Diplomarbeit

Local recurrence after resection of soft tissue sarcomas: a multifactorial analysis.

eingereicht von

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zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt an der

Universitätsklinik für Orthopädie und Orthopädische Chirurgie

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Graz, 07. Januar 2015

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Graz, am 07.01.2015 *Valentin Kainhofer eh*

Danksagungen

Herzlich danken möchte ich zunächst Herrn Univ. Prof. Dr. Andreas Leithner, der nicht nur die Erstellung meiner Diplomarbeit ermöglichte sondern auch für mein Interesse an diesem Teilgebiet der Orthopädie verantwortlich ist. Aufgrund seiner Motivation und Unterstützung war es mir darüber hinaus möglich an zwei internationalen Kongressen zum Thema Weichteilsarkome teilzunehmen, eine Erfahrung die ich nicht missen möchte. Bedanken möchte ich mich bei Frau Priv. Doz. Dr. Joanna Szkandera, für die stets äußerst rasche Hilfe und kompetente Unterstützung. Danke für die Betreuung sowohl durch fachliche Ratschläge und Korrekturen, als auch durch kurzfristige persönliche Termine zur Besprechung meiner Arbeit.

Bei meiner Familie möchte ich mich bedanken, für die Möglichkeit sorglos und konzentriert Medizin zu studieren. In meinen Entscheidungen konnte ich stets auf eure Ermutigung zählen und fand immer Rückhalt und Unterstützung, nicht zuletzt finanzieller Art. Bessere Voraussetzungen für meine Zeit an der Universität hätte ich mir nicht wünschen können.

Besonders bedanken möchte ich mich bei meiner Chiara, für die Unterstützung und die Motivation in meinen letzten zwei Jahren des Studiums. Du bist in so vielen Dingen ein Vorbild für mich und ich bewundere dich, deine Stärke und deinen Perfektionismus in Situationen in denen du ihn selbst nicht einmal erkennst.

Bei meinen Freunden und Studienkollegen möchte ich mich für die unvergessliche Zeit bedanken, die wir gemeinsam verbracht haben. Speziell erwähnen möchte ich dabei Profi Georg und Guiseppe skripti, in denen ich wahre Freunde gefunden habe und ohne die ich bestimmt nicht so viel Spaß und Erfolg im Studium gehabt hätte.
Abschließend möchte ich mich bei Walter Janisch bedanken, meinem Freund und ehemaligen Trainer und Lehrer. Durch ihn lernte ich ehrgeizig aber auch kollegial zu sein und durch seine eigene Begeisterung vertiefte er auch mein Interesse für den menschlichen Körper.

Zusammenfassung

Einleitung. Patienten mit Weichteilsarkomen, welche einer Therapie nach den aktuellen Guidelines zugeführt werden – das bedeutet vollständige Resektion und anschließende Strahlentherapie, wenn indiziert – können trotzdem keine Sicherheit haben, von lokalen Rezidiven verschont zu bleiben. Diese Studie zielt darauf ab, diverse Charakteristika von Patient und Tumor als mögliche Ursachen für Lokalrezidive zu analysieren.

Methoden. Es wurden 374 Patienten in diese retrospektive Studie eingeschlossen, die zwischen 1998 und 2013 mit einem Weichteilsarkom diagnostiziert und behandelt wurden. Die Analysen beinhalteten Informationen aus histologischen Untersuchungen, Operationsberichten und klinischen und radiologischen Befunden. Augenmerk wurde besonders auf die Faktoren Resektionsrand, Grading, Größe und Tiefe des Tumors, sowie Alter und Geschlecht der Patienten gelegt. Bezüglich des Faktors Resektionsrand wurden zwei verschiedene Klassifikationen angewandt und verglichen. Statistische Methoden beinhalteten die Kaplan-Meier Überlebenskurve, Log-rank Test, Cox Regressions-analyse, Kreuztabellen und den Chi-Test. Für die statistischen Analysen wurde das Programm SPSS, Version 22 verwendet.

Ergebnisse. In der einfachen Cox Regressions-analyse zeigten sich die Faktoren Alter (HR 4,19 für ≥50 Jahre, 95%CI=1,28–13,74, p=0,018) und Resektionsrand als signifikante Faktoren bezüglich Lokalrezidiv, wobei beide Klassifikationen des Faktors Resektionsrand signifikante Ergebnisse zeigten (R-classification: HR 5,62 für R1, 95%CI=2,67–11,84, p<0,01; UICC-classification: HR 10,08 für R1, 95%CI=2,87–35,41, p<0,01). In der multivariaten Analyse waren die signifikanten Faktoren Geschlecht (HR 2,24 für männlich, 95%CI=1,04–4,84, p=0,04), Alter (HR 3,77 für ≥50 Jahre, 95%CI=1,15–12,44, p=0,029), Grading (HR 2,70 für G2+G3, 95%CI=1,00–7,27, p=0,049) und Resektionsrand (R-classification: HR 7,94, 95%CI=3,52–17,94, p<0,01). Wenn die UICC-classification für den Resektionsrand eingesetzt wurde, resultierte diese als einziger signifikanter Faktor für Lokalrezidive (HR 9,44 für R1, 95%CI=2,57–34,68, p<0,01). In Kreuztabellen zeichnete sich der Trend ab, dass eine höhere Lokalrezidivrate in der unteren Extremität zu erwarten ist, im Vergleich zur oberen Extremität und Weichteilsarkomen des Stammes. In der Kaplan-Meier Überlebenskurve zeigte sich eine niedrigere Lokalrezidivrate wenn die UICC-classification angewendet wurde im Vergleich zur R-classification. Die Fünf-Jahres-Raten für Lokalrezidive nach R0-Resektion lagen bei 6 (UICC) bzw. 10 (R) Prozent.

Konklusion. Negative Resektionsränder sind ein Hauptfaktor für niedrige Lokalrezidivraten nach der Resektion von Weichteilsarkomen. In dieser Studie zeigten sich niedrigere Lokalrezidivraten, wenn ein minimaler Abstand von einem Millimeter als Resektionsrand eingehalten wurde. Weitere Faktoren die in Zusammenhang mit der Lokalrezidivrate gebracht werden konnten, waren Großteils mit Ergebnissen anderer Arbeiten der Fachliteratur in Übereinstimmung zu bringen und zwar das Alter, Grading und Geschlecht.

Abstract

Background. Patients with soft tissue sarcoma (STS) being treated following the standardized guidelines, i.e. resection and adjuvant radiation therapy for selected patients, can still not be guaranteed to remain free from local recurrence (LR) of the sarcoma at resection site. This study was designed to analyse various characteristics of patients and tumors and their potential impact on local recurrence.

Methods. This retrospective study included 374 patients, who were diagnosed with STS and underwent resection between 1998 and 2013. Analyses included histological reports, surgery reports and follow up for recurrence and survival of each patient with focus on the factors resection margin, grading, size, depth of the tumor and age and gender of the patient. Two different classifications were applied for the factor resection margin. Applied statistical methods were the Kaplan-Meier survival curve analysis, Log rank test, Cox proportional hazards model and cross tabulations with chi-square test. For statistical analyses SPSS 22 was used.

Results. In univariate cox regression analysis the significant factors for local recurrence resulted to be age (HR 4,19 for ≥50 years, 95%CI=1,28–13,74, p=0,018) and resection margin for two different classifications (R-classification: HR 5,62 for R1, 95%CI=2,67–11,84, p<0,01; UICC-classification: HR 10,08 for R1, 95%CI=2,87–35,41, p<0,01). In multivariate cox regression analyses the significant factors for LR were gender (HR 2,24 for male, 95%CI=1,04–4,84, p=0,04), age (HR 3,77 for ≥50 years, 95%CI=1,15–12,44, p=0,029), grading (HR 2,70 for G2+G3, 95%CI=1,00–7,27, p=0,049) and R-classification (HR 7,94 for R1, 95%CI=3,52–17,94, p<0,01). When the UICC-classification was applied for resection margin status it resulted as the only significant factor in multivariate cox regression analysis (HR 9,44 for R1, 95%CI=2,57–34,68, p<0,01). In chi-square analysis there was a trend for higher local recurrence rates in the lower extremity compared to the upper extremity and STS of the trunk.

Kaplan-Meier survival curve analysis showed a lower LR rate for R0 resection in the following the UICC-classification compared to the R-classification. Five-year LR rates were at 6 percent (UICC) versus 10 percent (R) respectively.

Conclusions. Negative resection margin (R0) is a crucial factor for low local recurrence rates. In our study, a favourable outcome for a minimal resection margin of one millimeter was observed as the local recurrence statistics resulted significantly lower when this definition was applied for the resection margin status. Further factors that were identified to be significant for local recurrence mainly go in accordance with the literature and were age, grading and gender.

Inhaltsverzeichnis

Glossar und Abkürzungen

18F FDG PET	18F-fluorodeoxyglucose positron emission tomography
AJCC	American Joint Committee on Cancer
CNB	Core needle biopsy
CNS	Central nervous system
CT	Computed tomography
DM	Distant metastases
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
FNCLCC	Federation Nationale des Centres de Lutte contre le Cancer
Gy	Gray, unit of absorbed radiation
HIV	Human immunodeficiency virus
HR	Hazards ratio
KM	Kaplan-Meier (survival curve analysis)
LR	Local recurrence
MFH	Malignant fibrous histiocytoma
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
OS	Overall survival
PCR	Polymerase chain reaction
RAD51	Eukaryote gene in DNA repair pathways
R0	negative resection margin
R1	microscopically positive resection margin
R2	macroscopically positive resection margin
Rb	Retinoblastoma (gene/protein)
stR	Standardized residuals
STS	Soft tissue sarcoma
UHPS	Undifferentiated high-grade pleomorphic sarcoma
UICC	Union International Contre le Cancer
US	Ultra sonography
VEGF	Vascular endothelial growth factor
WDL	Well differentiated liposarcoma
WHO	World Health Organisation
XPD	Xeroderma pigmentosum, group D; protein in DNA repair pathway
XRCC2	X-ray repair cross-complementing, group 2; protein in DNA repair pathway

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1 Introduction

Soft tissue sarcoma

Soft tissue sarcomas are rare malignant tumors deriving from mesenchymal tissue and constitute a heterogeneous group of tumors. These two facts alone demand high expertise and recommend treatment by a multidisciplinary team at specialized sarcoma centers in terms of providing best medical care for patients. (1-4) Since the different histologic and genetic subgroups of soft tissue sarcomas show different behaviour and reaction patterns concerning local recurrence after resection, sensitivity to radiation therapy and disposition to metastasize, the treatment has not reached satisfactory levels of survival rates yet. In treatment of soft tissue sarcomas different approaches were tested, discarded and approved since the beginning of the second half of the twentieth century. Resection of the sarcoma and application of radiation therapy (RT), depending from various factors, can cure about 50% of the patients with localized disease, which leaves the other half of patients, who develop metastases within a few years after diagnosis, to be treated in palliative intention.(5)

The European Society for Medical Oncology (ESMO) formed the European Sarcoma Network Working Group in order to find consensus about clinical guidelines concerning diagnosis, staging and treatment of soft tissue sarcomas.(4) Following the latest edition of these guidelines from 2014, diagnostic investigation of soft tissue tumors should consist of magnetic resonance imaging (MRI) as main imaging modality and subsequent multiple core needle biopsies performed by a surgeon or radiologist and histological diagnosis with a second opinion of an expert for STS-pathology if not primary performed in a reference center. The evaluation of the malignancy grade (6) and macroscopic qualities are valuable for prognostic and predictive statements. The pathology report after definitive surgery should describe integrity of the tumor and the status of the resection margins, including the exact distance to tumor, as this information is important especially for treatment decision concerning adjuvant RT. For staging purposes a chest spiral computed tomography (CT) has to be performed and further imaging procedures are applicable individually adapted to histologic type of the sarcoma and the likelihood of metastases or regional lymph node metastases. The surgery report should contain details like intraoperative diagnosis, surgical conducting and possible unfavourable events like contamination or tumor rupture. Surgery with the objective of a wide excision and negative resection margins (R0) is stated as the

standard therapy and needs to be performed by a specifically trained surgeon. If surgery could not reach negative resection margins, re-resection has to be taken into consideration and is obligatory in cases of R2 resection. Depending from the grading, depth and size of the tumor but also depending from surgical results (margin status) postoperative RT is applied, as its positive impact on local control could be proven. In cases of non-resectable tumors, chemotherapy combined with or without radiation therapy, isolated hyperthermic limb perfusion, or regional hyperthermia combined with chemotherapy are possible modalities of treatment. (4,7) The routine follow up can be applied differently based on the malignancy grade and tumor characteristics like depth and size, as these influence the probability and speed of recurrence of the disease after primary treatment. High-grade and intermediate-grade patients may be followed by examination at primary tumor site and additional chest X-ray or CT scan every 3-4 months for the first 3 years, then twice a year until the fifth year and after that once a year. It is suggested for low grade patients to be followed in longer intervals, as the relapse rates are lower as well. (4)

Local recurrence of soft tissue sarcoma constitutes an important factor in treatment and care of patients as it is associated with secondary metastases and tumor mortality and is a poor prognostic factor.(8,9) Therefore it is crucial to avoid local recurrence by applying multimodal treatment after excision of high grade tumors or following insufficient surgical treatment. Insufficient surgical treatment means not reaching R0 margin status and can be due to unplanned excision, intraoperative tumor rupture or contamination of the surgery field by unintentional incision of the tumor. (10,11) Ablative procedures can be performed in locally advanced tumors in case of infiltration of joints, vessels or nerves in order to reach R0 margin status in curative intention while also ulceration, uncontrollable bleeding or persistent pain can justify ablative procedures with palliative intention. The rates of amputations were reduced in the last decade. Treatment modalities like neo-adjuvant and/or adjuvant RT, isolated limb perfusion or systemic chemotherapy combined with local hyperthermia can provide good local control and improvements in overall survival. (12-16) As mentioned before, re-resection may be applied, especially when the prior excision was unplanned because of mistaking the tumor for a benign lesion or in patients with high grade tumors that were operated outside a reference center with uncertain results in the pathology report. Re-resection was shown to be beneficial regarding disease-free survival and some authors suggest it to be liberally applied where indicated and possible in patients with primary extremity soft tissue sarcoma as it improves chances for a disease free survival of those patients.(17)

The aim of the present study was to investigate possible factors for local recurrences after resection of soft tissue sarcomas. Several studies have been conducted in this field of interest, but the factors increasing the risk for local recurrence have not been clearly identified yet. Our hypothesis was that the resection margin status plays a crucial role in the local recurrence of soft tissue sarcomas. Further factors that were included in statistical analyses were factors like tumor grading, size, depth, patients' gender and patients' age at the moment of definitive surgery.

1.1 Epidemiology of soft tissue sarcomas

Adult soft tissue sarcomas are rare and occur with an incidence of 1,8-5/100.000/year in Europe which results in about 20.000 cases per year (18); in the United States about 11.000 cases are reported per year.(19) In adults, soft tissue sarcomas constitute only a small part of all malignancies (around 1%) while in children they make a bigger part of malignancies with around 7%. (20) In the histologically very heterogeneous group of soft tissue sarcomas (over 100 subtypes can be distinguished (21)), the most frequent subtypes in adults are pleomorph sarcomas, leiomyosarcomas, fibrohistiocytic tumors and liposarcomas while in children and adolescents (until the age of 20 years) rhabdomyosarcomas, fibrohistiocytic tumors, synovial sarcomas, other fibromatous neoplasms and unspecific subtypes are the most common STS.(22) According to an epidemiologic study including data (over 26.000 cases) from North American cancer registries, the five most common subtypes of soft tissue sarcomas (no age adjustment) are undifferentiated/unclassified STS, liposarcoma, leiomyosarcoma, dermatofibrosarcoma and rhabdomyosarcoma. Additionally with angiosarcomas and MPNST (malignant peripheral nerve sheath tumor) these entities represented over 75 % of all soft tissue sarcoma cases in this cohort.(23)

Males are equally or slightly more affected by soft tissue sarcomas than women (ratio between 1.0 - 1.2), except for leiomyosarcomas due to their frequent occurrence in the uterus.(23) Incidence rates for STS rise with higher age and after a peak incidence around the age of 20 years, patients over the age of 50 years constitute the group of most frequent STS diagnosis. Age is furthermore an unfavourable prognostic factor concerning survival: children and adolescents have a better outcome compared to patients with the same

histologic subtype and stage; patients over the age of 50 years demonstrate significantly inferior survival rates.(22-25)
The most frequent primary site of soft tissue tumors are the extremities including limb girdles, followed by retroperitoneal and intraperitoneal sites, followed by trunk and head/neck (percentages as in Table 1). (26)

Site	%
Lower limb and girdle	40
Upper limb and girdle	20
Retroperitoneal and Intraperitoneal sites	20
Trunk	10
Head and neck	10

Table 1. Site distribution of STS (26)

In a study by Burningham et al. (27) racial differences in incidence rates of STS were described. In their study they stated that Blacks have a higher overall incidence rate with 5.1 per 100.000 per year, while Withes had a rate of 4.5 per 100.000 per year. The following group would be American Indians/Asian Pacific Islanders with an incidence rate of 2.8 per 100.000 per year. There is evidence to show, that race is an influential factor for differences in incidence rates, but still: further investigations of genetic and biologic differences for better understanding of this factor are necessary. (27)

1.2 Etiology of soft tissue sarcomas

Corresponding to other malignant diseases it is difficult to clearly identify etiologic triggers for the development of soft tissue sarcomas. Yet some etiologic associations were confirmed for genetic factors, other endogenous factors as well as for exogenous and environmental factors. (28-41)
Patients with the diagnosis of neurofibromatosis type 1, which is one of the most common genetic diseases, have a higher risk for malignancies of the central nervous system (i.e.

optic gliomas) and soft tissue sarcoma, concerning in particular malignant peripheral nerve sheath tumors (MPNST). (28,29) The hereditary disorder of neurofibromatosis type 2 is not related with a higher risk of developing malignant tumors, but with mainly benign tumors of the nervous system like schwannomas, meningiomas and ependymomas. (30)

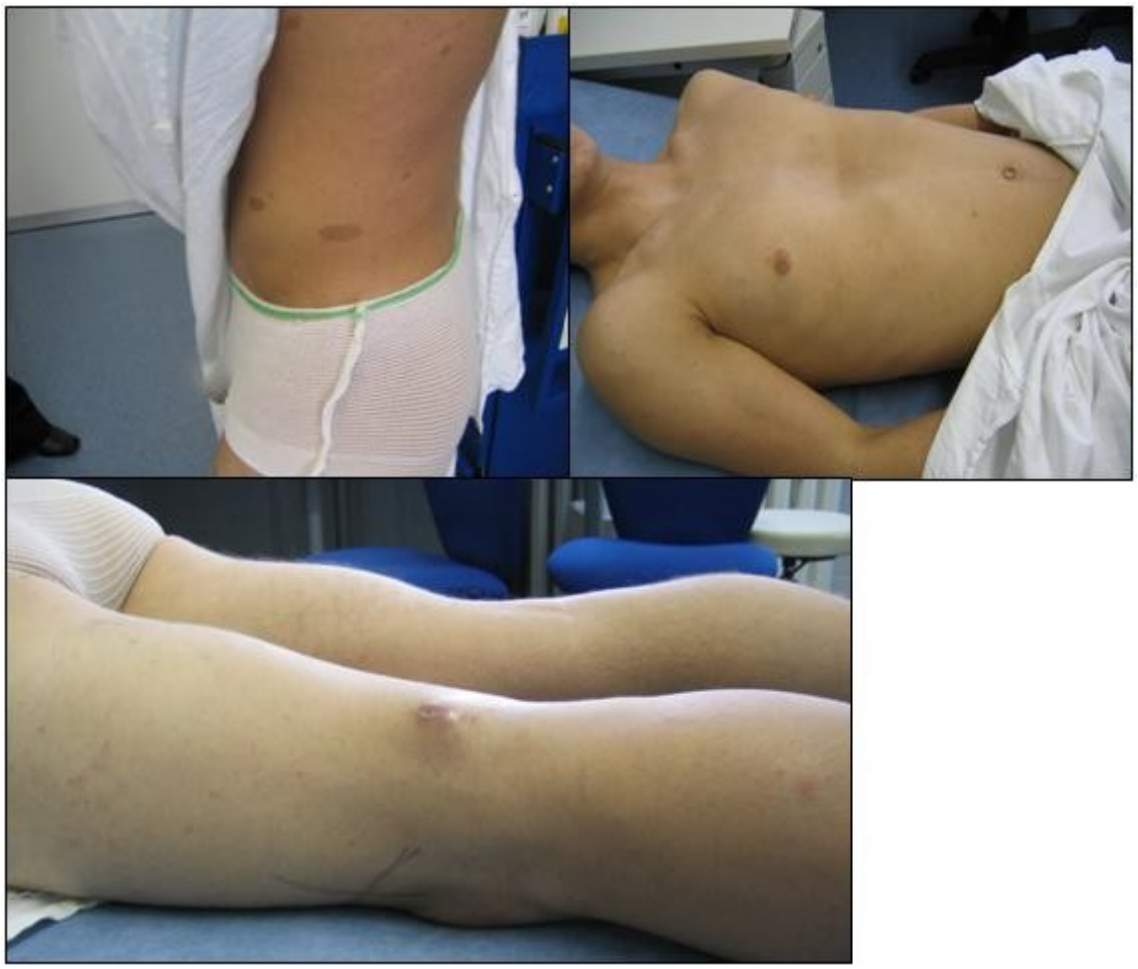

Figure 1. Neurofibromatosis in a 19 y.o. patient with MPNST (popliteal left)

Patients with hereditary retinoblastoma who most commonly develop a retinoblastoma in the early childhood mostly survive their retinoblastoma today. For those patients it is more likely to be affected by osteosarcomas and soft tissue sarcomas later on in life, as associations between alterations in expression of the Rb gene with lower levels of Rb protein and unfavourable clinical prognosis were shown. (31) There is strong evidence that the absence of the Rb protein correlates with tumor progression and metastases. Sporadic mutations of the Rb gene and alterations in Rb protein expression are often observed in soft tissue sarcomas.(31) The hereditary Li-Fraumeni syndrome is associated with

occurrence of soft tissue sarcomas like the rhabdomyosarcoma, undifferentiated pleomorphic sarcomas and pleomorphic liposarcomas. (32) It is based on a germline mutation of the p53 tumor suppressor gene and is characterized by an early onset of multiple tumor development – most commonly sarcomas but also breast cancer, CNS (central nervous system) tumors and hematopoietic malignancies.(32) The Gardner syndrome is related with adenomatous polyposis coli and is associated with a mutation of the APC gene. The syndrome comes along with so called Gardner fibromas, being benign plaque-like proliferations and desmoid precursor lesions, and desmoid type fibromatosis, which are locally aggressive fibroblastic-myofibroblastic neoplasms with infiltrative growth and tendency for local recurrence.(32) As further genetic syndromes that can be set into correlation with higher occurrence of rhabdomyosarcoma, the Werner syndrome and the Beckwith-Wiedemann syndrome should be named.(32)

Endogenous factors in the development of STS – other than genetic predispositions as mentioned above - are the immune system and the lymphatic vessels (i.e. chronic lymphatic edema in this matter). Patients with a disturbance in their immune system show a higher incidence of soft tissue sarcoma. (33,34,42) This relation exists mainly for HIV-infection and Kaposi's sarcoma but also other immune compromising therapies or diseases, like kidney transplantation or primary immune deficiency syndromes correlate with higher incidences of STS.(27,33,34) One author suggests, that increased risk also derives from infections like Herpes zoster, chicken pox and mumps. (35)

Chronic lymphatic edema can be the cause of angiosarcomas and this complication occurs with a higher frequency in women who underwent a mastectomy due to breast cancer (Stewart-Treves-syndrome; location in upper extremity or girdle) but it occurs also in patients with chronic lymphatic edema of other etiologic background. (43) Newer studies could show that these angiosarcomas occurring in the Stewart-Treves-syndrome can express phenotypes of blood and lymphatic capillaries. (36)

One of the most important exogenous factors for STS development is radiation in higher doses, e.g. if applied as radiation therapy (RT) in cancer patients. These patients may develop soft tissue sarcomas, osteosarcomas and angiosarcomas as secondary cancers after radiotherapy, in which the ionizing radiation exposure was found to be the key factor in several studies. (37,38,44) There is evidence of correlation between cumulative radiation dose and the risk of sarcomas; for the case of osteosarcomas, this correlation was found to be even linear.(37) A higher risk for STS was reported in relation to radiation therapy for cancers of the breast, cervix and ovaries and further for lymphomas. The latency time

between irradiation and secondary STS is estimated around 10 years and the risk for patients after radiotherapy increases about 8 – 25-fold. (38) They usually occur in the field of radiation or in the direct surroundings and especially younger patients under the age of 55 were described to be at a higher risk for STS after RT. (38)
Occupational factors such as job type and industrial exposure to chemicals like herbicides and chlorophenols need to be mentioned as possible exogenous causes for a higher STS-risk. (39) Study results are partially inconsistent, but various authors suggest a connection in this matter. The inconsistency in the findings is suspected to appear due to bias in the different study design and methodology: some works are based on registry data and their occupational information while others are based upon questionnaires and patient interrogation. Occupations, which are suspected to correlate with an increased risk for STS, are farmers, farm managers and gardeners who are assumed to be in contact with specific herbicides, pesticides and other chemicals. Especially dioxin and chlorophenols are better investigated on and are suspected to be in connection with increased STS incidence.(41) One study in the USA reported significant results concerning correlation between higher STS risk, high intensity chlorophenol-exposure (odds ratio = 1.79, 95% confidence interval 1.10-2.88) and duration of exposure.(39) Studies about dioxin (to be more precise 2,3,7,8-tetrachlorodibenzo-p-dioxin) are more contrary, as several works suggest no evidence for an elevated incidence level of STS (while other tumor entities may show elevated incidence).(40,41) Single studies showed higher risk for STS in persons in occupation as radiologists or health technologists; higher risks of STS were shown for persons chewing tobacco and for children to develop rhabdomyosarcomas if the parents consumed marijuana or cocaine in the year before the child`s birth.(27)

In conclusion, recent studies indicate that most soft tissue sarcomas appear sporadically and an etiologic cause cannot be identified in those cases. In some STS correlations to genetic predispositions or exogenous factors such as radiation, viral infections or exposure to chemicals can be identified.

1.3 Diagnosis of soft tissue sarcomas

1.3.1 Clinical presentation

Soft tissue sarcomas show nonspecific clinical features, as they do not show special symptoms and occur in almost all anatomical sites (as shown in table 1). Most STS are recognized by the patients as lumps or a painless swelling, often subsequently to minor trauma. Under these circumstances smaller STS are frequently mistaken as a benign lesion or also as a haematoma, which leads to nonsufficient excisional biopsies or unplanned excision of a malign tumor, without prior imaging. Depending from the grade of the sarcoma, the growth will proceed in a different velocity as low grade tumors (G1) usually grow slower. Especially high grade tumors grow in a spherical fashion and infiltrate their pseudo tumor capsule with micro satellites or small tumor nodes and can also infiltrate adjacent structures like nerves, vessels or organs. Therefore symptoms like paraesthesia, distal edema or other symptoms may occur. First symptoms of retroperitoneal STS may present as obstructive gastrointestinal problems or pain, due to compression of lumbar or pelvic nerves. The size of STS at primary presentation depends from tumor location: sarcomas of the head, neck and distal extremities are often smaller at presentation, as they are noticed easier and earlier than deep or retroperitoneal STS. Tumors of the head/neck region are mostly under 5 cm, while retroperitoneal sarcomas often present with a size of over 10 cm (in 60%). (45) Diagnosis for STS is mostly performed in the sixth or seventh decade of life with a median age of 55 years. Further differential diagnosis of a detected soft tissue mass can be benign lesions like lipomas, leiomyomas and neuromas or other malign lesions like primary or metastatic carcinomas, melanomas or lymphomas. (26,45,46) As mentioned before, it is clearly beneficial for the patient to undergo further investigation and treatment concerning a possible STS at a specialized center. The benefits that arise from this approach regard a better clinical course for the patients. (1-3,47) Referral to a specialized center may lead to early diagnosis, appropriate imaging and biopsy followed by adequate primary surgical treatment. (3,48) Also the application of additional treatment modalities and adequate follow up examinations may be conducted with better consistency to clinical practice guidelines after referral.(3)
After clinical examination with primary detection of an unclear soft tissue mass, the following steps should consist of imaging and histopathologic diagnosis of the tumor.

Referral of all patients with lesions likely to be a sarcoma would be recommended to be conducted as early as possible. For practice, this would mean referring all patients with deep soft tissue masses, superficial lesions bigger than 5 cm or soft tissue tumors arising in paediatric age. (4)

1.3.2 Imaging of soft tissue sarcomas

The correct approach in the selection of imaging modalities for investigations of soft tissue tumors plays a key role for various decisions, concerning the further clinical handling of these patients. After clinical examination the ultrasonography (US) can be an initial imaging modality to evaluate a yet unidentified soft tissue mass. Information like tumor size, the depth of the tumor, growth patterns (infiltrative growth / smooth capsule), involvement of adjacent structures, inner structure of the tumor and even the status of regional lymph nodes may be approximated. First reference points for subsequent steps like further imaging, biopsy and excision can be acquired. Ultrasonography can eventually provide support in procedures like guided core needle biopsy or fine needle aspiration.(49) Advantages of the ultrasonography are the easy and fast access to this examination, the possibility of repetition and if applicable also observation of progress (which can be an option for very small tumors). On the other hand there are some disadvantages of the US as it shows weak resolution and therefore worse assessment of deep tissue masses. As a certain level of experience is necessary for this investigation, there are various pitfalls to keep in mind. A number of non-tumoral conditions can imitate a soft tissue tumor or lead the examiner to a wrong diagnosis: haematoma, organizing haematoma and thrombi, muscle tear, anomalous muscles and diabetic muscle infarction can be named as such. Also some common tumor entities can be mistaken on US examination with other tumors ((atypical) lipomas and vascular malformations or (atypical) nerve sheath tumors and vascular leyomyomas). Among these possible misdiagnosis, the confusion of a soft tissue tumor for a haematoma is the most frequent. In order to avoid a delay of the definitive diagnosis of a STS, it is important for suspect or unclear results of a US examination to be followed by further imaging before biopsy.(50,51)

Plain radiography is not of high value for the diagnosis of soft tissue sarcomas. Though it can be useful to assess sarcomas of the bone and also calcifications of synovial sarcoma or osteosarcoma of the soft tissue, it is not capable of evaluating a soft tissue mass. In some cases it can be a useful method to evaluate the aggressivity of a lesion, looking at its effect

on the adjacent bone; another scenario in which radiography may be helpful is that of a primary bone tumor, presenting with a big soft tissue mass. In its role for detecting metastasis in the thorax, the normal radiography is being replaced by the spiral-computed tomography (CT) and it neither plays a role in primary diagnosis of intra-abdominal sarcomas, since calcifications that could be seen in extremities are often hidden by bowel gas.(52)

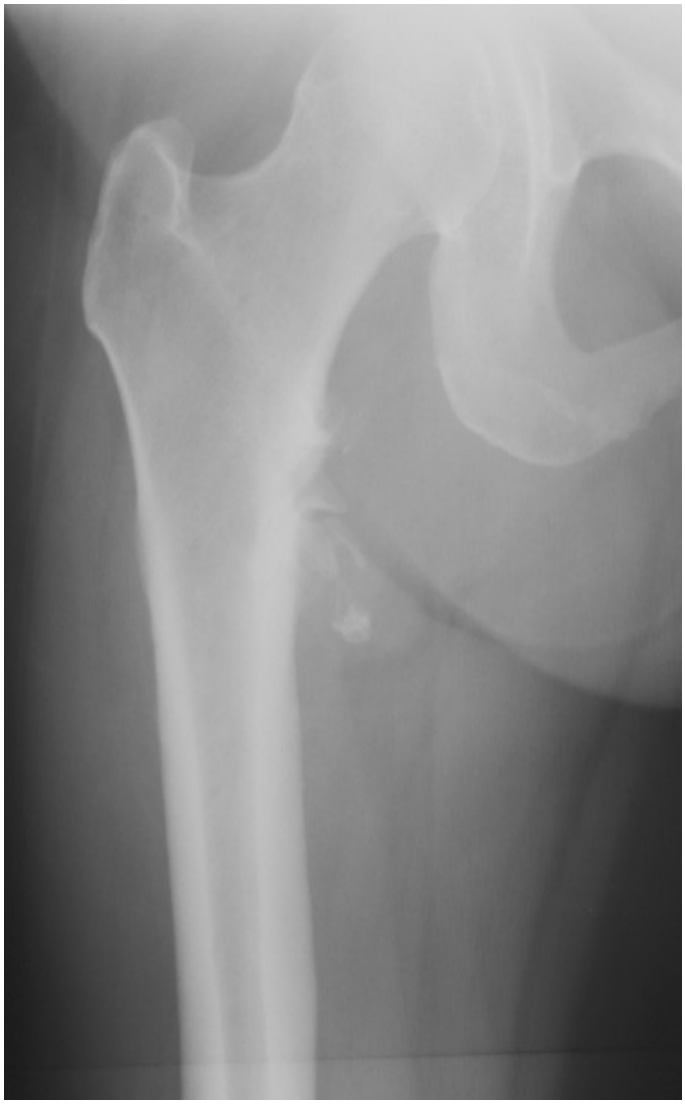

Figure 2. Plain radiography with signs of calcification in the right thigh in a 40 y.o. patient myoepithelioid sarcoma

The Computed tomography as already indicated is the best imaging modality in evaluation of lesions with intra-thoracic or intra-abdominal location. Therefore, it is the imaging modality of choice for staging patients with STS and it is the best tool for surgical planning

in the above mentioned locations.(52) The magnetic resonance imaging (MRI) is the procedure of choice for the investigation of soft tissue tumors, especially of the extremities. Via MRI, muscle groups, fat tissue, nerves and vessels can be delineated precisely in order to distinguish healthy tissue from a tumoral process. More advantages of the MRI consist of the multiplanar imaging and possibilities of special techniques like magnetic resonance angiography and other contrast media (gadolinium) enhanced imaging techniques. MRI currently constitutes the most sensitive imaging method for evaluation of a STS and eventual procedures of resection should be planned exclusively based on a recently performed MRI. Under the exception of selected cases where the MRI can outline the histology of a tumor (i.e. lipoma vs high grade liposarcoma), this method cannot provide a histologic diagnosis and therefore subsequent biopsy and pathological analysis of the lesion is mandatory.(49) Nevertheless, interesting studies and experiments are being conducted: new techniques in functional MRI imaging to identify physiological processes, metabolism and molecular properties of tumor cells are substance of investigations which pursue the goal of providing non-invasive in vivo diagnosis of histology. (53)

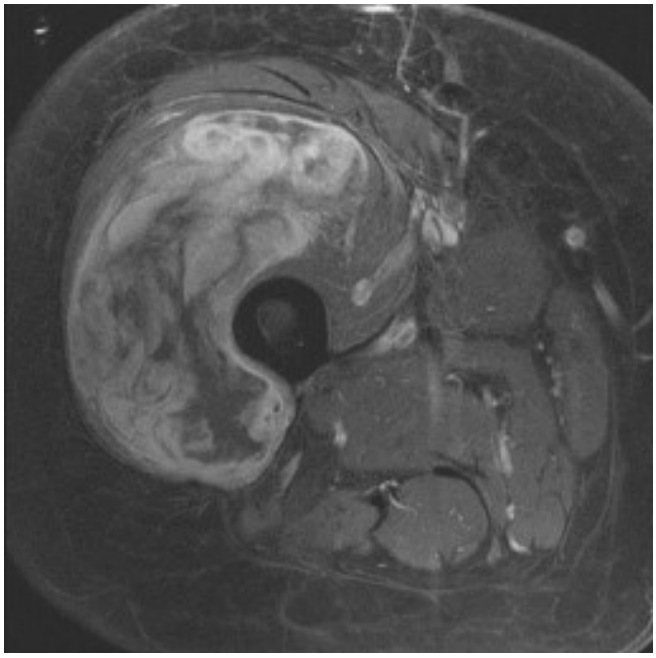

Figure 3. MRI of a leiomyosarcoma of the right thigh in a 71 y.o. patient

The 18F-fluorodeoxyglucose positron emission tomography (FDG PET) can give information about malignancy and grading of STS in primary diagnosis, considering some limitations. While this technique may distinguish between a benign lesion and a high-grade

malignancy, it is not reliable enough to decide whether a mass is a benign tumor or a low- to intermediate-grade malignant lesion. Further this technique allows distinguishing between different regions with different malignancies in the same tumor, which can be important in biopsy procedures and for evaluation of therapy response. It may also be applied to detect metastases of sarcomas in different organ systems; for detection of metastases in the lung spiral-CT is superior to the PET scan. However PET is not indicated as a standard diagnosis procedure or primary staging method of STS. The evaluation of a STS in the course of (neo-adjuvant) chemotherapy is another field in which FDG PET was shown to be beneficial. The assessment of response to therapy may be displayed better with the change of FDG uptake as criteria instead of change of tumor-size. Especially gastrointestinal stromal tumors (GIST) may increase in size as a sign for positive response to therapy, due to increasing necrosis and fluid accumulation, while the FDG uptake is decreasing correlating with lower tumor metabolism.(49,52,54)

1.3.3 Biopsy of soft tissue sarcomas

When clinical examination and imaging lead to the suspicion of a STS, histopathologic confirmation of the diagnosis is obligatory prior to any further treatment modality. The only exception to this may be a superficial, smaller than 3 cm lesion, which can be entirely removed by primary resection – a procedure called excisional biopsy. There are three techniques which are used to obtain tumor tissue for histopathologic investigations. The gold standard is the incisional biopsy as it shows the highest rate of accuracy in diagnosis (close to 100%) and furthermore provides advantages like achieving a high tumor volume and the possibility of intraoperative frozen section analysis. Disadvantages of this technique are the invasiveness and therefore the higher costs and complications like haematoma, infections or tumor contamination.(55) The other two procedures in clinical use are the fine-needle aspiration (FNA) and core needle biopsy (CNB). Of the above mentioned, FNA gives the lowest accuracy (50 – 70%) in diagnosis and grading of sarcomas. Because of the relatively lower accuracy and the incapability of providing specimen for ancillary studies including immunohistochemistry and molecular diagnostic analysis, FNA is losing in popularity amongst clinicians.(56) On the other hand more and more authors promote the imaging-guided CNB as a safe and accurate (up to 96%) method in biopsy of bone and soft tissue sarcomas.(55,57,58) Advantages compared to the incisional biopsy are seen in the facts that complications are fewer and less drastic as CNB

is less invasive and the procedure is faster. (55,57,58) Some authors suggest, that CNB is a safe and more accurate method for bony lesions than for soft tissue tumors and that for a suspected STS a higher expertise in conducting a CNB is demanded compared to open biopsy. (59)

1.4 Pathology of soft tissue sarcomas

The exact histopathologic analysis of soft tissue masses sustained from either biopsy or definitive resection of a tumor provides important information. Based on the morphologic and molecular status in combination with the immune-phenotype the tumor will be classified. This classification of a soft tissue sarcoma into one of the numerous subtypes is an important key factor in the course of disease and treatment of a patient. As mentioned before, the entity of STS is a very heterogeneous group of malignancies. This fact can be observed in studies conducted to evaluate the effect of chemotherapy in cases of generalised disease. The rates of response to chemotherapy agents are unsatisfactory and prediction of response to therapy is still a very challenging task. On the other hand more and more studies proof different response patterns for specific subtypes of STS to certain agents. It has been shown that the STS subtype angiosarcoma is sensitive to the vascular endothelial growth factor (VEGF) receptor inhibitor sorafenib, while in other STS subtypes only minimal effects could be observed.(60) Similar correlations were shown for the sensitivity of myxoid liposarcomas to trabectedin.(61) The synopsis of these and many other studies confirm the suspicion that STS demand a very particular and specific treatment based on histopathologic findings.

The WHO classification comprehends more than 100 different subtypes of soft tissue sarcomas and they are categorised by the tissue of origin, which the tumor has the most similarities with.(21) The main criterion therefore is the morphologic pattern of the STS; examples could be a liposarcoma, leiomyosarcoma, synovial sarcoma or angiosarcoma. In cases of unclear morphologic patterns, the next steps towards diagnosis would be immunohistochemical staining to identify specific tumor markers, for example desmin and caldesmon, S100 antigen, neurofilaments or cytokeratin.(62,63) If the tumor is still not in concordance with the above called classification and histogenesis stays uncertain, the tumor is diagnosed following the morphologic appearance (e.g. alveolar sarcoma, epithelioid sarcoma, clear cell sarcoma, Ewing sarcoma). (64) Another possibility to gain

certainty in diagnosis is using techniques like fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR), evaluating tumor tissue for specific genetic translocations or gene products that correlate with histologic subtypes; e.g. fusion genes like FUS-DDIT3 or EWSR1-DDIT3 which are present in myxoid liposarcoma. (64,65)

Histotype	%
Undifferentiated unclassified sarcoma (NOS)	35.9
Leiomyosarcoma	23.8
Liposarcoma	12.2
Fibrosarcoma	5.0
Angiosarcoma	4.7
Synovial sarcoma	2.2
Rhabdomyosarcoma	1.8
Malignant mesenchymoma	1.1
Epitheloid sarcoma	0.8
Primitive neuroectodermal sarcoma	0.5
Alveolar soft part sarcoma	0.3
Clear cell sarcoma	0.3

Table 2. Most frequent histotypes of STS in large cohort in Austria(18)

A recent development in the diagnosis of STS subtypes is the deletion of the "misnomer" malignant fibrous histiocytoma (MFH). (66) This STS-entity has been investigated on since the 1980s and it has early been hypothesized to be a final common pathway of some sarcomas.(67) Today the term undifferentiated high-grade pleomorphic sarcoma (UHPS) – synonymous to MFH – should be restricted to a certain group of tumors without a specific line of differentiation. Due to the use of immunohistochemistry and cytogenetics the term UHPS should be a diagnosis of exclusion and account for not more than 10 percent of adult sarcomas.(66)

1.4.1 Grading of soft tissue sarcomas

The grading of a STS intends to improve the prognostic value of histopathologic investigations on the specimen. An important objective of implementing a grading system was to further complete the already established TNM system of staging. The first authors, who invested big efforts in this matter, could eventually proof enhancement in prediction of outcome through the complemented TNM system. (68) However the design of the first grading systems developed in the time around the early 1980s could not find international consensus and the included criteria changed and sorted out in the course of many studies. (69) These days the two most important systems are those of the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and of the National Cancer Institute (NCI). Both systems are a three-tiered systems. The NCI grading system is mainly based on the histology of tumor, tumor location and the amount of tumor necrosis. The FNCLCC grading has likewise three criteria included in a scoring system. Depending on the factors tumor differentiation, mitotic activity and expansiveness of necrosis the scoring system will result in a final grade (one, two or three). In comparison of these two grading systems, the FNCLCC system has developed to be the internationally more used and has shown to be the more reproducible one. A study conducted to evaluate these two systems on the same patient cohort has shown a slightly superior ability to predict distant metastases and tumor mortality when applying the FNCLCC grading system.(70)

Tumor differentiation	**Necrosis (macro and micro)**	**Mitotic count (n/10 high power fields)**
1: Well	0: Absent	1: <10
2: Moderate	1: <50%	2: 10-19
3: Poor	2: ≥50%	3: ≥20
The sum of the scores of the three criteria determines the grade of malignancy. Grade 1: 2 and 3; Grade 2: 4 and 5; Grade 3: 6, 7 and 8		

Table 3. FNCLCC grading system (6)

On the down side, neither does the FNCLCC system cover all sarcomas, meaning that it is not applicable for all subtypes of STS. Grading is not recommended for epithelioid sarcoma, clear cell sarcoma, and angiosarcoma and is shown not to correlate well with

outcome in malignant peripheral nerve sheath tumors (MPNST). (69) Another problem in the pathologists' practice of grading and staging STS is the trend towards tumor sampling via core needle biopsy (CNB). As mentioned in the chapter biopsy, CNB is an accurate procedure for histologic diagnosis of a STS but it may bring difficulties in terms of grading. Various properties of the technique itself may lead to bias; sampling a low grade region and missing the high grade region of the tumor could be named as one. Furthermore, evaluation of expansiveness of necrosis in the tumor may undergo bias when obtaining specimens via CNB. It is important to be mentioned that grading needs to be performed prior to any treatment, as subsequently it may not be possible to differentiate for example between tumor necrosis and necrosis due to radiation or chemotherapy. (69,71)

1.4.2 Staging of soft tissue sarcomas

As in other malign tumor diseases, the staging of soft tissue sarcomas is an approach of evaluating the prognosis and outcome for patients and it provides key information based on which treatment modalities are selected. The staging classification developed by the Union Internationale Contre le Cancer (UICC) in collaboration with the American Joint Committee on Cancer (AJCC) is the internationally most used system and finds application in the National Comprehensive Cancer Network (NCCN) guidelines. The system has undergone various modifications and is currently available in its 7th edition, published in 2010. (72) The UICC/AJCC staging system for STS is based on the factors primary tumor size, tumor depth (i.e. relation to muscle fascia), lymph node status, presence of distant metastases and grading of tumor. (Table 4) The FNCLCC grading system is the preferred classification scheme, since it was shown to be more accurate in prediction of distant metastases and tumor mortality, as described above.

Primary tumour (T)			
TX	TX Primary tumour cannot be assessed		
T0	T0 No evidence of primary tumour		
T1	Tumour 5 cm or less in greatest dimension		
T1a	Superficial tumour		
T1b	Deep tumour		
T2	Tumor >5 cm in greatest dimension		
T2a	Superficial tumour		
T2b	Deep tumour		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage IA			
T1a	N0	M0	G1, GX
T1b	N0	M0	G1, GX
Stage IB			
T2a	N0	M0	G1, GX
T2b	N0	M0	G1, GX
Stage IIA			
T1a	N0	M0	G2, G3
T1b	N0	M0	G2, G3
Stage IIB			
T2a	N0	M0	G2
T2b	N0	M0	G2
Stage III			
T2a, T2b	N0	M0	G3
Any T	N1	M0	Any G
Stage IV			
Any T	Any N	M1	Any G

Table 4. AJCC staging system for STS(73)

Recent discussions on changes in the latest edition (7^{th}) of the staging manual in respect to the prior one bring various impulses for future developments of STS-staging and outcome prediction. The most relevant adaption from the 6^{th} to the 7^{th} edition concerning STS is probably the change of lymph node positive but distant metastases free (N1M0) disease from a stage IV to stage III tumor. Another reason that may lead to "stage shifting" of tumors is the fact that depth of tumor is not stage-effective anymore. Another novel implementation is the recommendation of the FNCLCC grading system, bringing a change from a four-tiered to a three-tiered grading system.(74) One important argument that needs to be considered when a tumor undergoes stage shifting is that this information is in first line a predictor of outcome and needs to be detached from automatic treatment adaption. Many studies and clinical trials designed to evaluate treatment efficacy and modalities were conducted on the basis of tumor staging, since in this way the tumor attributes are similar and results are comparable. However this fact may not lead to the conclusion that the coefficients therapy efficacy and tumor staging correlate directly. The correct correlation to state would be that success of therapy correlates with tumor attributes (like size, depth, lymph node status etc.). It is therefore recommendable to adapt treatment to tumor attributes and not automatically to the staging level. (75)

The before named changes in staging are being criticized by authors based on estimations drawn from a study that included more than eight thousand STS cases.(74) The new stage III classification of N1M0 STS is being discussed as not being the most precise assignment. The outcome for these patients (N1M0) has been shown to be intermediate, as the disease specific survival was inferior to G3T2 (N0M0) disease but superior to patients with M1 disease. Therefore it is also suggested to constitute a unique staging class for N1M0. (74) The dichotomous classification of primary tumor size (≤5 cm or >5cm) is reviewed as being too imprecise. When a four-tiered classification for the factor size was applied (≤5cm, >5-10 cm, >10-15cm, >15cm) significant difference in outcome regarding survival was seen between each step. (76) The factor depth of tumor has furthermore been shown to be significant for prognosis, but is not stage relevant anymore in the new edition. (77) A great challenge for the current staging method, corresponding with the difficulties of grading of STS, may lie in the histologic heterogeneity of this group of tumors. Different tumor subtypes like dedifferentiated liposarcoma and pleomorphic sarcoma may both be grade III but however show different overall survival outcomes. (74)

Summing up there is an array of possibilities to specify and try to improve prediction of outcome for STS. The challenge seems to lie in maintaining the practicability and

feasibility of staging systems for clinical use. In this regard also other approaches have been suggested, referring to nomograms and specific staging for anatomic site or tumor subtype.(72,74) These nomograms intend to estimate tumor survival taking into account various clinical and also histopathologic attributes of individual cases. (24) One example would be a liposarcoma specific nomogram, which was designed to estimate 5- and 12-year disease specific survival probabilities for patients with primary liposarcomas. (78) It was developed using an enormous cohort of more than nine hundred liposarcoma cases and comes up with many very specific features like differentiation of histologic variants (well differentiated, myxoid, round cell, pleomorphic etc.), to name only one of them. (78) Intensive international collaboration in studies and investigations is probably the most promising approach of getting a grip on precise grading, staging and eventually molecular classification of STS.

1.5 Treatment of soft tissue sarcomas

As the introduction already provided a short outline about the treatment of soft tissue sarcomas, this chapter will go more into detail on this matter. The focus will be put on the management of STS of the extremities and the trunk and also some peculiarities of the treatment of retroperitoneal STS will be given. According to the cohort of this study, gastrointestinal stromal tumors (GIST) and Kaposi's sarcoma are not represented and will therefore not be highlighted in the argument.

1.5.1 Resection of soft tissue sarcomas

Surgical resection is the standard treatment for virtually all soft tissue sarcomas with the exception of rhabdomyosarcomas. The main goal of surgery, which should be conducted at a specialized sarcoma center, is to reach negative resection margins. For the resection technique itself this means resecting the tumor in a divergent manner, removing it en-bloc with a rim of healthy tissue around it. It is important that the tumor is not being violated during surgery, meaning that it must not be incised or opened. It is crucial that the tumor mass remains intact at all times and that tumor rupture and outpouring of necrotic material or myxoid tumor mass is evited. Tumor rupture is associated with a decreased outcome of

overall survival, metastases free survival, decrease in metastases free interval and higher local recurrence in stage III STS. (10) Procedures that are recommended after an unfavourable event of tumor rupture or contamination include closure of the incision with normal tissue over the site of contamination, extensive irrigation and immediate re-excision. As a consequence also adjuvant therapy modalities like radiation therapy may be considered if not planned in advance. (11,79) Concerning the surgical technique it is furthermore important to adapt to a number of specific circumstances. The expansiveness of resection may depend on factors like histologic subtype, preoperative therapies and presence of anatomical barriers like intact muscular fascia, periosteum or epineurium. To give an example, in the case of an extracompartimental atypical lipomatous tumor the intent of resection can be a marginal resection.(4) Also limb salvage may be a reason to restrict resection to a certain degree, always after assessment of risk vs. functional benefit and certainly in consensus with the patient.

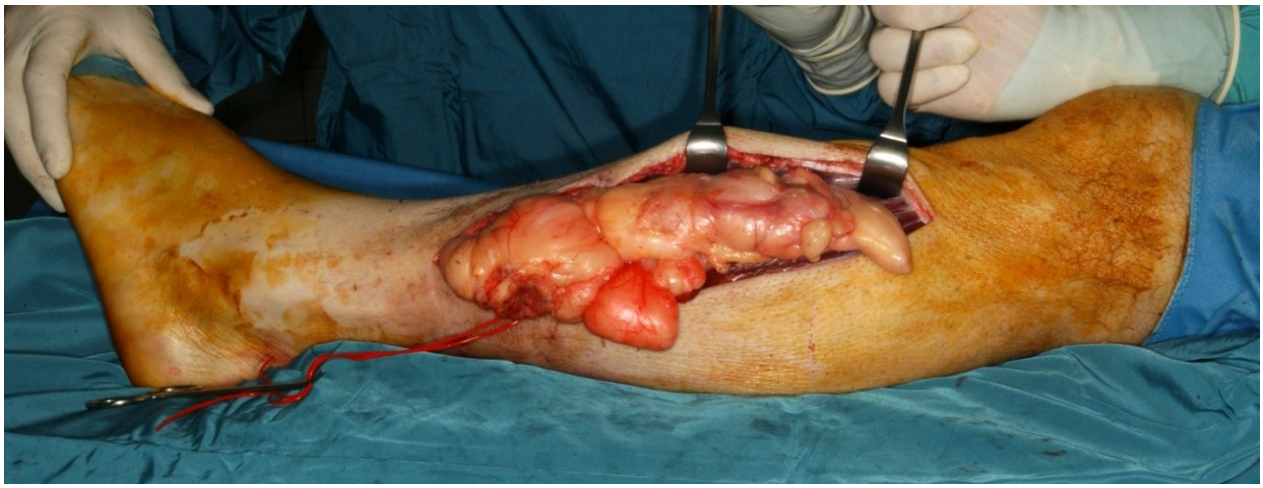

Figure 4. Marginal resection of an atypical lipomatous tumor/well differentiated liposarcoma

While on the one side periosteum - if intact - is well suitable as an anatomic barrier for tumor growth, it is on the other side not recommendable to execute periosteal stripping if not necessary. Periosteal stripping in tumor surgery is associated with a higher risk of pathologic fractures subsequent to radiation therapy.(80,81)

The surgical management of peripheral nerve involvement in STS of the extremities constitutes an important factor for functionality and morbidity. As the involvement of mixed motoric and sensory nerves of the extremities (i.e. sciatic, femoral, tibial, peroneal nerves and musculocutaneous, axillary, median, radial and ulnar nerves) used to frequently

lead to amputation, nowadays a more differentiated approach to the topic plays a major part in increasing the rate of limb salvage. Since studies have shown that functional outcome after selected nerve resection, e.g. of the sciatic or the peroneal nerve, were however objectively and subjectively preferable to amputation, surgeons are more prone to limb sparing surgery if accordable with the goal of adequate tumor margins.(82,83) A first assessment of nerve involvement especially in STS of a limb can be performed by history taking and clinical examination. In these first steps definite information about nerve involvement is rare, but signs like pain, paraesthesia, muscular atrophy or distal motoric malfunction can give important clues. MRI is the imaging modality of choice to evaluate the peripheral nerves. Based on the MRI decision making about the possibility to save a nerve is in many cases feasible, with the main criteria being a surgical access to the nerve. If the nerve is surrounded by tumor in its complete circumference, it is not advisable to try to save it as this would mean opening the tumor and creating a not recommendable positive margin.(84) In some cases the decision on nerve salvage must be made intraoperatively if it is not possible to differentiate tumor involvement from the MRI. A suitable and approved technique for nerve salvage is the epineural dissection. Subsequent to a final intraoperative evaluation of nerve involvement this technique is feasible if at least 90° of the circumference of the nerve are visible and not covered or adjacent to tumor. It should be executed as the last step of tumor preparation: after covering the wound with drapes for the case of tumor violation, a longitudinal incision of the epineurium using a fresh scalpel is made and the nerve fascicles can be lifted out of their epineural sheath. In a study on sciatic nerve resection compared with epineural dissection no worse oncologic outcomes were seen in the second group (additional RT was applied pre- or postoperatively) and functional outcomes were not negatively affected. (85) If a nerve is not salvageable there are various approaches in further treatment. A personalized decision in dialogue with the patient needs to be taken, aligning the goals and requirements of the patient with those of the surgeon. As for lower extremities a simple resection of a single nerve will result in acceptable function, peripheral nerve resection in the upper limb may demand greater efforts to restore adequate function. When resecting one of the three upper limb nerves, techniques to restore function can be a distal nerve transfer, reconstruction via nerve conduits or tendon transfers. However if the nerve involvement expands to multiple nerves, for example femoral and sciatic or median and ulnar nerves, amputation will be the most adequate option as the saved limb will bring more difficulties and challenges than function

and benefit. Expectations for improved management in restoring nervous function lie in research concerning regeneration and reprogramming of peripheral nerves.(86)
The involvement of vascular structures is another important factor in STS surgery. Similar to the situation of nerve involvement in the tumor, close but adequate resection for salvage of vascular structures is feasible. If combined with radiation therapy before or after resection, the local tumor control is not inferior when a tumor margin consists of a vascular adventitia. This means that in the case of involvement of a major extremity vessel it is a safe technique to perform a longitudinal incision and preparation of the adventitia in order to preserve a rim of healthy tissue adjacent to the tumor.(87) When the preservation of vascular structures is not feasible in concordance with appropriate tumor margins, vascular resection and reconstruction is a possible solution. This might be the case when the tumor completely encases the vascular structure or when a tumor arises from the vessel wall. Reconstruction of major vessels subsequent to tumor resection can be done by reversed saphenous vein graft, femoral vein or synthetic grafts. Even if there is a relative flexibility for reconstruction provided by these techniques, there are however higher rates of complications after vascular resection and reconstruction that need to be considered. Consistent peripheral limb edema, deep venous thrombosis or protracted wound healing, resulting in the necessity of subsequent tissue transfer, occurs after resection of STS with vascular involvement.(88) These patients are also under higher risk of amputation due to vascular failure. The functional outcomes are satisfactory and also local tumor control was shown not to be inferior. (89-91)

1.5.2 Resection margin

The resection margins play a key role in resection of a soft tissue sarcoma. It is furthermore a very controversial topic, as there is not necessarily clear consensus in literature on the behalf of the definition of adequate resection margins. Many descriptions of what is adequate may be found (92), and from adjectives like radical, compartmental, wide or close (93) until metric limitations ranging from three centimeters (94) to microscopic evaluation a big variety is represented.(95-97) A curative intent, with few exceptions, is understood as a resection with negative margins, called an R0 resection.(4) In the ESMO guidelines, the decision about whether a margin is adequate or not is being shifted into a multidisciplinary setting where surgeons, pathologists and radio oncologists are to decide about the success of the resection. As mentioned before, a resection with a

rim of healthy tissue around it is recommended and factors like histopathologic subtype, preoperative therapies and presence of anatomical barriers need to be considered.(4)
The NCCN guidelines recommend resection with negative margins and “appropriately” wide margins; further, adjuvant radiation therapy for tumors that were resected with margins closer than one centimeter or in cases of microscopically positive margins on bone, major blood vessels or nerves is suggested.(7)
In a review by authors from Germany the so-called R-classification is used as their choice for description of tumor margins.(98) In this classification an R0 resection means that the surgical margins are macroscopically and microscopically negative for tumor cells; R1 would mean a surgical margin which is microscopically contaminated or marginal tumor resection along a pseudo capsule; R2 would describe an intralesional tumor resection. In the above mentioned review, the german authors also discuss the variety of different definitions of minimal resection margins. They mention different textbooks and studies that name a range of two to three centimeters as appropriate while other studies went “closer” and stated margins >10 mm or even 1 mm uncontaminated margins as safe. Also the possibilities of even closer but negative margins – margins closer than 1 mm but free of tumor cells – are discussed. (99,100) Conclusively in this review the R-classification is described as best suited for clinical needs in routine practice. (98)
In another literature review concerning the TNM-staging system applied by the International Union against Cancer (UICC), the category of residual tumor (R-classification) was emphasized. (101) It is mentioned that various authors suggested and preferred a classification of residual tumor in resection specimens, which respects a 1 mm cut-off. The suggested classification – from this point called UICC-classification – would state an R0 margin as margins ≥1 mm; R1 would mean margins that are <1 mm to the tumor and R2 would however mean macroscopic tumor contamination. (101) (Table 5)

R-classification	UICC-classification
R0: tumor does not reach resection margin a/o intact barrier; allows margins <1 mm	**R0:** resection margin ≥1 mm
R1: microscopic tumor contamination of margin	**R1:** resection margin <1 mm
R2: macroscopic tumor contamination	**R2:** macroscopic tumor contamination

Table 5. Comparison of R- and UICC- classification of resection margin

The detection of positive resection margins should result in therapeutic consequences or at least consideration of closer follow up, especially if this was not the planned result of surgery. The status of surgical margin is widely seen as the most important surgical factor for local control and failure should not easily be accepted.(102) In statistical analyses of most studies resection margin status has not consistently been shown to be directly correlating with decreasing survival rates. Indeed positive resection margins are shown to increase the risk for distant metastases, which themselves are a risk factor for inferior overall survival. (8,99,102,103) In a rather recent study that was conducted to evaluate the impact of resection margin status on overall survival, a correlation of positive resection margin with worse OS was confirmed. (104) Interestingly, in that study patients with microscopically positive resection margins were grouped together with patients with clear margins that were 2 mm or closer in width (=”inadequate margin”). Inferior overall survival was shown in this group with inadequate margins. Further noticeable was the low cumulative 5-year probability of local recurrence of 4,1 percent in that study, which the author explained by mentioning the high rate of additional radiation therapy (70 %). (104) If a resection margin is planned as a close and possibly R1 resection in order to preserve critical structures like vessels, nerves or bone, adjuvant radiation therapy should be the logic consequence to reach appropriate local control.(105) Studies have proven that also preoperative radiation therapy is a good option to maintain local control.(106) Another study on a large cohort suggests that local recurrence and disease specific survival may be inferior in those cases, but the authors suspected that this is due to aggressive tumor biology and that resection technique alone is less accusable.(105)

1.5.3 Re-resection

In the case of R1 resection margins as an unexpected result of surgery or as the result of a "whoops" procedure before referral to a specialized center, re-resection of the tumor bed should be considered. On the one hand, there have been endorsing results in terms of local control after re-resection, but on the other hand, this procedure contains some difficulties. The success of local control via re-resection may depend from variables like contamination at primary procedure, tumor biology and the intention or non-intention of performing an aggressive second procedure. (105) The effect of partial resection with subsequent re-resection seems not to be leading to inferior results in terms of local control and overall survival in most studies. However there has been shown a higher rate of metastases in this group of patients. (107,108) Furthermore the subsequent morbidity has shown to be higher after re-resection (more functional impairment) as well as the need for secondary plastic surgery has shown to be higher after re-resection. (47) Another study has shown, that the importance of a planned and careful procedure of primary tumor resection cannot be emphasised enough.(109) Following results shown in this study, it is stated that similar or even better local control after a re-resection-procedure shown in the past, may be biased by selection and referral. Smaller and superficial tumors are more frequent in the group of re-resected tumors and should therefore be expected to show a better outcome a priori.(48) These tumors are more often subject of a whoops-procedure as they are more frequently confused with benign lesions and less often primarily referred as their bigger and deep counterparts.(109) Conclusively re-resection is recommendable after R1 resection, mandatory for R2 resection margins and may be completed with additional radiation therapy if adaptable. (17)

1.6 Radiation Therapy

Radiation therapy is the second major treatment modality for soft tissue sarcomas as its combination with surgery has been proven to be beneficial in terms of local control. (110) The complementation of surgery with local radiation therapy is more effective than either modality alone. The local control rate in the setting of conservative surgery and additional radiation therapy can be improved by approximately 20 percent compared to surgery alone. (110) The intent of radiation therapy is to minimize vital tumor cell load at the site of disease and in the best case to eliminate micro satellites of tumor or microscopic tumor

contamination which may remain after surgery. The established radiation dose to eradicate residual tumor lies between 50 and 65 Gy depending from the modality of therapy.(111) The greatest effect of radiation therapy has been described for high grade tumors and its application is substantial after surgery with confirmed contamination of resection margins. (112) Systemic reviews show that the local control rate for extremity and trunk wall STS with negative and microscopically positive resection margins reach values around 90 % and a beneficial effect for local control even for intralesional resection could be shown. (13) As mentioned before treatment recommendations suggest the application of radiation therapy for so called high risk tumors with the attributes of high grade, larger than 5 centimeters and deep to muscular fascia. The factor high grade is in general handled as an indication to consider adjuvant radiation therapy. (4,7)

As radiation therapy entails side effects like higher rates of wound complications, bone fractures, lymph edema and tissue fibrosis the decision on not applying it in all cases needs to be taken with care.(113) Literature provides discussions on which criteria and predictive factors allow surgery alone to be the treatment of choice. A project at the Memorial Sloan-Kettering Cancer Center (MSKCC) was conducted to construct a nomogram to facilitate the assessment of whether radiation therapy needs to be applied or not.(114) The idea is to individually calculate a score for STS-patients based on five factors (age, size, margin status, histology and grade), which will predict the probability of local recurrence in the first three and five years after resection. Even if the prediction of this nomogram is not a hundred percent reliable (concordance index of 0.74) it may however be a useful tool for adjuvant treatment decisions. (114) (Figure 5) According to this nomogram and the guidelines surgical resection alone should be reserved for low grade, superficial and smaller than 5 centimeter lesions. Cases of low grade STS - other than well differentiated liposarcomas or atypical lipomas - that are larger in size (>5 cm) but superficial should lead to a discussion about the indication of radiation therapy in a multidisciplinary setting.(4,114)

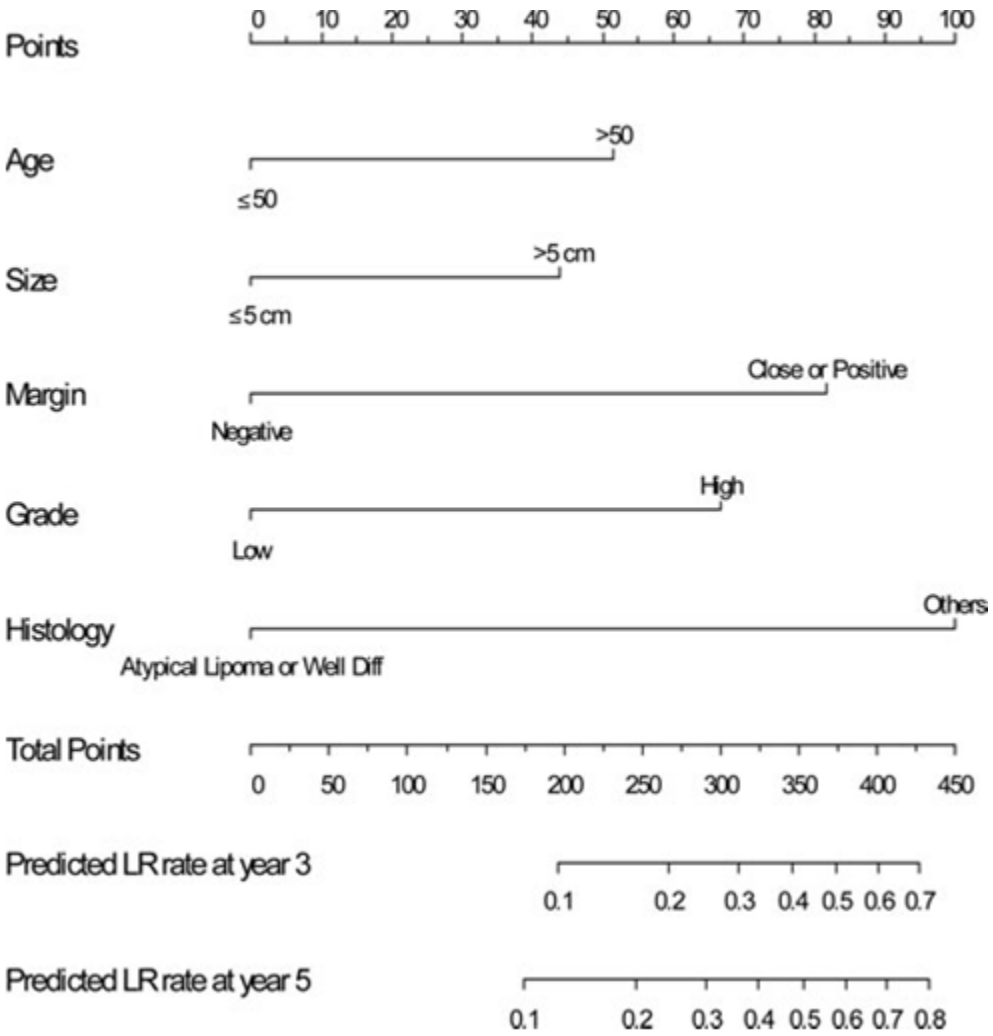

Figure 5. Nomogram for assessment of local recurrence of STS, MSKCC (114)

1.6.1 Preoperative versus postoperative radiation therapy

Based on the literature the decision between preoperative versus postoperative radiation therapy is not driven by the oncologic outcome as the first line criteria. Oncologic considerations like local control, distant metastasis and overall survival have been shown to be equal for the two investigated radiation techniques. (113,115) The generally used dose for preoperative RT is 50 Gy with an additional postoperative boost of 16-20 Gy when the pathology report confirms contaminated resection margins; on the other hand the dose for postoperative RT ranges around 66-70 Gy in most protocols. The fractions of RT are usually 2 Gy per day. (113,115)

The more important considerations for the application of pre- or postoperative RT concern the entailed complications of the treatment modalities. For preoperative RT the rates of wound complications that demand secondary surgery or intensified wound care are higher

(35 versus 17 % (115)). The more frequent complications of postoperative RT include late effects like fibrosis with field contracture and even necrosis. (113) Also the rates of limb edema and joint stiffness seem to be higher in postoperative RT. (106,111,116) Comments on the mentioned study suggest that the management of the early wound complications may be easier to handle. There are also suggestions that the decision can be made depending from the site of tumor. As higher rates of wound complications in the lower extremity have been observed a postoperative RT setting could be preferable at that location. The lower dose and possibly smaller radiation field of the preoperative RT may be preferable in the upper limb as neurovascular structures can benefit and functional outcome could be better. (106,113,115)

1.7 Chemotherapy

Chemotherapy is not part of the standard treatment recommendations for adult type localized STS, as numerous studies of various therapy protocols could not provide results that would justify such recommendations. (117-119) A rather recently published multicentre randomised controlled trial did not show advantage of adjuvant chemotherapy after resection, when administered in patients with high grade, non- metastatic disease. The overall survival and relapse-free survival did not reveal significant differences between the two groups (adjuvant CT versus no CT).(117) Nevertheless, resection and radiation therapy will apparently not directly influence and improve systemic control, prevention of distant metastasis and therefore overall survival of STS. Consequently, further treatment modalities and options are required in terms of improving oncologic outcomes.
Scenarios that evoke consideration of chemotherapy in a multidisciplinary setting include intermediate or high grade, large tumors, nodal involvement and recurrent tumors. Primary unresectable tumors naturally demand additional therapy options as well. In the case of systemic disease with pulmonary metastases or other distant metastases, chemotherapy should be applied. Palliative chemotherapy is the standard treatment for extrapulmonary metastatic disease.(4)
The main chemotherapy agent for treatment of STS is the anthracycline doxorubicin and literature does not provide evidence, that multi agent chemotherapy would be superior in terms of survival rates to single agent therapy with doxorubicin. (120) One of the latest studies on the topic investigated whether intensified doxorubicin plus ifosfamide therapy could improve oncologic outcomes for patients with locally advanced, unresectable or

metastatic high grade STS. (120) The findings indicate that there is no support for the intensified therapy as overall survival was not superior; slightly better outcomes were seen for the response rate and median progression-free survival. At the same time, adverse events and toxicity were clearly more frequent in the intensified therapy group. (120) One randomised phase III study has shown that chemotherapy with regional hyperthermia provides better oncologic outcomes than chemotherapy alone. (16) This relatively new technique includes chemotherapy (EIA protocol: etoposid, ifosfamide and doxorubicin) and regional hyperthermia that aims to heat up tumor tissue to 42°C over 60 minutes during the chemotherapy. The rates of local control, disease-free survival and overall survival were favourable in the combined treatment group.(121)

There is an ongoing discussion concerning the benefit of chemotherapy regarding overall survival based on various randomised clinical trials and their inclusion in meta-analyses. Meta-analyses (122,123) claim to see evidence for superior outcome while some of the most recent randomised clinical trials (117) alone do not support these findings. (72) Another trend in chemotherapy of STS seems to go into the topic of histology based therapy, as higher response rates of single histologies to specific agents have been shown(4)

1.8 Non-resectable soft tissue sarcomas

In cases of locally advanced soft tissue sarcomas decision making in terms of treatment modalities becomes more complex. Extensive tumors may become unresectable due to unfavourable site or involvement of neurovascular structures to an extent that would not permit the salvage of a functional limb. In some patients surgery is not feasible due to the clinical situation with high morbidity. There is no international consensus for the treatment of such cases and the variety of options between referral centers is big. Many scenarios are described in literature ranging from radiation therapy alone to combined chemoradiotherapy or other local treatment modalities to systemic chemotherapy in a palliative setting. (121,124-126)

Studies that investigated the role of radiation therapy in this setting concluded that there are chances for local control of STS. (124,127) Cases with gross residual disease after biopsy or resection and the impossibility of further surgery were evaluated after treatment with RT. The estimated 5-year local control rate was at 30 – 45 percent, ranging at rates that reach less than half of local control rates after surgery plus RT. Local control was

reported to be inferior especially for large tumors with a diameter larger than 10 centimeters. (124) Furthermore a better outcome concerning overall survival and local control could be shown with doses higher than 63 Gy when compared to doses lower than this cut off. In union of the above named numbers for local control and a 5 –year overall survival rate of 35 percent there is however a significant portion of patients that could be treated successfully by definitive RT. (124)

An option for local treatment of STS that can be used as induction therapy prior to surgery or as a tool to reach resectability is isolated limb perfusion (ILP). The modality is a regional chemotherapy technique that can be applied for extremity STS. The idea of the procedure is that after isolating the affected limb from the systemic circulation, chemotherapy agents can be administered in high doses without creating adverse systemic effects. Large diameter cannulas are being inserted in the external iliac artery and vein for the lower limb and in the axillary vessels for upper limb treatment. Via these cannulas a regional chemotherapy of the limb is possible after excluding superficial veins from the circulation using a tourniquet. Additionally the isolated limb is being put under elevated temperatures between 38°C and 42°C. Corresponding to a review of literature (125), several studies have been conducted to investigate tumor response to ILP using different agents. The most effective combination with the best risk profile seems to be tumor necrosis factor alpha (TNF-α) plus melphalan. (15,125,128,129) This technique was found to increase the limb salvage rate drastically even in cases with highly endangered limbs. In a cross section of many studies response rates lie between 63 percent and 96 percent and limb salvage ranges between 58 percent and 94 percent. (15,128) However, ILP is an invasive procedure and does come along with adverse effects like edema, erythema or even necrosis that may lead to amputation anyways. New techniques with different chemotherapy agents are being developed and investigated on, for example the isolated limb infusion (ILI). This is a less invasive technique using percutaneous catheters and it has shown promising results with 80 percent response rate in first studies; larger studies are mandatory for its evaluation however. (125)

In this setting of advanced and primary non-resectable disease the decision to choose the appropriate treatment strategy is a very delicate one. Many factors like histology of tumor, age and co-morbidity of the patient, site and size of tumor must be respected and taken into consideration in order to find the best solution for the patient.

1.9 Local recurrence

Local recurrence (LR) of soft tissue sarcoma is an important topic and is the main focus of this study. The rates of LR naturally fluctuate between reference centers but range between 10 and 18 percent for most studies for STS that have been resected with or without additional radiation therapy. (102,130,131) Possible factors for the occurrence of local failure have been narrowed down in literature in the last three decades. While criteria like resection margin and grade are generally accepted as factors for LR (and partially for survival (132)), there are others that are more discussed and uncertain like age and tumor site. (102)

The meaning of local recurrence of soft tissue sarcomas itself is controversial. It seems obvious that LR is a negative outcome for the patient as it is bonded with emotional distress, additional surgery and subsequently higher morbidity including wound complications etc. It is furthermore linked with higher costs due to further and more intensive follow up and treatment necessity.(133,134) The impact of local recurrence on the development of distant metastases (DM) and overall survival (OS) is understood differently by various authors.(8,9,133,135) Early studies of the oncologic impact of local recurrence frequently come to the conclusion that there is a significant predictive value of LR for DM and OS.(8,9) As a counterpart to this association, other studies have found minor importance of local recurrence for DM and correlate higher rates of metastases with more aggressive tumor biology and higher tumor grade.(133,135) A recent publication of a single institution experience found direct impact of LR on survival but not on distant metastases.(136) The findings of that study are deduced to the fact that many patients died from loco-regional disease, which provides the explanation of worse local control impacting on survival(136) Conclusively, it is hard to tell if LR is a causative factor for worse survival or if it is an indicator in the course of aggressive tumor disease.

For the detection of local recurrences it is important to guide and motivate the patients to go through diligent follow up examinations. Typically for soft tissue sarcomas, the scheme for follow up may depend on several factors. As the malignancy of a lesion furthermore determines the speed at which local recurrence and also distant metastases will occur, this criterion should be respected in the follow up period.(4,104) While high risk lesions generally relapse in the first 2 to 3 years after resection, low risk tumors usually relapse later and less frequent. (4,137) MRI of former tumor site is probably the most appropriate imaging technique for investigations on local recurrence although it has not been shown to be beneficial for every STS patient.(138) As distant relapse most frequently arises in the

lungs, CT scan is likely to pick up metastases more reliably. In practice the follow up of surgically treated high-grade patients will consist of examinations every 3 to 4 months in the first 2 to 3 years with a following reduction to 2 examinations per year until the fifth year and annual assessment after the fifth year. For low grade patients follow up may mean examinations every 4 to 6 months with longer interval thoracic imaging in the first 3 to 5 years and subsequent annual follow up. (4)

Factors, whose predictive value for LR could be established by numerous reported series, include positive resection margin status and presentation with locally recurrent disease itself. (103,133,139) Further factors in this context would be age of patient over 50 years and high grade of tumor.(130,139) Some series also confirmed that patients who received adjuvant radiation therapy were less probable to suffer from local failure.(136,140) The variables of tumor depth in relation to fascia (superficial or deep to it) and size of tumor at presentation show more conflicting results.(102) As described separately tumor violation as an adverse event in surgical procedure causes higher rates of LR.(139)

The treatment of locally recurrent disease resembles the general algorithm as for primary STS. The objective of treatment is once more the surgical excision with negative resection margins. However, as it is discussed as an unfavourable factor for other oncologic endpoints (DM, OS), application of more extensive pre- and postoperative treatment modalities should be considered.(4,7) It has been reported that amputation rates in treatment of LR rise, as secondary resection for recurrent disease naturally demands more extensive surgical procedures.(140)

1.10 New predictors for the clinical course of STS

New predictors for the clinical course of STS are subject of investigations. Based on the background that DNA repair mechanisms play a role in cancer development, a group of polymorphisms in pathways of these mechanisms has been analysed for a possible association with LR and OS in STS. The results of a recent study do not indicate an association between certain polymorphisms in the genes RAD51, XRCC2 and XPD - components in DNA repair mechanisms – and time to recurrence and overall survival.(141) One study that was published in 2014 demonstrated for the first time that there was a correlation between elevated preoperative uric acid levels and increased cancer specific survival in patients with STS.(142) The inflammatory blood marker c-reactive

protein (CRP) has been evaluated in its impact on oncologic outcomes in STS patients. It has been shown that elevated CRP levels correlated with inferior results concerning cancer specific survival and disease free survival.(143) In that same work the CRP level was successfully added into the Kattan nomogram and elevated pre-operative CRP levels resulted as an independent predictor for poor prognosis in STS patients. Similar results were reported for elevated pre-operative fibrinogen levels, which predicted poor outcome in STS patients.(144) Evaluating fibrinogen levels has been shown to be improving the predictive value of the Kattan nomogram and to be an independent prognostic parameter. Further investigations on inflammatory processes and tumor micro-environment focused on pre-operative levels and relations of inflammatory cells. In these studies it could be shown that there are certain pre-operative cell ratios with independent predictive value for oncologic outcomes in STS patients.(145,146) An elevated pre-operative neutrophil/lymphocyte ratio (145) and a low pre-operativ lymphocyte/monocyte ratio (146) have been shown to correlate with poor prognosis for patients with STS.

The awareness of these independent predictors gives reason for enthusiasm for further developments in this field. The above named predictors – uric acid, CRP, fibrinogen and inflammatory cell ratios – are cost effective and ubiquitous methods to assess prediction of clinical outcome for patients with STS. Further studies may be expected that integrate these predictors in systems that could be the basis for individualised decision making in the treatment of STS. (142-146)

2 Material and Methods

To conduct this study, data of patients with soft tissue sarcomas that have been treated at the department of Orthopaedics and Orthopaedic Surgery at the Medical University of Graz, were included in a retrospective analysis.

2.1 Dataset

Our analysis is based on a dataset that includes soft tissue sarcoma patients that underwent surgical treatment between 1998 and 2013 at the above named institution. This dataset included patients' demographics like age and gender and further disease related information like histologic diagnosis (21) and surgical treatment modality.

2.1.1 Completion of dataset

In order to execute more detailed analysis of the soft tissue sarcoma cases, a completion of this dataset was conducted. The patients' files were reviewed and surgical and pathological reports of biopsies and/or definitive surgery were analysed. Further collected data concerned neo-adjuvant or adjuvant therapy.
The final dataset comprehended data for age and gender of the patients, and the tumor characteristics histology, size, depth, grade and localisation. Information about the treatment modalities includes the modality of surgery, resection margin status and administration of radiation therapy and chemotherapy. The endpoints were the occurrence of local recurrence, distant metastases and death of patients. The inclusion criteria contained the diagnosis of a STS and surgical resection with/without adjuvant treatment modalities, treated between 1998 and 2013. Patients with the diagnosis of a rhabdomyosarcoma or a desmoid tumor were excluded while atypical lipomatous tumors (=low grade liposarcomas) were included. Patients that were lost to follow up were excluded.

2.1.2 Patients and definition of characteristics

Between 1998 and 2013 there were 374 patients who underwent surgical treatment at the department of Orthopaedics and Orthopaedic Surgery at the Medical University of Graz and were included in this retrospective study. Follow up was performed until September 2013. Patients were referred to the department either with primary disease or after resection at peripheral hospitals with diagnosis of a sarcoma in the pathologists' reports in 116 cases. Surgical conduction with a limb sparing approach was feasible in the majority of cases and was performed by specialised surgeons. The primary intent of surgery was to conduct a wide resection with macro- and microscopically negative resection margins. The only exceptions in the intent of surgery were (low grade) atypical or well differentiated liposarcomas, in accordance with modern recommendations and guidelines. (4) In the second half of the analysed period, for these tumors a marginal resection was planned, as these tumors show no tendency for local recurrence in the extremities.(4,147)
In the multidisciplinary approach, high risk patients were administered adjuvant radiation therapy as a standard technique. The main criteria that led to adjuvant RT were high grade of tumor, large size of tumor and adverse events like intraoperative tumor violation. Criteria for administration of chemotherapy consisted of high risk for systemic disease (following nomograms and multidisciplinary evaluation), primary inoperable tumors with neurovascular involvement and gross residual disease after prior whoops procedures. (4)
Follow up schedules consisted of following the patient every two to three months in the first three years, then every six months until the fifth year, thereafter annually. Examinations comprehend clinical examination, MRI of tumor site and CT and plain radiography of the lungs in alternation and ultrasound of the abdomen.
For statistical analysis the above described factors underwent univariate and multivariate evaluation and were defined as follows. The patients' demographics were defined as male versus female and ager under 50 years versus 50 years or older. Categories for tumor histology were divided into seven categories, namely liposarcoma, leiomyosarcoma, myxofibrosarcoma, fibrosarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor (MPNST) and others. The factor size was analysed using five centimeters or larger versus smaller than five centimeters as cut off. The depth of a tumor was described in its relation to the fascia with deep versus superficial. In this context deep means that the tumor is localised deep to the fascia or involves the fascia. The grading of tumors was analysed with the dichotomous pattern of low grade versus high grade. Low grade comprehends G1

tumors following the FNCLCC grading system and high grade includes all others, so-called G2 and G3 tumors. Localisation of the tumor was divided into five categories, including lower extremity, upper extremity, thoracic/trunk, head/neck and retro-/intra-abdominal. The extremity categories also included the upper or lower girdles, respectively. Biopsy and resection specimens were examined and diagnosed by three specialized pathologists throughout the whole series and in few particular cases another reference STS pathologist was consulted. Since the factor resection margin status was of special interest for our study, we conducted more complex analysis in this matter. We used two different classifications for the resection margin status for the same study population to subsequently confront the results and reach a conclusion about advantages or disadvantages of each. As far as the provided information in the pathology reports allowed it, we applied the R-classification, which allows margins closer than one millimeter to be regarded as R0, and opposed it to the UICC-classification, which declares margins closer than one millimeter as positive resection margins (R1). (For a more clear description of the applied classifications see chapter 1.5.2. Resection margins and Table 5.)
For the additional treatment modalities radiation therapy and chemotherapy there were again dichotomous categories; the same goes for the end point data that most importantly concern local recurrence. Local recurrence was registered from the day of surgical procedure to LR or date last seen or death of the patient. Follow up period of patients was registered as months between date of surgical procedure and end point or date last seen or death of patient, respectively.

2.2 Statistical analysis

For statistical analysis our primary end point was local recurrence with a special emphasis on the factor resection margin. We conducted univariate and multivariate cox regression analysis for both the R- and the UICC-classification to assess the hazard ratio of R0 versus R1 resection margins in the two classifications. Further, the time depended local recurrence rates for 5- and 10 years were determined using the Kaplan-Meier survival curve analysis and comparing the factors with the log-rank test.
The demographic and other tumor specific factors were partially included in the multivariate cox regression analysis, since this method includes a time-coefficient. The factors age, grading, depth, size and gender were added to the factor resection margin in

the multivariate analysis. Descriptive statistics were computed using the chi-square test and Fisher's exact test, where applicable.

As additional interest we conducted analysis for overall survival of patients, defining the end point as death of patient or date last seen. For this end point also LR and distant metastases were included as factors in the multivariate analysis and resection margins status was replaced. Distant metastases were investigated using chi-square and Fisher's exact test in cross-tabulations to estimated trends for possibly causative factors. For statistical analyses we used SPSS (version 22, IBM SPSS Statistics, 2013) and we considered p-values below 5% as significant results.

3 Results

3.1 Clinical data and presentation of patients

In the period between 1998 and 2013 there were 374 patients that were treated at the before mentioned reference center and could be included in our study. Our analyses included 184 female and 190 male patients with a percentage of 50,8 % male patients. With a count of 296 there were more than 70 % of patients that were 50 years or older. The mean age at definitive surgery was 59 years with a range between 16 to 96 years. The most frequent tumor localisation was the lower extremity (including girdle) with 59,1 %. The localisations lower extremity, upper extremity plus thoracic/trunk accounted for 96,5 % of patients, which leads to the deduction that following results are mainly valid for soft tissue sarcomas of the extremities and trunk.
The most frequently seen histology was myxofibrosarcoma with 27,8 % followed by liposarcoma and leiomyosarcoma. The category of otherwise diagnosed STS comprised 23,0 % of patients which was a higher percentage than for leiomyosarcoma. The STS in our study concerned mainly high grade tumors as 79,9 % of patients were G2 or G3 tumors. This conclusion was also represented by the percentages of staging following the AJCC staging system, where stage III was the most frequent with 35,0 % followed by stage II A with 27,8 %, both of which describe high grade tumors (with few exceptions, see chapter 1.4.2 Staging of soft tissue sarcoma). Approximately two thirds of STS were located deep to fascia with a count of 247 and a percentage of 66,0 % deep located tumors. The included tumors were mainly large tumors with 269 tumors that had the size of 5 centimeters or larger in the pathology report. This represented 71,9 % of soft tissue sarcomas being large tumors. The exact numbers and percentages clinical data are provided in table 6.

	Absolute count (n)	Percent (%)
Included patients	374	100,0
Sex		
Female	184	49,2
Male	190	50,8
Age		
<50 years	105	28,1
≥50 years	296	71,9
Localisation		
Lower extremity	221	59,1
Upper extremity	89	23,8
Thoracic/trunk	51	13,6
Retro-/intraabdominal	8	2,1
Head/neck	5	1,3
Histology		
Myxofibrosarcoma	104	27,8
Liposarcoma	92	24,6
Leiomyosarcoma	42	11,2
Synovial sarcoma	31	8,3
MPNT	15	4,0
Fibrosarcoma	4	1,1
Other	86	23,0
Grading*		
Low grade (G1)	74	19,8
High grade (G2 +G3)	299	79,9
AJCC stage*		
I A	16	4,3
I B	57	15,2
II A	104	27,8
II B	42	11,2
III	131	35,0
IV	23	6,1
Depth of tumor		
Superficial	127	34,0
Deep	247	66,0
Size*		
<5 cm	104	27,8
≥5 cm	269	71,9

Table 6. Clinical and patient related data

- * data for grading, size and therefore stage are missing for 1 patient in total

3.2 Additional treatment modalities and end point data

The counts of treatment modalities that were additionally applied to surgical resection are presented in table 7. In 243 cases additional postoperative radiation therapy was applied for high grade tumors and in cases of low grade tumors with uncertain condition of resection margins. Another variable in this matter were amputations that received additional radiation therapy in a minor part of cases. There were 30 amputations in total which represents 8 % of cases.

In total 76,6 % of high grade tumors received additional radiation therapy. In total there were 78 cases where neo-adjuvant and/or adjuvant chemotherapy was administered, which means that 21% of patients underwent chemotherapy. Of those patients with chemotherapy, 93,6 % were high grade tumors and 78,2 % of CT-patients concerned tumors larger than 5 centimeters.

	Absolute count (n)	Percent (%)
Radiation therapy		
No RT	131	35,0
RT	243	65,0
Chemo therapy*		
No CT	293	79,0
CT	78	21,0

Table 7. Additional treatment modalities

- * 3 patients with missing data concerning chemotherapy

Included in our analyses there were following counts for our defined end points. Local recurrence as the primary end point and greatest interest of our study showed a percentage of 8,8 % and a count of 33 patients with LR. The mean follow up period for this end point as defined before was at 47,2 months with a range between 2 and 178 months. Distant metastases were seen in 83 cases making up 22,2 % of patients of which 23 cases were primary metastases, in concordance with the numbers for stage IV disease described before (Table 6) . Overall survival as defined before showed 122 patients and 32,6 % of death with a mean follow up period of 49,9 months. The described counts and percentages are presented in table 8.

	Absolute count (n)	Percent (%)
Local recurrence		
No LR	341	91,2
LR	33	8,8
Distant metastases		
No DM	291	77,8
DM	83	22,2
Overall survival		
No death	252	67,4
Death	122	32,6

Table 8. End point data

3.2.1 Resection margin status

The results of the surgical procedures, when defined by resection margin status after definitive surgery, are shown in table 9. In the R-classification the count of positive resection margins was at 32 resulting in a percentage of 8,6 % positive resection margins. In the UICC-classification the count of positive resection margins was at 47 with a high percentage of 30,7 %. The analysis of the UICC-classification was conducted with the limitation that in only 153 cases the necessary information was provided in the pathology report. There was a trend towards more detailed reporting from the beginning of the study period until the more recent years.

	Absolute count (n)	Percent (%)
R-classification		
R0	342	91,4
R1	32	8,6
UICC-classification*		
R0	106	69,3
R1	47	30,7

Table 9. Results of surgical resection: margin status in the two different calssifications

- * limitation for the UICC-classification, as only 153 had the necessary data provided in the pathology report.

3.3 Local recurrence

Following tables and descriptions assess relevant factors or suspected relevant factors for local recurrence that were included in uni- and multivariate cox regression analyses. Trends for LR in selected cases will further be described.

3.3.1 Univariate cox regression analysis of local recurrence

In univariate cox regression analyses the factors that reached significance were age and resection margins, both when the R- or the UICC-classification were used. For the factor age there was a higher risk for patients at the age of 50 years or older to suffer from local recurrence than for patients under the age of 50 years. The hazards ratio (HR) for LR, which was computed in univariate analysis was at 4,19 for patients ≥50 years. The p-value was at 0,018 and the results are therefore assumed significant.
The results for the two different classifications of the resection margin status were both significant with p-values smaller than 0,01. For the R-classification the hazards ratio for local recurrence after R1 resection versus R0 resection was at 5,62. For the UICC-classification the R for LR after R1 resection was at 10,08 while the same limitations as mentioned before are valid for this classification. The factors sex, localisation, grading, depth and size did not reach significance in univariate cox regression analysis. The described data and results are listed in table 10.

	Hazard ratio	95% Confidence interval	p-value
Sex Male (vs. female)	1,751	0,85 – 3,61	0,129
Age ≥50 years (vs. <50 y.)	4,19	1,28 – 13,74	**0,018**
Localisation Non-extremity (vs. extremity)	1,11	0,43 – 2,88	0,83
Grading High grade (vs. G1)	1,81	0,70 – 4,70	0,22
Depth Deep (vs. superficial)	1,35	0,61 – 2,99	0,47
Size ≥5 cm (vs.<5 cm)	1,76	0,72 – 4,26	0,21
R-classification R1 (vs. R0)	5,62	2,67 – 11,84	**<0,01**
UICC-classification R1 (vs. R0)	10,08	2,87 – 35,41	**<0,01**

Table 10. Univariate cox regression analyses for LR

3.3.2 Trends for local recurrence

While for the cox regression analyses the localisation of the tumor and its impact on local recurrence rates was defined in a dichotomous manner (non-extremity vs. extremity), a more differentiated approach was tried using cross tabulations. A more detailed categorisation was applied with the subgroups upper extremity, lower extremity, thoracic/trunk, head/neck and retro-/intra-abdominal.
In table 11 the calculations of the cross tabulation are described. While the chi-square test shows a significant p-value of 0,014 for this analysis, the applicable value of these results needs to be considered with care. There is a slight trend for higher LR rates in STS of the lower extremity and a lower LR rate for STS in the thoracic/trunk region. The upper extremity takes a median position between the two before named and the other localisations may not be interpreted as valid, as the numbers for these tumors are low in our study (13 STS of retro-/inra-abdominal and head/neck regions in total).

	No LR	LR	Total
Localisation			
Upper extremity	83 (93,3 %)	6 (6,7 %)	89
Lower extremity	199 (90 %)	22 (10 %)	221
Thoracic/trunk	50 (98 %)	1 (2 %)	51
Retro-/intra-abd.	6 (75 %)	2 (25 %)	8
Head/neck	3 (60 %)	2 (40%)	5
			p-value 0,014

Table 11. Cross tabulation for localisation of STS and LR

3.3.3 Multivariate cox regression analyses for local recurrence

3.3.3.1 R-classification

When the R-classification was applied for the resection margin status, the significant factors for local recurrence in multivariate cox regression analysis were gender, age, grading and resection margin. For the factor gender, male patients had a hazard ratio of 2,24 for local recurrence, with a p-value of 0,040. This factor was not significant in univariate analysis. The factor age remained a significant factor in multivariate analysis. Patients at the age of 50 years or older had a HR of 3,77 for LR when compared to younger patients, and the p-value was 0,029. The factor grading showed a statistically significant association with LR in multivariate analysis with a HR of 2,70 for high grade with a p-value of 0,049.

The factor resection margin status, applying the R-classification was an even more clear risk factor for LR in multivariate analysis than in univariate analysis. After an R1 resection the HR for LR was at 7,94 compared to R0 resection, with a p-value <0,01. The exact numbers are also visible in table 12.

	Hazard ratio	95% Confidence interval	p-value
Sex Male (vs. female)	2,24	1,04 – 4,84	**0,040**
Age ≥50 years (vs. <50 y.)	3,77	1,15 – 12,44	**0,029**
Grading High grade (vs. G1)	2,70	1,00 – 7,27	**0,049**
Depth Deep (vs. superficial)	1,45	0,62 – 3,36	0,39
Size ≥5 cm (vs.<5 cm)	1,18	0,46 – 3,05	0,73
R-classification R1 (vs. R0)	7,94	3,52 – 17,94	**<0,01**

Table 12. Multivariate cox regression analysis for LR, using R-classification for resection margin status

3.3.3.2 UICC-classification

When the UICC-classification was applied for the definition of resection margin status, the only significant factor for local recurrence was resection margin status. The factors gender, age, grading, depth and size did not reach significance in this analysis. For resection margin status R1 in the UICC-classification the HR for LR was 9,44 with a p-value of <0,01. The described results are listed in table 13.

	Hazard ratio	95% Confidence interval	p-value
Sex Male (vs. female)	0,97	0,34 – 2,80	0,95
Age ≥50 years (vs. <50 y.)	3,41	0,44 – 26,27	0,24
Grading High grade (vs. G1)	1,17	0,39 – 3,56	0,78
Depth Deep (vs. superficial)	1,06	0,34 – 3,28	0,92
Size ≥5 cm (vs.<5 cm)	1,74	0,36 – 8,34	0,49
UICC-classification R1 (vs. R0)	9,44	2,57 – 34,68	**<0,01**

Table 13. Multivariate cox regression analysis for LR, using UICC-classification for resection margin status

3.3.4 Kaplan-Meier survival curve analyses for local recurrence

For the factor resection margin status and its two different classifications in this study, Kaplan-Meier survival curve analyses were conducted to get a more detailed idea of local recurrences over time. The 5-year local recurrence rate for all cases was at 12 % and at 10 years the LR rate was at 16 % (Figure 6).

When the KM curve was analysed including the factor resection margin we retained following results: For the R-classification, after R0 resection the 5-year LR rate was 10 % and after 10 years LR was at 12 %. After R1 resection the 5-year LR rate was at 34 % and the 10-year LR rate was at 51 %. These results had a p-value of <0,01 in the log-rank test and are illustrated in figure 7. For the UICC-classification, after R0 resection the 5-year and 10-year LR rates were at 6 %. After R1 resection the 5-year LR rate was at 33 % and after 10 years LR was at 48 %. The results are illustrated in figure 8.

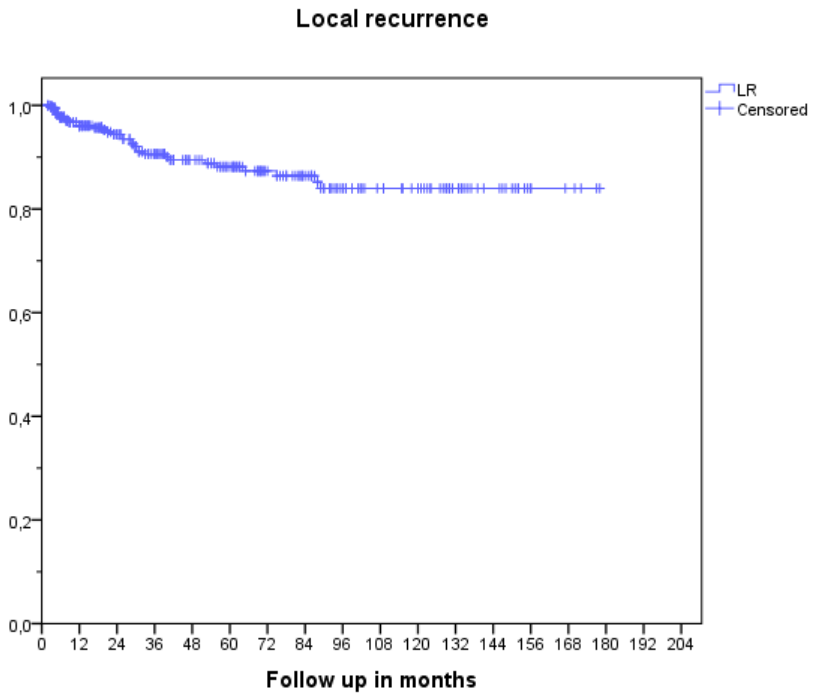

Figure 6. KM curve for local recurrence, all cases

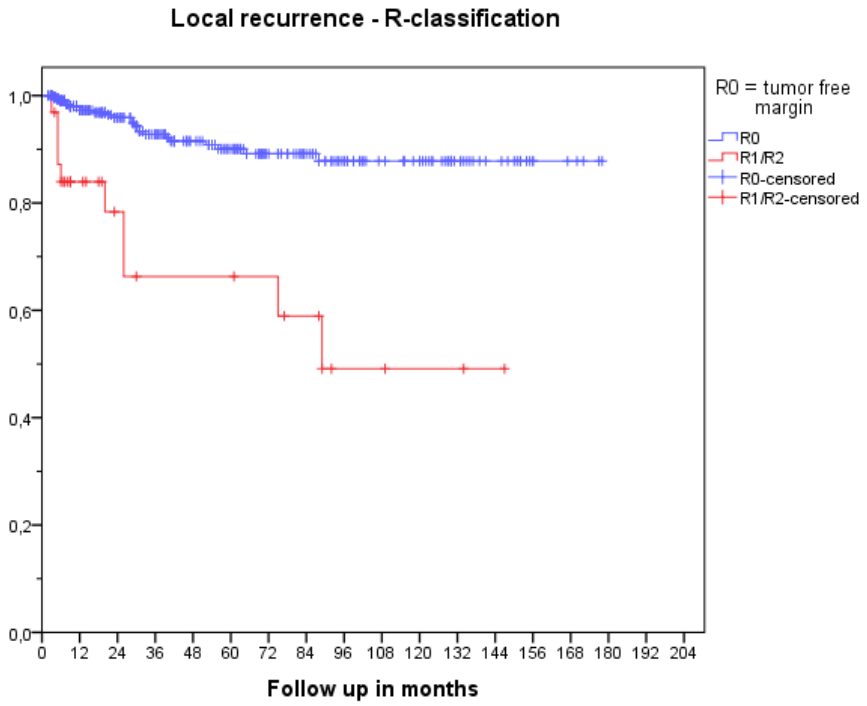

Figure 7. KM curve for LR, resection margin status defined by R-classification

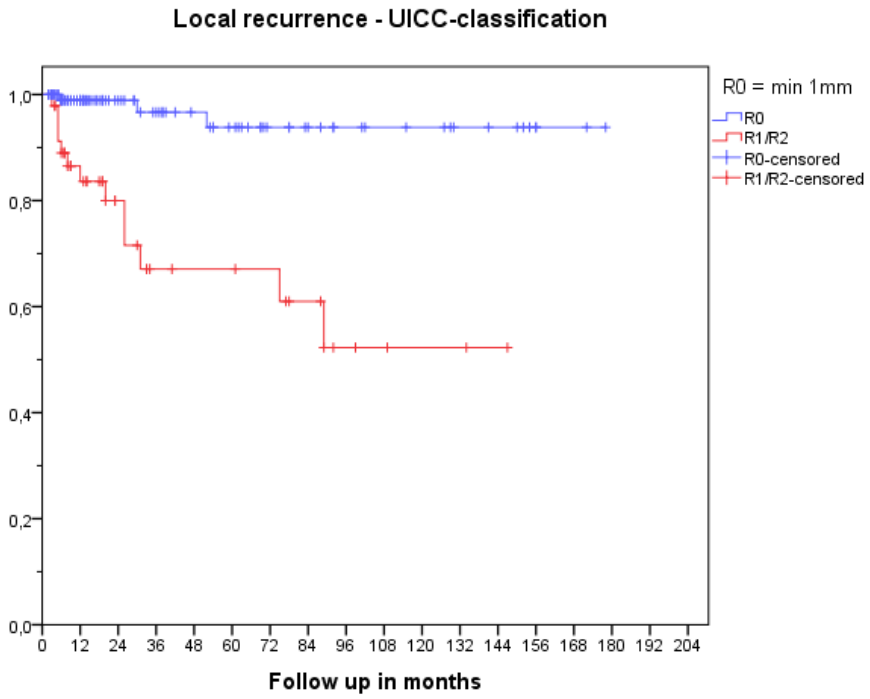

Figure 8. KM curve for LR, resection margin status defined by UICC-classification

3.4 Distant metastases

As distant metastases are of interest due to their role as oncologic factors for survival and outcome, we conducted simple analysis in order to assess factors that might influence the occurrence of DM. Using cross tabulations we could distinguish various factors to show a trend for higher or lower probabilities for developing distant metastases.
For local recurrence, chi-square test showed significant results with a p-value <0,01 for the association of LR and a higher rate of DM (standardised residual for LR and DM was 2,8). The factor age reached significance in the chi-square test with a p-value of 0,022; although the standardised residuals (stR) did not surpass the 1,96 landmark. The trend shows lower DM rates for patients under the age of 50 years. For the factor grading, there was a significant trend towards lower DM rates in low grade tumors. There was a percentage of 5,4 % of DM in low grade soft tissue sarcomas with a stR value of -3,1. The p-value was <0,01 in chi-square test.
The other factors that were included in chi-square testing did not reach significance. Not significant factors in the cross tabulations for DM were resection margin (R-classification p-value 0,17; UICC-classification p-value 0,21), localisation (p- value 0,28), depth (p-value 0,59) and size (p-value 0,25). The significant factors and corresponding numbers can be seen in table 14.

	No DM	DM	Total
Local recurrence			
No LR	273 (80,1 %)	68 (19,9 %)	341
LR	18 (54,5 %)	15 (45,5 %, stR 2,8)	33
			p-value <0,01
Age			
<50 years	90 (85,7 %)	15 (14,3 %)	105
≥50 years	201 (74,7 %)	68 (25,3 %)	269
			p-value 0,022
Grading			
Low grade (G1)	70 (94,6 %)	4 (5,4 %, stR -3,1)	74
High grade (G2+3)	220 (73,6 %)	79 (26,4 %)	299
			p-value <0,01

Table 14. Cross tabulations and chi-square test for DM (significant factors)

3.5 Overall survival of soft tissue sarcomas

Additionally, we analysed the overall survival rate of soft tissue sarcomas using multivariate cox regression analyses and Kaplan-Meier survival curves.
In multivariate cox regression analysis, the three factors age, grading and distant metastases at presentation reached statistical significance in their influence on overall survival (OS).
Patients who were 50 years or older had a hazard ratio of 2,14 for death in OS analysis with a p-value of <0,01. For the factor grading, high grade tumors showed a higher risk of death. The HR for high grade tumors was 3,50 with a p-value of <0,01. The factor that seemed to have the strongest negative influence on death in OS, were distant metastases at presentation. Patients who had DM at presentation showed a HR of 4,24 for death with a p-value of <0,01. The factors gender, depth, size and local recurrence did not show significant results. The results of the multivariate cox regression analysis for OS are presented in table 15.

In the Kaplan-Meier survival curve analysis estimations of overall survival of patients with STS were executed. The overall survival at 5 years was at 69 % and after 10 years the survival rate was at 50 %. The curve for overall survival is presented in figure 9. When the factor DM at presentation was included in the KM survival curve analysis the 5-year OS was at 72 % when no DM were present at presentation and at 20 % when DM were seen at presentation. Described numbers are illustrated in figure 10.

	Hazard ratio	95% Confidence interval	p-value
Sex			
Male (vs. female)	0,73	0,51 – 1,06	0,099
Age			
≥50 years (vs. <50 y.)	2,14	1,31 – 3,49	**<0,01**
Grading			
High grade (vs. G1)	3,50	1,85 – 6,61	**<0,01**
Depth			
Deep (vs. superficial)	0,94	0,60 – 1,46	0,79
Size			
≥5 cm (vs.<5 cm)	1,42	0,87 – 2,31	0,161
Local recurrence			
LR (vs. no LR)	1,28	0,74 – 2,21	0,377
Distant metastases at presentation			
DM (vs. no DM)	4,24	2,50 – 7,19	**<0,01**

Table 15. Multivariate cox regression analysis for OS

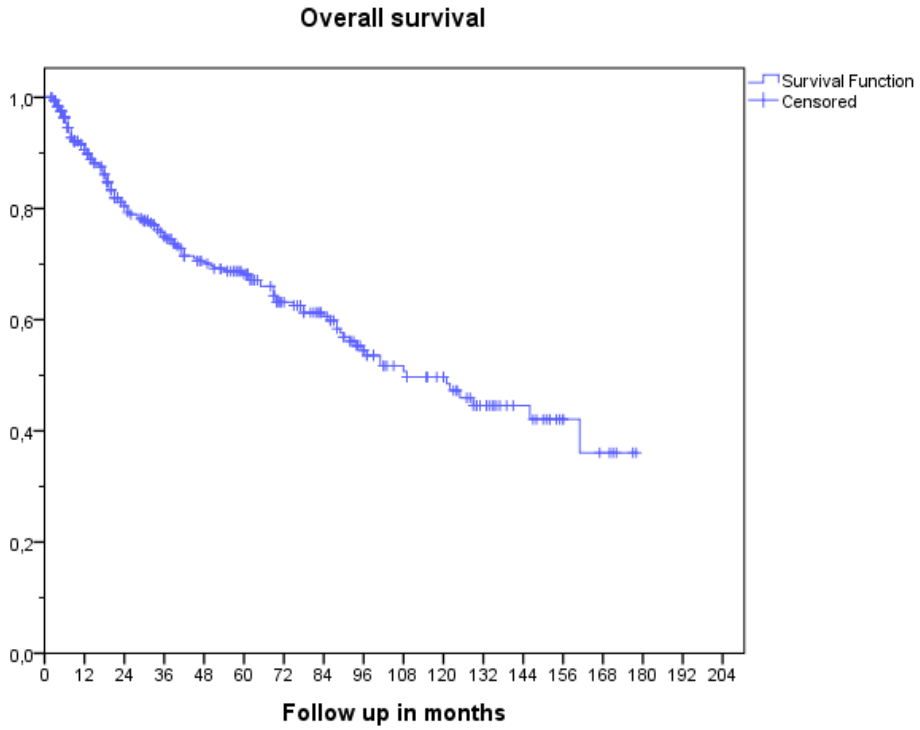

Figure 9. KM curve for overall survival

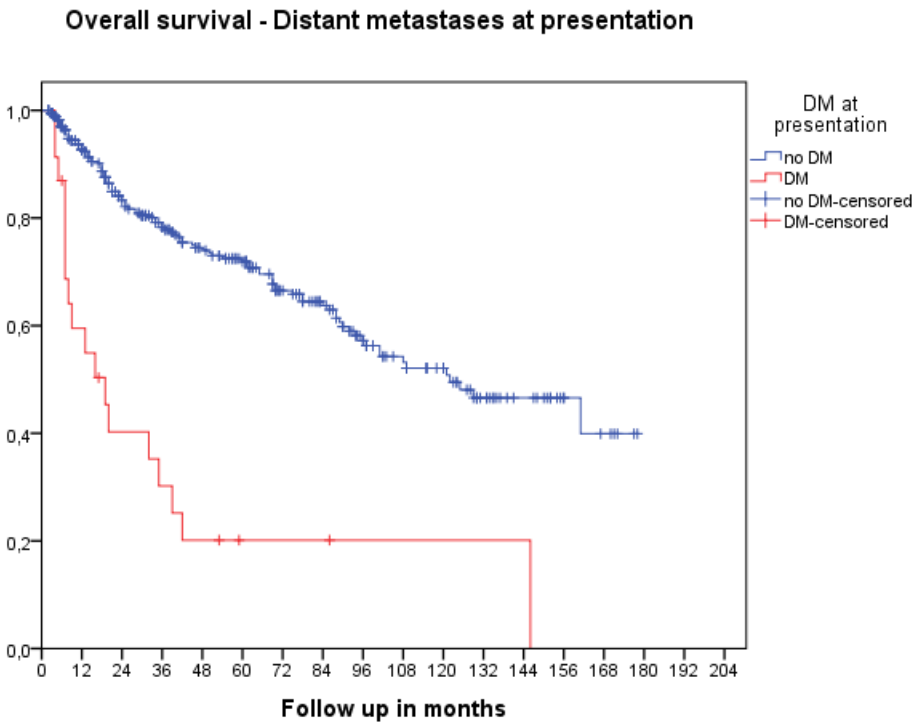

Figure 10. KM for overall survival, differentiated for factor DM at presentation

4 Discussion

In this study of 374 patients with soft tissue sarcomas of mainly extremities and trunk wall the factor resection margin resulted to be a significant factor for local control of disease. Two different classifications for the resection margin width have been applied to the same study cohort and in both cases the result showed high significance in univariate as well as in multivariate statistical analyses. These findings go in concordance with literature, as resection margin status has been well established as a crucial factor for local recurrence over the last decades. (72,97,102,103,148)

4.1 Local recurrence

The two discussed definitions of resection margin status aroused interest, since there are no clear and internationally uniform recommendations on the exact width of resection margin and its impact on local recurrence. Therefore an investigation on the benefit and advantages of different recommendations seemed to be of importance. In recent works there were two main criteria that found application in studies of resection margins. On the one hand, resection margins were stated positive (R1) when tumor tissue microscopically extended to the resection margin. Specimens that had a tumor free margin of any width to the tumor were considered with negative (R0) resection margin status. In a report from 2012 that applied this definition, the hazard ratio for local recurrence after R1 resection reached a value of 3,25 and remained one of the significant factors for LR, together with presentation status (primary disease vs. recurrent disease at presentation).(148)
Other study groups defined resection margin status as positive or negative depending on an one millimeter limitation. In detail this means that a resection margin that was closer than one millimeter in its width was defined with positive resection margin status.(97) A publication in 2013 that used the definition of tumor within one millimeter to margin as positive resection margin status, reported local recurrence after R0 resection in only three percent of cases.(95) In the same study the hazards ratio for LR after R1 resection was at a value of 6,88 in cox regression analysis.(95)
According to the definitions described above, this study used exactly these two classifications of resection margins to evaluate local recurrence rates in our cohort. The R-

classification allowed resection margins closer than one millimeter and defined a microscopically tumor free resection margin as negative (R0).(98) Complementary, a resection margin with tumor cells at the inked margin was defined as positive (R1). The UICC-classification (101) in this study, defined a resection margin status as negative (R0) when the tumor cell free margin was at least one millimeter in its width. This classification stated a resection with tumor cells within one millimeter to the margin as positive resection margin (R1).

In the univariate analysis of our study both classification reached high significance as factors for local recurrence when resection margins were positive (R1), with $p<0,01$ for both the R-classification and the UICC-classification. The hazards ratio for LR after R1 resection in the R-classification was at 5,62 while in the UICC-classification it was at 10,08. In multivariate analysis the value for HR after R1 resection were at 7,94 and 9,44 respectively with a $p<0,01$ for both the R-classification and the UICC-classification. The fact that in both modalities the hazards ratios of the UICC-classification show higher values suggests that this classification shows a higher discrimination between R0 and R1 resection and its impact on local recurrence. The multivariate analysis with the UICC-classification inserted for resection margin status, resulted with resection margin as the only significant factor for LR, which underlines the importance of this classification. Considering the Kaplan-Meier curve analyses, one might say that the results take the same line. In comparison of the 5-year local recurrence rates, the UICC-classification shows a lower LR rate after R0 resection (6 percent LR after 5 years compared to 10 percent LR after 5 years in the R-classification). Subsequently, these findings implicate that a resection margin closer than one millimeter results in a higher risk for local recurrence.

There are some limitations to be kept in mind concerning these analyses as mentioned before: first, the UICC-classification could only be adapted in 153 cases in total as the necessary information about the exact metric distance between tumor and resection margins was not provided in all pathology reports. Second, a higher percentage of positive resection margins naturally result from the more strict definition of the UICC-classification. In the decision on additional treatment modalities however, also other variables need to be taken into account. The higher number of positive resection margins may not automatically lead to an increase in the application of radiation therapy in the same proportion, but tumor properties like histology, grading, size and depth still need to be considered in concordance with guidelines.(4)

In a publication of a French research group in 2012 a new and interesting approach to the topic was introduced. (96) The intent of their study was to investigate on the significance of infiltrative proliferation and satellite nodules of soft tissue sarcoma. These tumor properties were suspected to be relevant in terms of local and systemic aggressiveness. A modified classification system of resection margin was applied: the factors margin width and tumor contour were the main criteria. When a resection margin was closer than one millimeter it was further evaluated according to its contour resulting in R0M when nodules were absent and tumor was well contoured (or margin ≥1 mm) or R1M in presence of nodules and a poor contour of tumor. The authors found a more precise and reproducible discrimination for the resection margin status and confirmed satellite nodules as prognostic factors for local and systemic aggressiveness. This modified classification may be a useful tool in assessing patients' risk for recurrent disease.(96)

In univariate cox regression analysis the only factor besides resection margin status that reached significance was age. Patients at the age of 50 years or older had a hazards ratio of 4,19 for local recurrence in univariate analysis. In the multivariate analysis (using R-classification for resection margin status) age of 50 years or older was also a significant factor, resulting with a hazards ratio of 3,77 to suffer from local recurrence. This finding goes in accordance with other studies that have shown a correlation between higher age and LR.(102) One study that confirmed the same results of higher risk for local recurrence with higher age, explained their findings based on an imbalance in variables at presentation and treatment options.(149) The authors state that their cohort of older patients presented with a higher percentage of high grade tumors. Further they report that older patients' treatment resulted more often with positive resection margin and there was a lower frequency of definitive surgery and additional treatment modalities like radiation therapy and chemotherapy for older patients. These facts may confound the correlation between older age and higher LR rates. (149)

In multivariate cox regression analysis using R-classification for resection margin status, grading was identified as a significant factor for LR. High grade tumors (G2 plus G3 STS) showed a hazards ratio of 2,70 for local recurrence in comparison to low grade (G1) soft tissue sarcomas. This result can again be compared with other works that found high grade of tumors to be disadvantageous in terms of local recurrence.(102,137,139) This fact can be seen as another confirmation that high grade tumors need to be considered for additional treatment modalities, such as adjuvant radiation therapy in first line.

Another factor that was found to be significant in the same multivariate analysis was gender with a higher risk for local recurrence in male patients. These findings cannot be confirmed by other works (104) and may be considered as questionable as gender did not reach significance in univariate analysis in our study. The factors depth of tumor and size at presentation were not found to be significant factors for local recurrence, which goes in a line with other studies in literature as they have more contradictory been associated with LR.(102,103) Soft tissue sarcomas located deep to fascia have been declared to be associated and/or confounded with high grade of tumors and subsequently depth was mostly excluded as independent factor for oncologic outcomes.(102,103)

4.2 Overall survival

In further analysis of our cohort for the endpoint overall survival, the results of higher age and grading being adverse factors for survival in soft tissue sarcomas were found. These findings are in concordance with literature. (102,131,139) In our analysis size did not show significance as an adverse factor for overall survival (tumor 5 cm or larger). In literature however, size is described as an important factor for overall survival and tumor mortality respectively.(102,131) It has been stated that resection margin status has an impact on mortality in soft tissue sarcomas.(104) It is well established that resection margin is correlated with poor survival outcomes due to correlation with local failure and distant metastases.(97,139), but also a more direct impact on survival has been suggested, which was not confirmed by the results of our study.(136)

In our study the factor with the greatest impact on overall survival in multivariate analysis was the presence of distant metastases at presentation with a HR of 4,24 and a $p<0,01$ for death. Furthermore, a clear difference in overall survival was seen in the Kaplan-Meier survival curve analysis, where the 5-year overall survival rates with and without distant metastases at presentation were at 20 % and 72 % respectively. Metastatic disease has been described as the most common cause of death in patients with soft tissue sarcomas of the extremities. (139) Local recurrence did not show significance in multivariate analysis for overall survival and did not go in concordance with other works.(8,136) However in the analysis of trends for distant metastases, local recurrence did show a significantly higher percentage in developing DM. Other factors that showed such trends towards development of DM were age and grading. These results go hand in hand with being predictors for lower overall survival.

5 Conclusion

Soft tissue sarcomas are a rare disease and need to be treated at reference centers according to updated guidelines. As the main treatment modality consists of surgical resection and optional adjuvant radiation therapy, the evaluation of resection margins is an important criterion of treatment quality. In our study the most favourable outcome was observed for a minimal resection margin of one millimeter (UICC-classification), as the local recurrence statistics resulted significantly lower when this definition was applied for the resection margin status. Further factors that were identified to be significant for local recurrence mainly go in accordance with the literature and were age, grading and gender.
Referring to the results of this study it seems to be appropriate to state resection margins with a minimal width of one millimeter as negative resection margin status, on which further decision in the treatment of soft tissue sarcomas may be based. Consistent reporting of resection margins in width and even tumor contour are important fundamentals in the treatment of soft tissue sarcomas.

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