination to a specialist centre. In the end, neither surgeons want to have a „whoops“-experience, nor patients want to be diagnosed with cancer after initial „curative“ treatment.

Key Facts

- Neither painlessness nor a long-lasting history of superficial tumours rule out STS, which is why these lesions often undergo unplanned excisions
- STS undergoing unplanned excisions tend to be smaller and are rather located superficially than in the deep
- Due to elusive clear resection margins during definite surgery, plastic reconstruction and administration of adjuvant RTX is more often necessary following an unplanned excision in comparison to initial oncological surgery
- Patients with prior unplanned excisions do not have an impaired prognosis following secondary oncological surgery
- The development of a local recurrence after an unplanned excision and re-resection is a poor prognostic factor

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