Diplomarbeit

Diagnosis and therapy of intra-abdominal and retroperitoneal metastases in patients with soft tissue sarcoma

eingereicht von

Angelika Johanna Schaffler

zur Erlangung des akademischen Grades

Doktor(in) der gesamten Heilkunde

(Dr. med. univ.)

an der

Medizinischen Universität Graz

ausgeführt am

Universitätsklinik für Orthopädie und Orthopädische Chirurgie

unter der Anleitung von

Univ.-Prof. Dr. Andreas Leithner
Priv. Doz. Dr. Joanna Szkandera
Dr. Dimosthenis Andreou

Graz, 27. Oktober 2015

Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbstständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

Graz, am 27. Oktober 2015 *Angelika Johanna Schaffler eh.*

Danksagungen

Ganz besonderes bedanke ich mich bei Herrn Univ.-Prof. Dr. Andreas Leithner für die Bereitstellung des hoch interessanten Themas und für die Möglichkeit meine Diplomarbeit an der Klinik für Orthopädie und Orthopädische Chirurgie in Graz verfassen zu können.

Großer Dank gebührt Dr. Dimosthenis Andreou für die ausführliche Unterstützung bei der Datenauswertung, außerdem half er mir stets mit seinem Fachwissen und konstruktive Kritik bei schwierigen Fragen weiter.

Weiters bedanke ich mich bei Priv. Doz. Dr. Joanna Szkandera für ihre Hilfe bei der Fertigstellung der Datenbank und für ihre Unterstützung bei der Korrektur meiner Diplomarbeit.

Außerdem möchte ich mich bei Dr. Per-Ulf Tunn für die interessante Zeit im Sarkom-Zentrum Berlin-Brandenburg bedanken, sowie bei allen Kollegen mit denen im Laufe der Zeit zusammenarbeiten durfte.

Bei meiner Mutter bedanke ich mich ganz besonders, da sie mich nicht nur finanziell sondern vor allem emotional unterstützt hat und bei so mancher Frage sofort mir Rat und Tat bei Seite stand.

Besonderer Dank gebührt meinen Großeltern, die mich bei schlechter Laune immer wieder motivierten weiter zu machen und mir gelernt haben niemals aufzugeben.

Weiters bedanke ich mich bei all meinen Freunden für eine wunderschöne Studienzeit in Graz, sowie für das gemeinsame Lernen, die kollegiale Hilfe und viele unvergessliche Erlebnisse.

Zuletzt bedanke ich mich bei allen, die mich in den letzten Jahren begleitet und unterstützt, interessante Gespräche geführt oder unvergessliche Momente erlebt habe.

Zusammenfassung

Fragestellung: Intra-abdominelle und retroperitoneale Metastasen sind bei Patienten und Patientinnen mit Weichteilsarkomen relativ selten. Das Ziel dieser Studie war es, die Inzidenz solcher Metastasen und die häufigsten Histologien zu erfassen sowie den optimalen diagnostischen Algorithmus zu definieren.

Methodik: 558 Patienten mit extra-abdominellen Weichteilsarkomen wurden zwischen 2000 und 2009 mit kurativen Ansatz behandelt. Es erfolgte eine retrospektive Datenanalyse. Es wurden nur Patienten, die ein Event-freies Follow-up von mehr als 24 Monaten, sowie jene, die bereits davor ein Event hatten eingeschlossen. Die mittlere Nachsorgezeit betrug für alle Patienten 58 (4-148) Monate. Zum Vergleich voneinander unabhängiger Faktoren wurde der exakte Test nach Fisher verwendet. Zur nicht parametrischen Analyse diente der Mann-Withney U Test, weiters wurden die Überlebenskurven mit der Kaplan-Meier-Methode berechnet und mit dem Log-rank-Test verglichen.

Ergebnisse: 28 (5,0%) der 558 Patienten entwickelten intra-abdominelle Metastasen nach einer mittleren Nachsorgezeit von 32 (1 -100) Monaten. 12,5% aller Patienten mit myxoiden Liposarkomen entwickelten intra-abdominelle oder retroperitoneale Metastasen, es zeigte sich im Vergleich zu 4,6% der Patienten mit anderen Histologien ein statistisch signifikanter Unterschied (p=0,044). Es ergab sich kein signifikanter Unterschied in der mittleren Tumorgröße zwischen Patienten, die keine oder eine intra-abdominelle Metastase entwickelt haben (9,5 vs. 8,9 cm; p=0,177). 90% der Weichteilsarkome, die abdominell metastasierten, waren < 5 cm. Sechs der 28 Patienten präsentierten sich mit Symptomen, wie abdominellen Schmerz oder Ileus. Mit der Anzahl von Patienten, die wir in dieser Studie einschließen konnten, konnten wir keinen statistisch signifikanten Unterschied im post-metastatischen Überleben zwischen Patienten mit intra-abdominellen Metastasen oder jenen mit Metastasen in anderen Lokalisationen nachweisen (geschätztes Überleben nach Kaplan-Meier: 25.5 Monate vs. 55.8 Monate; p=0,092). Schlussfolgerung: Das myxoide Liposarkom hat im Vergleich zu anderen Histologien, ein größeres Risiko, intra-abdominelle Metastasen zu entwickeln. Da solche Metastasen meist in Routineuntersuchungen (Ultraschall oder CT), noch vor spezifischen Symptomen, erkannt werden, sollte routinemäßig eine abdominelle Bildgebung bei Patienten mit myxoiden Liposarkomen, im Zuge der Nachsorge erfolgen.

Abstract

Background: Intra-abdominal metastases are rare in patients with soft tissue sarcomas (STS). The aim of this study was to define the incidence of these metastases, identify the histological subtypes, which most frequently develop such metastases and determine the optimal diagnostic approach.

Methods: The files of 558 consecutive patients with an extra-abdominal STS treated with curative intent between 2000 and 2009 were retrospectively analyzed. The mean age at presentation was 57 years (range, 18-96 years). In the study patients with an event-free follow-up of 24 months and those who had an event before were included. The mean follow-up amounted to 58 (4-148) months for all patients. Fisher's exact test was used to compare unrelated samples. Non-parametric analyses were performed with the Mann-Whitney U test. Survival curves were calculated with the Kaplan-Meier method and compared with the log-rank test.

Results: 28 patients (5.0%) developed intra-abdominal metastases after a mean follow-up of 32 (1-100) months. 12.5% of patients with myxoid liposarcoma developed intra-abdominal metastases, compared to 4.6% of patients with other histologies, a difference which was statistically significant ($p = 0.044$). There were no significant differences in mean tumor size between patients who developed intra-abdominal metastases and patients who did not (9.5 vs. 8.9 cm, $p = 0.124$). 90% of all STS patients with such metastases showed a primary tumor diameter of > 5cm.Six out of 28 patients presented symptoms like abdominal pain or ileus.

There were no statistically significant differences in post-metastasis survival between patients who developed intra-abdominal metastases and patients who developed metastases in other localizations (estimated survival by Kaplan-Meier: 25.5 months vs. 55.8months, $p = 0.092$).

Conclusion: Patients with myxoid liposarcoma appear to have a significantly higher risk for intra-abdominal metastases, compared to patients with other histologies. Metastases in these locations appear to be generally diagnosed in routine tests prior to specific symptoms. Therefore routine imaging of the abdominal cavity in patients at a higher risk for intra-abdominal metastases appears to be justified.

Table of contents

Eidesstattliche Erklärung i
Danksagungen ii
Zusammenfassung iii
Abstract iv
Table of contents v
Glossary and abbreviations vii
List of figrues viii
List of tables viii
1. Introduction 9
1.1. Aim of the study 10
2. Soft tissue sarcoma 11
2.1. Epidemiology of soft-tissue sarcomas 11
2.2. Etiology of soft-tissue sarcomas 12
2.3. Diagnosis of soft-tissue sarcomas 13
2.3.1. Clinical features & growth 13
2.3.2. Imaging modalities 14
2.3.3. Biopsy techniques 17
2.4. Pathology of soft-tissue sarcoma 18
2.4.1. Special histopathological subtypes 19
2.4.2. Grading system for soft-tissue sarcomas 20
2.4.3. Staging of soft-tissue sarcomas 22
2.5. Treatment of primary soft-tissue sarcomas 24
2.5.1. Resection of primary soft-tissue sarcomas 24
2.5.1.1. Resection margins 27
2.5.1.2. Re-resection 30
2.5.2. Radiation therapy of primary soft-tissue sarcomas 31
2.5.2.1. Adjuvant radiation therapy 31
2.5.2.2. Neoadjuvant radiation therapy 32
2.5.3. Chemotherapy of primary soft-tissue sarcomas 33
2.5.4. Isolated limb perfusion 34

2.6. Local recurrence 35
2.7. Metastatic disease 35
2.7.1. Intra-abdominal and retroperitoneal metastatic disease 37
2.8. Follow-up 39
2.9. Prognosis and new predictive factors Follow-up 40
3. Material & Methods 41
3.1. Dataset 41
3.2. Completion of dataset 41
3.3. Patients and definition of characteristics 42
4. Results 46
4.1. Presentation of patients and clinical data 46
4.2. Treatment modalities and end point data 49
4.3. Metastatic disease 51
4.3.1. Extra-abdominal metastases 51
4.3.2. Intra-abdominal metastases 53
4.3.2.1. Clinical features, detection and therapy 54
4.3.2.2. Characteristics of primary tumour of abdominal metastases 55
4.4. Patients survival 57
5. Discussion 59
5.1. Incidence and distribution of abdominal metastases 59
5.2. Detection modalities and therapy 60
5.3. Risk factors for abdominal metastases 61
6. Limitations 63
7. Conclusion 64
8. References 65

Glossary and abbreviations

18F FDG PET	18F-fluorodeoxyglucose positron emission tomography
AJCC	American Joint Committee on Cancer
CNB	Core needle biopsy
CRP	C-reactive protein
CT	Computed tomography
CTX	Chemotherapy
EMA	Epithelial membrane antigen
ESMO	European society for medical incology
EORTC	European Organisation for Research and Treatment of Cancer
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
FNCLCC	Federation Nationale des Centres de Lutte contre le Cancer
GIST	Gastrointestinal stromal tumours
Gy	Gray, unit of absorbed radiation
HIV	Human immunodeficiency virus
HR	Hazards ratio
KM	Kaplan-Meier (survival curve analysis)
ILP	Isolated limb perfusion
LR	Local recurrence
MFH	Malignant fibrous histiocytoma
MLS	Myxoid liposarcoma
MPNST	Malignant peripheral nerve sheath tumor
MRI	Magnetic resonance imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NOS	Not otherwise specified soft-tissue sarcoma
OS	Overall survival
PCR	Polymerase chain reaction
PTFE	Poly tetra fluoro ethylene
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)
RTX	Radiation therapy
SMA	Smooth muscle actin
STS	Soft tissue sarcoma
TNF	Tumour necrosis factor
UHPS	Undifferentiated high-grade pleomorphic sarcoma
UICC	Union International Contre le Cancer
US	Ultra sonography
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

List of figures

Figure 1. Site distribution of soft-tissue sarcoma
Figure 2. MRI of a myxoid liposarcoma of the right upper leg in a 63y.o. patient
Figure 3. Liver metastases of 64 year-old patient with myxoid liposarcoma
Figure 4. Kaplan-Meier survival curve for all 558 STS patients
Figure 5. Kaplan-Meier curve of post-metastatic survival

List of tables

Table 1. Most common entities of STS in a cohort of 5333 patients in Austria (28)
Table 2. Principal histological parameters of the FNCLCC grading system
Table 3. Classification of resection margins by Enneking et al. (127)
Table 4. R-classification vs. UICC- classification of resection margins in STS
Table 5 Distribution of primary metastases in 608 patients
Table 6. Clinical and patient related data.
Table 7. Additional treatment modalities
Table 8. End point data
Table 9. Distribution of metastases
Table 10. Histological subtypes of extra-abdominal metastases
Table 11. Distribution of intra-abdominal and retroperitoneal metastases
Table 12. Clinical features, detection and therapy concepts
Table 13. Histological subtypes of intra-abdominal metastases.
Table 14. Chi-Square-Tests for characteristics of patients and primary tumour.

1. Introduction

With 1-2% of all cancer diseases, soft tissue sarcomas are one of the rarest forms of malignant tumours. The term STS combines a number of various histological subtypes that emerge from mesenchymal tissue. Therefore, patients with suspicious soft tissue masses must be referred to highly specialized institutions to achieve optimal clinical outcomes (1,2).

The occurrence of metastases is especially related to an inferior outcome, and therefore an early detection of metastatic lesion is essential to provide optimal therapy. (3,4) The incidence of metastatic disease for trunks or extremity STS ranges from 40% to 50% and the spread usually happens hematogenously (5-7). Generally, the most common site for metastases is the lung, whereas certain subtypes, i.e. epitheloid sarcoma and clear cell sarcoma - are more likely to develop lymph node metastases. (5,6,8,9)

In contrast to pulmonary metastases, metastatic lesions in the abdominal cavity are relatively rare and occur usually at an advanced stage after tumour cells have already spread to other sites. The incidence of isolated abdominal metastases varies between 2.9% and 5.0%. (10-12) The diagnosis of these metastatic lesions is difficult because of the unspecific symptoms that often occur just as the metastatic disease has reached a large extent and complicate effective therapy. (10,11) This is why it is crucial to establish guidelines for efficient follow-up protocols that may include regularly imaging of the abdominal cavity. Presently, the guidelines differ drastically. Whereas radiographs and CT scans of the chest are part of the regular follow up in most of the currently established guidelines, only the guidelines by the National comprehensive Cancer Network (NCCN) recommend abdomen and pelvis CT scan for certain subtypes – myxoid liposarcoma, leiomyosarcoma, epitheloid sarcoma, angiosarcoma – during the follow-up examination. (18) Furthermore, the Society of Surgical Oncology suggests CT scans of the chest for high-grade lesions <5cm and thoracic and abdominal CT scans for patients with >5 cm myxoid liposarcoma as initial staging. (7)

To the contrary, CT or ultrasounds of the abdominal cavity are currently not part of the follow-up recommendation of the clinical practice guidelines of the European Society of Medical Oncology (ESMO). (1)

However, the detection of certain risk factors for the development of abdominal metastases would be beneficial, as the decision whether a patient should or should not undergo abdominal imaging would be easier. Farther, only high risk patients would be exposed to CT scan associated radiation and others would be saved from additional unnecessary and excessive therapy associated with false positive findings.(19,20) Due to the rare occurrence, soft tissue sarcomas, especially with abdominal metastases, have been described in rather small series with a limited number of patients. Recently published studies concerning abdominal metastases from soft tissue sarcomas and their detection by Kings et al. and Thompson et al. have stated that only insufficient results regarding certain risk factors are provided, due to limited data. (12,13)

1.1. Aim of the study

The aim of this study is to provide an update on the incidence and survival pattern as well as on clinico-pathological factors of soft tissue sarcomas that tend to develop intra-abdominal metastases more frequently. The identification of certain risk factors should ease the decision if the follow-up for certain patients should include imaging of the abdominal cavity to detect metastatic lesion earlier. Furthermore this information should help to evaluate the efficiency of established treatment regimes and guidelines.

2. Soft tissue sarcoma

2.1. Epidemiology of soft-tissue sarcomas

Soft-tissue sarcomas are defined as a group of various tumour types that mainly arise from mesenchymal tissue of the embryonal mesoderm and ectoderm. (21) At present, more than 50 different histological subtypes that include low-grade as well as very aggressive high-grade tumours have been identified by the World Health Organization (WHO). (22-24) The most common tumour entities in adulthood are pleomorphic sarcomas, leiomyosarcomas, fibrohistiocytic tumours and liposarcomas, whereas in childhood (age < 18 years) rhabdomyosarcomas, fibromatous tumours and synovial sarcomas are more commonly observed. (25)

Sarcomas of the soft tissue account for up to 21% in infancy, compared with just 1-2% of all malignant tumours in adults; consequently, they are part of the rarest tumour diseases in adulthood. The incidence rate lies between 1.8 - 5.0/100,000 per year - with 2.4/100,000 new diseases annually in Austria the rate is located in the lower half of the international incidence rate. (26-29)

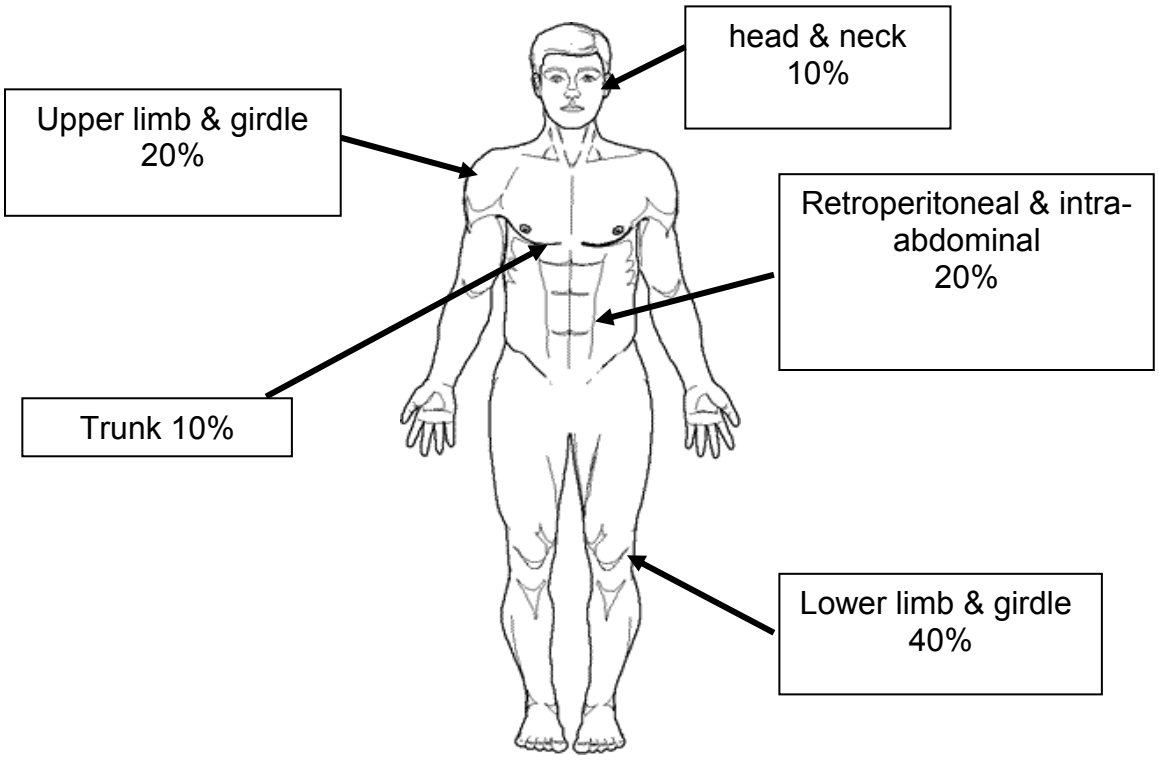


Figure 1. Site distribution of soft-tissue sarcoma (30)

The primary tumour can potentially develop at any anatomic location, although the most common sites are the lower extremities (40%), the upper extremities (20%), the trunk (10%), the retroperitoneum (20%), as well as the head and neck (10%). (30)

2.2. Etiology of soft-tissue sarcomas

The exact pathogenesis of soft-tissue sarcomas remains relatively unknown. One of the main risk factors is radiotherapy, e.g. during the therapy schedule of breast cancer. The majority of radiation associated sarcomas were histologically identified as a pleomorphic sarcoma or angiosarcoma. (31,32)

Moreover, a genetic susceptibility could be shown in various studies. For example, patients with Li-Fraumenii-Syndrome- which is associated with a germ line mutation of the tumour-suppressor p53 – tend to develop sarcomas of the soft tissue or the bone in up to 30%. Patients with Neurofibromatosis type 1 are more likely to develop a malignant peripheral nerve sheath tumour (MPNST). (33-35) Furthermore, those patients have an increased risk of radiation-associated sarcomas. (36-39) Moreover. - a rare enchondromatosis -called Maffucci-Syndrome is associated with the occurrence of multiple angiosarcomas. (40,41)

A couple of studies - mainly performed in Sweden – have stated that the exposure to certain biochemical substances like phenoxyaceticacid, chlorophenols or dioxin - which are especially used in farming and forestry - is an often-underestimated risk factor. (42,43). Furthermore, a higher risk of STS in association with viral infections like the Ebstein-Barr-Virus (44) or with scar tissue (45) has been identified.

2.3. Diagnosis of soft tissue sarcoma

2.3.1. Clinical features & growth

In the majority of cases, a sarcoma of the soft tissue presents as an asymptomatic lump that often cannot be moved, especially if they are profound to the fascia. (45) Often, they are discovered randomly - for example, after a trauma - and then often misinterpreted as a post-traumatic hematoma or a benign lesion. Therefore, smaller sarcomas are often insufficiently resected without previous imaging. These circumstances increase the risk of post-interventional complication like edema and hematoma. However, the main risk of insufficient resection is the spreading of sarcoma cells. Other potential differential diagnoses of a suspicious soft-tissue tumour are benign lesions like leiomyomas, lipomas or neuromas, as well as other malign processes like primary or secondary carcinomas, lymphomas or melanomas. (21,25)

The size of the primary tumour often depends on the location. Sarcomas of the limbs tend to be diagnosed prior to those of the abdominal cavity or retroperitoneum, as progression and an increasing size is noticed earlier. However, most of the diagnosed sub-fascial malignant tumours of the extremities have a median diameter of 9 cm.(46)

Soft-tissue sarcomas show a centrifugal growth mainly in a longitudinal fashion along natural barriers such as fascia, blood vessels or nerves. STSs that are bounded by normal anatomic barriers are defined as intracompartimental. In comparison to benign lesions - which are limited by a capsule out of fibrovascular tissue - sarcomas suppress the reactive tissue into a pseudo-capsule with digitiform or nodular satellite lesions. (47) The progression of tumour size is closely related to tumour grade: on particular, high-grade tumours tend to grow faster in comparison to low-grade sarcomas.

Due to a compression of surrounding anatomic structures symptoms like paraesthesia, pain, edema and swelling can occur. The five alerting criteria for malignancies are pain, swelling, a size > 5 cm, profound and subfascial location and a rapid growth.

Any soft-tissue tumour that fulfills these criteria is suspect and must be evaluated. (27,48,49) However, a recent study by Smolle et al. published in 2015 had investigated these factors and could show that pain is the weakest factor to predict malignancy of STSs. (50)

It is obligatory to treat soft-tissue sarcomas with a multimodality therapy concept that requires a multidisciplinary approach. Given that STSs are relatively rare, patients with a suspicious soft-tissue mass should be referred as soon as possible directly to a sarcoma center that provides the experience and demanded multidisciplinary team. (1,2) Initially after detecting a suspicious mass of soft tissue, the medical history of the patient should be obtained and a clinical examination, laboratory diagnostic and radiological imaging should be performed, followed by a biopsy, which is crucial for the histological diagnosis and the further therapy.

2.3.2. Imaging modalities

Radiologic imaging for the evaluation of suspicious soft tissues mass is decisive in terms of identifying the local extent of the tumour and the stage of disease. Furthermore, it is necessary for the planning of guided biopsies, efficient diagnosing and the following clinical procedures and treatment of the patient.

The clinical examination is often followed by ultrasonography (US). It is an ideal initial imaging method given that it is rather inexpensive as well as non-invasive and it can be easily and rapidly used. Moreover, it is not radiation-associated. Therefore, it can be performed repetitively during follow-up examination to observe a potential progression of smaller lesion. (51,52) US can provide an initial impression of the size, depth and an approximate location of the tumour, as well as information about irregular margins, intratumoural structure or the potential involvement of surrounding structures. Even a rough evaluation of the regional lymphatic nodes is possible. In addition, color doppler can be used to define the vascular situation in the soft-tissue mass.

However, certain expertise is required as a number of benign lesions like hematoma, thromboses, muscle infarction in association with diabetes mellitus, lipomas or vascular malformations can be misinterpreted as a STS. (53,54) Therefore, an exact determination of dignity is not always possible and makes further imaging before biopsy necessary.

In contrast to sonography, X-ray imaging is more rarely used, given that it shows a lower sensitivity concerning the detection of primary soft-tissue sarcoma. (51,55).

Nevertheless, the use of plain radiography is justified to identify calcificated areas in some sarcomas like synovial sarcoma, extraskeletal osteosarcoma, alveolar soft-part sarcoma or epithelioid sarcoma. (56-58)

Moreover, X-ray of the chest as part of the staging imaging to detect primary metastases is widely replaced by computed tomography (CT). However, CT has a rather limited role in the primary detection of extremity soft-tissue sarcomas, whereas it is more often used for the exclusion of tumor calcification or cortical bone destruction. (59) Nonetheless, it represents the ideal imaging method to detect primary intra-thoracic, intra-abdominal and retroperitoneal soft-tissue tumours. (60,61) Furthermore, CT is an essential feature for different interventions, like aspiration and biopsy.

Given that magnetic resonance imaging (MRI) with contrast enhancement provides exact information about soft tissue, it is the preferred imaging method for detecting and staging STS, especially prior to surgical management. (62) It shows a sensitivity of up to 91% and a specificity of up to 97%. (59). The main pulse sequences used to identify the tumour are the T2-weighted sequences with and without fat suppression and a T1-weighted sequence before and after gadolinium injection. Moreover, it is important that all diameters in three planes are measurable. (55,59) Another special technique is the magnetic resonance angiography, which provides detailed information about the intratumoral vascular status. In the MRI, intratumoral changes like necrosis or bleedings can be detected, while a difference of intensity, homogeneity and pattern of enhancement between tumour and normal tissue can also be seen. (60,62,63) Despite the accuracy of the MRI, it currently cannot identify the definitive histology of a tumour in most cases, except liposarcomas.

Therefore, further evaluation of the suspicious soft-tissue mass is obligatory. Future development in MRI technology concerning the imaging of functional, pathophysiological and metabolic processes might aid non-invasive histological diagnosis. An advantage to standard biopsy techniques would be the in-vivo 3D characterization of the entire tumour mass. (64)

At present, the 18F-fluordeoxyglucose positron emission tomography (FDG PET) is the imaging modality of choice for metabolic processes, whereby it is highly sensitive and specific in detecting STS. (65) Especially in the distinction between benign lesion and aggressive high-grade sarcomas, it is a beneficial imaging modality. It may also be useful in pre-bioptic imaging, detecting distant metastases and assessing neo-adjuvant chemotherapy. (63,65,66) However, it still plays a subordinated role in clinical routine.

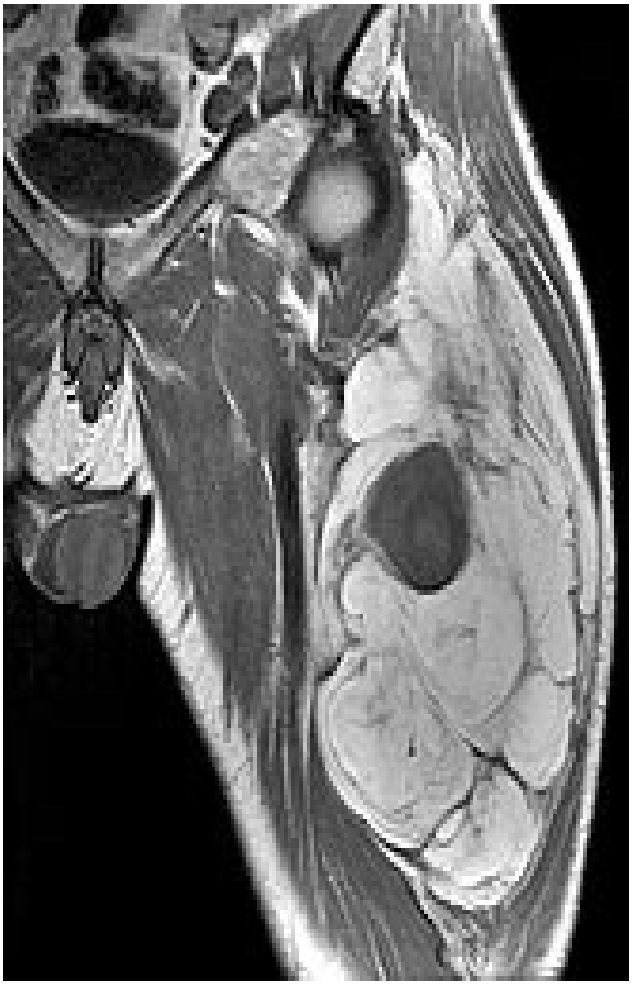


Figure 2. MRI of a myxoid liposarcoma of the right upper leg in a 63y.o. patient

2.3.3. Biopsy techniques

If malignancy cannot be excluded with non-invasive imaging methods, a biopsy must be performed. The aim of a biopsy is to obtain sufficient tumour tissue to identify the histology of the tumour. Prior to biopsy, the later surgical resection of the sarcoma should be planned with the surgeon who will perform it. Inadequate biopsy may result in tumour seeding and induce an amputation rather than a limb-sparing excision. To avoid a spread of tumour cells, the biopsy track is ideally placed in the plane of the following incision, whereby it can be easily removed during final surgery. (67,68)

The technique of choice is the core needle biopsy (CNB), a secure exact and economic method. Moreover, certain authors state that the CNB of a soft-tissue tumour should be performed by an experienced orthopedic surgeon, given that knowledge of the expected entity, size and location of necrosis is essential to avoid incorrect findings. (69,70) At least three cylinders of 14-16 G should be taken out of different parts of the lesion to receive sufficient tissue samples. (55) MRI, CT or sonography-guided procedures show an accuracy of 93%, as cystic or necrotic areas can be avoided. (71,72)

Fine-needle aspiration biopsy (FAB) is seen as a controversial technique. In newer studies, it shows an accuracy of 50 – 70%. (69,73) In older reviews, even an accuracy of up to 95% was described in combination with clinical and imaging features, especially in centers with experienced cytopathologists. (68,74)

Incisional biopsy is a reliable open technique to receive an adequate amount of tissue for diagnosis and the method of choice, as a high tumour volume can be obtained and an intraoperative frozen section analysis can be performed. However, the higher costs, the invasiveness and potential complications- e.g. hematoma, infection or tumour seeding - of this procedure must not be neglected.

The incision should be made in a longitudinal fashion by the surgeon who will perform the final intervention. In case of malignancy, the tumour must be resected en-bloc with wide margins, as well as the biopsy track. (21,68,75) If the suspicious lesion is located superficially on the limbs or trunk and < 3 cm, an excisional biopsy with minimal resection margins can be performed.

2.4. Pathology of soft-tissue sarcoma

The exact histopathological diagnosing of soft-tissue tumours remains a challenge for pathologists, given that STS are less frequent compared to epithelial tumours. (23) This is why samples of suspicious tumours tend to be sent to a reference pathologist. However, accurate histopathologic analyzing in addition to radiological imaging is essential for the decision about the resectability of the tumour and neoadjuvant therapy, as well as for predicting the clinical course. Pathologic features that are closely related to management and clinical outcome are histology, grade, staging, size and depth. (76)

Due to recent developments in molecular diagnostic procedures, the differential diagnosis and identification of histological subtypes has improved. As already mentioned, the WHO summarizes a large number of heterogeneous tumours with the term soft-tissue sarcoma. They are mainly divided by the tissue of origin or the tissue that most strongly resembles in histological pattern to the suspicious sarcoma. Typical examples are liposarcoma, myxoid liposarcomas, leiomyosarcoma or synovial sarcoma. Roughly two main subgroups can be distinguished morphologically: sarcomas with pleomorphic phenotype and those with a non-pleomorphic morphology. If the precise categorization by histological appearance is not achievable, further pathological examinations concerning the morphologic pattern (e.g. clear cell sarcoma, round cell sarcoma, alveolar sarcoma, epithelioid sarcoma, Ewing sarcoma, etc.) or immunohistochemistry for the detection of specific markers is essential for a careful assessment and to exclude differential diagnosis. (77,78)

Frequently used markers for the differential diagnosis of myoid, fibroblastic, nerve sheath and perineural cell tumours as well as synovial or epithelioid sarcomas are CD34, desmin, AE1/AE3, S100 protein, epithelial membrane antigen (EMA) and alpha smooth muscle actin (SMA). (79-81)

Furthermore, a more precise subdivision in malignant soft-tissue tumours with and without molecular aberration can be made, whereby fluorescence in-situ hybridization (FISH) or polymerase chain reaction (PCR) are performed. (82, 83)

2.4.1. Special histopathological subtypes

Due to a recent advancement in histopathological diagnostic techniques like immunohistochemistryh or cytogenetics, the term malignant fibrous histiocytoma (MFH) - the most frequently diagnosed STS in the past - should be avoided. (1,84,85) Research on this specific soft-tissue sarcoma subtype that combines a number of heterogeneous and probably not even related sarcomas has been conducted since the late-1980s, although the histiogenesis has remained controversial. (86,87) Nowadays, MFH has been replaced by the term undifferentiated high-grade pleomorphic sarcoma (UHPS), although this should be exclusively used for certain tumours without a particular cell line differentiation. (73) Further developments in genomic profiling may reveal that currently undifferentiated sarcomas can be classified more specifically. The term not otherwise specified soft-tissue sarcoma (NOS) is synonymously used for UHPS. Generally, NOS can be divided into pleomorphic, spindle cell, round cell and epithelioid subsets, although they do not have any specific histological characteristics other than the lack of identifiable line of differentiation. (46)

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 1. Most common entities of STS in a cohort of 5333 patients in Austria (28)

2.4.2. Grading system for soft-tissue sarcomas

Given that histological typing is insufficient to predict the clinical course and outcome for some STS, grading systems aim to increase the prognostic value of histopathological testing. Grading is mainly based upon intrinsic qualities of the primary tumour, like necrosis and mitotic activity. Although the importance of grading was already mentioned in the late-1940s, the first grading systems were only established in the late-1980s. (88-90) However, these systems were not internationally accepted and histological parameters have been included, excluded or changed during recent years. (91) Nowadays, the two most commonly used systems are those of the French Federation of Cancer Centers Sarcoma Group (FNCLCC) and the National Cancer Institute (NCI). Both of them use a three-grade scale. The principle parameters of the NCI system are histologic typing and gross assessment of necrosis. (90) The FNCLCC grading includes dedifferentiation, the microscopic amount of necrosis and mitotic rate in a scoring system. The sum of the scores ultimately results in a grade (G1, G2, G3) that determines malignancy. More information is seen in table 2.

As the FNCLLC grading appears to be more accurately defined and probably more easily reproduced, it is currently the most widely used system. (91) A study performed by Guillou L. et al. investigated both systems on the same cohort, revealing a slightly elevated ability to predict distant metastatic disease and tumour mortality when applying the FNCLCC grading. Due to the rarity of STS, the entire group was considered as a single entity. (92)

Therefore, grade cannot be clearly established as a prognostic predictor for every single different histologic subtype. (93,9) Especially for epithelioid sarcoma, clear cell sarcoma, alveolar soft-part sarcoma, angiosarcoma, rhabdomyosarcoma as well as Ewing sarcoma and malignant peripheral nerve sheath tumours (MPNST), grade provides lesser information than histological typing; therefore, grading is not recommended for these entities. (91,94)

Another challenge for pathologists in grading and staging STS is the tendency for tumour sampling via CNB. Even if it is an accurate procedure for histological typing, it may show limitations in terms of grading, given that it is prone to sampling error with the risk of providing a better prognosis based upon a false grading. Due to the fact that the assessment of necrosis may undergo bias, as the amount of tissue provided by CNB may be insufficient. Further sampling errors may occur if samplings are obtained exclusively in a low grade region. (95,96) Moreover, it is crucial that grading is preformed prior to any neoadjuvant therapy, given that the distinction between tumour necrosis and necrosis due to radiation or chemotherapy is not possible.

Histologic parameter	**Definition**
Tumour differentiation	Score 1: well, closely resembling normal adult tissue Score 2: moderate, certain histological typing Score 3: poor, undifferentiated, embryonal, synovial sarcomas, doubtful type
Tumour necrosis	Score 0: no necrosis Score 1: < 50% necrosis Score 2: ≥ 50% necrosis
Mitotic rate (n/10 high-power field)	Score 1: 0 – 9 mitoses Score 2: 10 – 19 mitoses Score 3: > 19 mitoses
Histological grade	Grade 1: total score 2, 3 Grade 2: total score 4,5 Grade 3: total score 6,7,8

Table 2. Principal histological parameters of the FNCLCC grading system

2.4.3. Staging of soft-tissue sarcomas

In addition to grading, staging is an approach to evaluate the prognosis and clinical outcome for patients with soft-tissue sarcomas. Furthermore, it provides essential information to determine the best therapy concept. The currently internationally used staging classification was established by the Union Internationale Contre le Cancer (UICC), in collaboration with the American Joint Committee on Cancer (AJCC). The UICC/AJCC staging is mainly based upon anatomic characteristics of the primary tumour, such as size, depth, lymph node status, as well as distant metastases and histological grading. As mentioned above, the FNCLCC is the preferred grading system, given that it shows a higher accuracy in predicting distant metastases and tumour mortality. (97) Based upon the results of latest research, the system has undergone multiple modifications. At present, the 7th edition - published in 2010 - is available. (98)

Recent controversies regarding changes in the new edition prompted various impulses for further developments of staging and prognosis. A significant modification from the 6th to the 7th edition concerning soft-tissue sarcomas is the change of lymph node positive but distant metastases free (N1M0) disease from stage IV to stage III. Furthermore, tumour depth is no longer stage effective. (97) In case of stage shifting, it is crucial to consider that it goes along with a change in prognosis but not automatically with an adaption of treatment. However, there is no direct correlation between therapy efficacy and tumour staging. The correct conclusion is rather that the success of therapy is related to tumour characteristics (e.g. size, depth, lymph node status, etc.). Thus, therapy should be adjusted to tumour attributes and not directly to the soft-tissue sarcoma staging level. (99)

The aforementioned adoptions of the 7thedition led to criticism by several authors, due to the results of a study investigating more than 8,000 STS cases. It has been discussed as the new stage III classification of N1M0 STS is stated not to be the most exact assignment. For patients with an N1M0 sarcoma, the outcome has been shown to be intermediate, since the disease-specific survival was better than that of patients with M1 and inferior to patients with G3T2 (N0M0) disease.

Accordingly, a unique staging class for N1M0 is suggested. The currently used two-tiered classification for primary tumour size (≤5 cm or >5 cm) is stated as being too imprecise. With four classes (<5 cm, 5 to 10 cm, 10 to 15 cm, and > 15 cm) being applied, a significant difference in outcome concerning the overall survival was observed by each step. (100,101) Furthermore, it is controversial that tumour depth is no longer stage relevant, even if it seems to be a significant prognostic factor. (102)

Moreover, the diversity of histology of soft-tissue sarcomas is a great challenge for the latest staging classification, due to the difficulties of grading. Indeed, even if two different subtypes - like the dedifferentiated liposarcoma and the pleomorphic sarcoma - have the same grade, the overall survival outcomes will be diverse. (100)

Overall, there is a huge continent of possibilities to specify and improve the prediction of clinical course for soft-tissue sarcomas. However, the challenge appears to be in maintaining the practicability and especially the reproducibility of staging systems in clinical routine. Given that the development of staging classifications is a process of research and advancement, further changes will take place in the future. Referring to this, specific staging systems for anatomic sites and histological subtypes have been suggested. (98,100) In these special nomograms, tumour survival should be predicted based upon clinical and histopathologic characteristics for each individual case. (103) For instance, a special postoperative nomogram was designed for liposarcomas, estimating a 5- and 12-year disease-specific survival. To develop the nomogram, the dataset of more than 900 liposarcoma cases was investigated with special regard to the differentiation of histologic variants (pleomorphic, round cell, myxoid, etc.), depth, size and margin status. (104) The most promising approach for developing an accurate classification for grading, staging and potentially even for molecular characteristics seems to be an intensive worldwide cooperation in research.

2.5. Treatment of primary soft-tissue sarcomas

The main focus will be placed upon the therapy schedule of STS of the extremities and the trunk, as well as the neck and the head. Given that primary retroperitoneal soft-tissue sarcomas, gastrointestinal stromal tumours (GIST) and Kaposi's sarcoma are excluded from the study, their treatment will not be specially mentioned here.

At present, the standard concept includes three therapy options (surgery, radiotherapy, chemotherapy), which are individually combined for each patient according to their stage, histological typing and other clinical features. As previously mentioned, for an optimal clinical and oncological outcome the treatment of any soft-tissue sarcoma should be conducted in a specialized center, as it requires a high level of expertise and experience. Nonetheless, the role of chemotherapy is still not as clear as the role of radiation. (105)

2.5.1. Resection of primary soft-tissue sarcomas

The principal treatment for almost every soft-tissue sarcoma is surgical resection. The main aim of surgery is to achieve a wide resection with negative surgical margins. If possible, it represents the cornerstone of therapy and the most effective treatment for extremity and trunk tumours. (105, 106) Therefore, the sarcoma should be removed en-bloc with a border of healthy tissue around. During resection, the sarcoma must not be incised, opened or violated in any manner, to ensure that the tumour remains intact for the entire time. It is crucial to avoid the rupture of the sarcoma and the outpouring of necrotic tissue or tumour material, especially myxoid mass. Shelling out the tumour mass along the pseudo capsule or tumour rupture are especially linked to an higher risk of local recurrence in stage III STS, a decrease in overall survival outcomes and metastases-free survival. (106)

In case of such an unfavorable event, closure of the incision with healthy tissue, extensive lavage and immediate re-excision are the procedures of choice to achieve a better clinical outcome. Further adjuvant chemotherapy and especially radiation is used to decrease the risk of local recurrence. (107,108)

Especially the extent of surgery depends on several factors, e.g. the histological entity, staging level, neoadjuvant therapy and co-morbidity of the patients. For extracompartmental atypical lipomatous tumours, marginal excision is sufficient. (109) Moreover, anatomical constraints are a challenge, as surgical techniques must be adapted. Intact periosteum is seen as a natural barrier for tumour growth; therefore, periosteal stripping must not be performed, if evitable. Several studies have shown that periosteal stripping during surgery is related to a higher risk of pathologic fractures, especially after radiation. (110-112)

Peripheral nerve involvement in soft-tissue sarcomas is an essential part of surgical management, given that it is crucial for later functionality and morbidity. Initially, nerve involvement can be evaluated by patient history and clinical presentation. At an early stage of nerve involvement, definitive signs are rare, although pain, paraesthesia, muscular atrophy or even distal motoric malfunction can often be seen. Further evaluation of peripheral nerves is usually achieved by MRI. This imaging modality is essential for decision-making, as it can often determine the probability of saving a nerve and identifying the ideal surgical access to the peripheral nerve. If MRI does not provide sufficient information, the decision concerning nerve salvage must be taken intraoperatively. The involvement of sensory and motoric nerves of the extremities (e.g. peroneal, femoral, sciatic, etc.) often resulted in amputation. Nowadays, the assessment of risk and functional benefit leads to an increase in limb salvage surgeries. (113)

As recent studies have stated that functionality after selected nerve resection is objectively and subjectively superior to amputation, limb-sparing surgery is recommended if adequate resection margins are achievable. (114) By contrast, it is usually not advisable to attempt nerve salvage in case of a completely tumour-surrounded circumference of a nerve, as this would mean opening the tumour and creating un-acceptable positive resection margins. (115)

An adequate, practical and accepted technique for nerve salvage is epineural dissection. (116) During surgery, nerve involvement should be evaluated again before the decision for epineural dissection is taken. This technique can be performed if at least 90° of the nerve circumference is in sight and not surrounded or connected to the tumour mass. This procedure should be conducted as the last step of tumour preparation.

Before a longitudinal incision of the epineurium with a fresh scalpel is made, it is recommended to cover the wound with drapes to prevent tumour spread in case of tumour violation. Subsequently, the nerve fascicles can be lifted out of the epineural sheath and every fiber that is aligned to the sarcoma or enters the tumour mass must be eliminated. In a study on sciatic nerve resection, Clarkson et al. showed that sciatic nerve resection compared to epineural dissection is not superior in oncologic outcome, while patients who underwent epineural dissection were not negatively affected in functional outcome. (116,117)

However, nerve salvage is not always feasible, despite plenty of different treatment options being available. Nonetheless, the decision concerning the ideal treatment should be taken in cooperation with the patient regarding their personal needs and goals in life. Especially in the lower extremity, functional deficits after a single nerve resection can be offset by bracing, showing generally acceptable results. Conversely, nerve resection of the median, ulnar or radial nerves in the upper limb is frequently related to devastating limitations in function and subsequently has a principal impact on daily routine. Therefore, it is usually followed by procedures to recreate suitable function, like reconstruction with autogenous nerve grafting, tendon or distal nerve transfer. (118,119) In the event of multiple nerve involvement, adequate reconstruction is often not achievable. Therefore, amputation is the treatment of choice, since limb salvage is associated with more difficulties in function than benefits. Consequently, peripheral nerve involvement remains a main issue in limb salvage surgery for soft-tissue sarcomas. Despite many surgical procedures being available to handle these sarcomas at present, further research and development in the reprogramming and regeneration of nerves may eventually make amputation and currently used techniques obsolete. (117)

Another challenge for surgical treatment is the involvement of vascular structures. It is crucial to consider the benefit of adequate resection margins, vessel salvage and later morbidity. It is usually diagnosed in MRI and MRI angiogram, which is considered the gold standard. A proven surgical technique if major extremity vessels are adjacent to the tumour is to perform the preparation of adventitia after a longitudinal incision, whereby a rim of healthy tissue will remain around the vessel-tumour interface. (120)

If resection is combined with neoadjuvant or adjuvant radiation therapy, the local tumour control is not reduced if resection margins contain vascular adventitia. (121,122,123) When the maintenance of major vessels is not realizable to achieve appropriate tumour margins, resection and subsequent reconstruction of the involved vascular structure is recommended. These procedures are required if the tumour arises from the vessel wall, or the vessel is completely embraced by the sarcoma mass. Autologous reverse saphenous vein graft is frequently used for the reconstruction. Given that the vein is not always suitable for a graft, artificial interponates out of poly tetra fluoro ethylene (PTFE) or Dacron are used. (124)

Despite different well-established techniques for vascular resection and reconstruction, an elevated risk of complications is observed. In particular, the incidence of persistent peripheral limb edema, deep venous thrombosis or wound healing deficit followed by tissue transfer is higher after surgery of a sarcoma with vascular involvement. Due to vascular failure, those patients are more likely to undergo later amputation. (125-127) Several studies have shown that local tumour control and oncological outcome is not inferior, and functional outcomes of patients who undergo vascular resection were satisfying. (127-129)

2.5.1.1. Resection margins

Essentially, the primary treatment of extremity STSs is based upon surgery with adequate marings that usually led to amputation in the past, whereby limb-sparing surgery has been established as the gold standard at present. (1,7) Therefore, adequate resection margins play a crucial role in prognosis, as insufficient resection significantly increases the risk of local recurrence. (130 -132)

However, it is a controversial issue, as there is no accordance in literature concerning a clear definition of adequate resection margins. Currently, a variety of descriptions of what is a sufficient resection is available, whereby Enneking et al. suggested the terms intralesional, marginal, wide and radical, further he distinguish contaminated resections and wide contaminated resections, in this case the tumour is completely removed but the capsule has been opened intra-operatively.(133)

Other authors prefer metric measurements ranging from 3 - 5 cm (134-136) or microscopic evaluation. (132,137-140)

	Resection level	Pathological evaluation	R status
Intralesional	In the tumour	Positive margins	R2, R1
marginal	Extra capsular, in reactive tissue	Positive margins	R1
wide	Outside of reactive tissue	Negative margins	R0
radical	extracompartmental	Negative margins	R0

Table 3. Classification of resection margins by Enneking et al. (133)

However, a resection with negative margins is seen as a curative intent -aside from few sarcoma types - and it is called an R0 resection by the ESMO guidelines. (1) Furthermore, they state that the decision concerning whether resection margins are acceptable should be taken by a multidisciplinary team where surgeons, oncologists, pathologists determine the success of the surgical therapy. Regarding primary sarcoma characteristics (subtype, size, localization, anatomical limitations, etc.) as well as neoadjuvant treatment concepts, the goals of every resection should generally be negative margins and a rim of healthy tissue around the sarcoma.

Other guidelines published by the NCCN suggest negative resection margins or appropriately wide margins, while a more precise definition is missing.

Furthermore, in case of an inadequate resection with margins smaller than 1 cm or microscopically positive margins on bone or main neurovascular structures, adjuvant radiation therapy is recommended. (18,141). In a review, several studies were compared that suggest a system to evaluate resection margins where 1 mm is accepted.

The recommended classification by the International Union against Cancer (UICC) defines a R0 resection with margins ≥ 1 mm, R1 with margins <1 mm and R2 resection is characterized by positive macroscopic margins. (142,143)

In 2009, German authors published a review of several studies and stated that the so-called R-classification is the most suitable and practical for clinical routine. In this system, R is the abbreviation of “residual”. An R0 is defined as a resection with macroscopic and microscopic negative margins and without distant tumour disease. Therefore, a sarcoma can only be classified as R0 if the pathologist has access to clinical data of the patient or a form written by the responsible surgeon that includes relevant information. R1 is characterized by microscopic positive margins or a resection along the pseudo capsule, whereas R2 means an intralesional tumour resection. If appropriate evaluation of resection margins is not feasible, the margins should be classified as RX. (139)

R status	R-classification	UICC-classification
R0	negative margins, intact anatomic barriers < 1 mm	margins: ≥1 mm
R1	negative macroscopic margins positive microscopic margins	margins: <1 mm
R2	positive macroscopic margins	positive macroscopic margins

Table 4. R-classification vs. UICC- classification of resection margins in STS

The R-classification is significantly related to therapy success, has an essential impact on future therapy concepts and is seen as an essential prognostic factor. Furthermore, STSs with contaminated resection margins are more likely to develop metastases - especially at an earlier stage - and they have a higher risk of inferior overall survival. Several authors state that resection status is the principal surgical factor. (139,140,144,145)

Thus, sarcoma with inacceptable margins should be managed with re-resection or adjuvant treatment concepts such as radiation therapy. (146) Even if inadequate resection shows a negative impact on local recurrence, metastatic-free survival and overall survival, factors like tumour aggressiveness and biology must play a major role in tumour control, given that local recurrence and metastatic disease also occurs after R0 resection. (147)

2.5.1.2. Re-resection

At early stage, STSs are often mistaken for benign soft-tissue tumours; therefore, they are frequently excised with insufficient margins before they are finally referred to a specialized sarcoma center. Re-resection is the recommended procedure if the sarcoma was initially resected in a so-called whoops procedure or if unexpectedly a R0 resection could not be achieved in primary surgery. (148) The whoops procedure is defined as the incomplete resection of the tumour by a surgeon who is not aware of the diagnosis. (149) The result of secondary resection depends on various factors, including tumour spreading and contamination during the initial surgery, biological tumour characteristics (subtype, grading, etc.). (147) Another coefficient is the aggressiveness or re-resection, which should be adapted to the needs of the patient.

However, functional outcome can be inferior in such cases, whereby subsequent morbidity can be higher and secondary plastic surgery is more commonly required (150) Several authors state that initially insufficient resection in combination with a second operation with or without subsequent adjuvant radiation therapy is not inferior or even better in disease-specific survival and local control, compared to patients who received a single surgery. (151-153) Contrary to local tumour control, a higher risk of distant metastases has been observed. However, the results of these studies are probably due to referral and selection bias. (148,153)

Moreover, small and superficial sarcomas generally show a better clinical outcome and as they are more likely to be re-resected they comprise a great part of the evaluated cohorts. (154) In summary, it can be said that secondary operation is obligatory for R2 resection and recommended in case of primary R1 resection, apart from the liposarcoma G1, as it is less aggressive and a R1-resection is acceptable.

2.5.2. Radiation therapy of primary soft-tissue sarcomas

Especially since limb-sparing therapy concepts are recommended, radiation therapy (RTX) is an important treatment option for soft-tissue sarcomas. Both neoadjuvant and adjuvant concepts show equally good results in local control, distant metastasis and overall survival. (155) O.Sullivan et al. observed in their study a slightly improved overall survival for patients who underwent neoadjuvant RTX. (156) Therefore, particularly the radiation-related complications must be taken in consideration when the decision is made concerning whether neoadjuvant or adjuvant radiation concepts should be performed. As the risk of wound complication is higher in the lower extremities, post-operative RTX could be favorable at this site. (156) By contrast certain authors state that in the upper limb, neurovascular structures and the functional outcome could benefit from the lower dose and the smaller radiation field of neoadjuvant RTX. (155-157)

2.5.2.1. Adjuvant radiation therapy

The currently recommended radiation dose for adjuvant RTX regarding the tumour appropriate treatment concept amounts to about 60 - 70 Gy. Usually a fraction of 2 Gy is applied daily. (158) The aim of RTX is to reduce the number of vital sarcoma cells at the site of primary tumour. Furthermore, it should erase micro satellites or microscopic tumour contamination after an R1-resection.

It has been proven that RTX has a beneficial impact in terms of local control, given that it can be increased by around 20% if surgery and RTX is combined. (159)

In their review, Strander et al. observed a local control for sarcomas of the trunk and extremities of up to 90% if negative and microscopically positive resection margins were subsequently treated with RTX. Furthermore, even for intralesional resected sarcomas, a benefit in local control could be seen. (160)

A recently published prospective study stated that the main value of RTX is the local control with acceptable treatment-associated morbidity, given that a statistically significant improvement of overall survival could not be proven. (161) Therefore, RTX must be considered in case of positive resection margins, primary tumours > 5 cm and tumours profound to muscle fascia.

Additionally, in high-grade sarcomas, radiation is recommended since the major effect of radiation has been shown for these sarcomas, particularly in combination after surgery. (162)

RTX represents an effective treatment modality, although it is associated with various acute and long-term side effects. Typical and frequent short-term complications are skin reactions such as erythema, acute swelling or pruritus. Often seen long-term effects are bone fractures, joint stiffness, lymph edema, tissue fibrosis and tissue indurations, as well as chronic infections, wound complications and necrosis. (155,163)

The decision to perform RTX should always be made in consideration of these complications. However, there remain no well-defined criteria in which cases RTX is beneficial and when surgery alone is sufficient. Therefore, the Memorial Sloan-Kettering Cancer Center (MSKCC) published a nomogram to evaluate the need for RTX. (164) In this system, a score for each sarcoma patient is calculated based upon five factors, namely tumour size, age at diagnosis, resection margin status, histological subtype and grade. The score attempts to prognosticate the likelihood of local recurrence in the first three and five years after diagnosis. With a concordance index of 0.75, the normogram is not 100% reliable, although it will probably be helpful to facilitate the decision concerning whether RTX is necessary. Generally the in the surgical guidelines of ESMO and according to the mentioned normogram, surgery alone should only be performed in low-grade, superficial sarcomas or in tumours < 5 cm. (1)

2.5.2.2. Neoadjuvant radiation therapy

Given that neoadjuvant and adjuvant radiation therapy show equal results in terms of oncologic outcome, preoperative RTX is especially recommended in sarcomas that are initially inoperable; for example, due to anatomic barriers or difficult anatomic situations like periarticular sarcomas. (155,156,165) The suggested dose for neoadjuvant radiation therapy is about 50 Gy (2 Gy per day).

In case of positive resection margins, adjuvant radiotherapy is additionally performed with a boost of 10-16 Gy. (166) A high sensitivity of myxoid liposarcoma to RTX was reported by several studies several years ago. (167-169)

In a recent study, the sensitivity to radiotherapy of myxoid liposarcoma (MLS) and MFH has been compared, where by a reduction of 59% in median tumour volume of MLS was observed in MRI. (170)

2.5.3 Chemotherapy of primary soft-tissue sarcomas

In literature, the positive effect of chemotherapy (CTX) is controversial and thus CTX is currently not part of standard treatment concepts for localized soft-tissue sarcomas. For the treatment of soft-tissue sarcomas, the mainly used chemotherapeutic agents are doxorubicin, an anthracycline and ifosfamide. A recent trend in chemotherapy is to use histology-specific chemotherapeutic agents or other combinations to increase the response rate. (171)

The advantage of neoadjuvant chemotherapy theoretically lies in downsizing the tumours to render the sarcoma more resectable and the subsequent surgical procedure less morbid. Especially in combination with RTX, it should present an early therapy for micro metastases, help to increase local control rates - especially in high-grade sarcomas - and should reduce the required radiation dose. (172) Preoperative CTX should be considered as a treatment option for patients with large or high-grade sarcomas, as well as for those deemed as borderline resectable. (166,173)

The decision concerning whether CTX should be performed should be taken regarding the patient's age, any co-morbidity, as well as the histological subtype, as a highly varying chemosensitivity between different sarcoma types has been observed. Especially for the extraskeletal Ewing sarcoma and rhabdomyosarcoma, systemical chemotherapy is essential. (174-176) Furthermore, the MLS as well as the synovial sarcoma have a significantly higher responsiveness to CTX than other STS, with literature having reported response rates of ≥50% for synovial sarcomas. (177-179) However, despite these results, the benefit of neoadjuvant CTX remains controversial.

Similar to neoadjuvant CTX, the role of adjuvant chemotherapy is debatable, although it is probably beneficial for certain chemosensitive subtypes. Furthermore, it might be considered in cases where RTX is not recommended for local recurrence as nearby critical structures would be affected.

Recently published reviews have reported that none or just little overall survival benefit was observed for patients treated with adjuvant chemotherapy. (180,181) Moreover, the largest study on adjuvant CTX with doxorubicin and ifosfamid with the data of EORTC 62931 could not prove the benefit from chemotherapy in progression-free survival, local control or overall survival. Woll et al. state that superior survival in other studies is probably due to the effect of improved surgery techniques and the more frequent use of adjuvant RTX. (180) In 2010 Italiano et al. evaluated the effect of adjuvant CTX and observed in a large cohort of 1513 adult patients that adjuvant chemotherapy is especially beneficial grade 3 STS. (182) However, concerning the benefit of CTX for STS, several unanswered questions remain, thus rendering further evaluation and studies necessary.

2.5.3 Isolated limb perfusion

As mentioned before limb-sparing surgery has become an important part of the treatment of STS and should be achieved, if feasible. Especially in case of huge or non -resectable tumours neoadjuvant CTX or RTX are preformed. Another treatment modality to reduce sarcoma size, is the isolated limb perfusion (ILP) with tumour necrosis factor alpha (TNF-α) or Melphalan.

The aim of ILP is to administer the chemotherapeutic intra-arterially directly at the area of tumour to maximize the effect. (183) Several studies showed that neoadjuvant isolated limb perfusion with TNF- α and melphalan with a limb salvage rate of 87% is and effective treatment modality especially for STS in the lower extremity and high-risk STS and it improves in combination with tumour resection local control.(184-186)

2.6. Local recurrence

Local recurrence (LR) occurs in 10% to 18% of all STS patients, depending on the reference center and the therapy concept, surgery with or without RTX. (146,187,188) Typical risk factors for LR are insufficient resection margins and high grade, while rather controversial factors are age and the site of the sarcoma. (146,189) Generally, high-risk STSs tend to relapse during the first two or three years after resection, whereas LR of low-risk sarcomas occurs less frequently and usually later. (1)

The main impact of LR of sarcomas is relatively unclear, although a negative effect for clinical outcome has been observed, due to psychological distress and further surgeries often associated with higher morbidity and an increased rate of wound complications.

Furthermore, it is associated with augmented financial costs, as an intensive follow-up and treatment is required. Therefore, it is crucial to motivate patients to regularly participate in diligent follow-up examinations to detect LRs as early as possible.

2.7. Metastatic disease

Especially large, deep and high-grade STSs tend to develop metastatic disease usually in the first 2-3 years after competition of primary treatment. The risk of metastases for theses sarcomas lies between approximately 40% and 50%. (5-7) By contrast, low-risk sarcomas tend to metastasise later and less frequently. Metastatic spread of extremity STS usually happens hematogenously. (5)
Several studies have shown that the lung is the most frequent site for metastases from extremity soft-tissue sarcomas. Isolated lung metastases develop in 20-50% and are associated with a poor prognosis. (21,190,191) By contrast, the incidence of lung involvement with disseminated disease has been reported around 70% to 80%. (6,8,192)

For many authors, pulmonary resection - when possible - is the ideal treatment for patients with pulmonary metastases of extremity STS, as long-term survival is possible. (21,6,193) The European Organization for Research and Treatment of Cancer – Soft Tissue and Bone Sarcoma Group evaluated 255 patients who were treated with pulmonary metastasectomy and observed an overall survival rate of 54% at three years and 38% at five years. (3) Other authors have reported inferior five-year survival rates, ranging from 25-35%. (194-196)

Certain subtypes - like epithelioid sarcoma, clear cell sarcoma and rhabdomyosarcoma - are more likely to develop metastases in regional lymph nodes. However, this type of metastatic disease is rare and accounts for less than 5% of all metastases. (21,5,9,197)

Other less frequent metastatic sites of extremity STS are bone, brain, mediastinum as well as intra-abdominal or retroperitoneal locations or liver. (1,21) In particular, the MLS has a high extrapulmonary metastatic potential. (198,1)

The median survival after detecting distant metastases of all STS ranges from 11 to 15 months and 20-25% of those patients are still alive after two - three years. (3,4) In case of unresectable metastatic disease systemic treatment provides essential symptom palliation, prevents fast progression and may prolong survival. Individualized systemic therapy is crucial and must be adapted to several factors (e.g. histology, biological behavior, comorbidities, patient's preference, etc.).

As already mentioned above, the response to chemotherapy depends on certain factors, like performance status, previous response to chemotherapeutic agents, age, presence of hepatic metastases, tumour grade, histology and the duration of the disease-free interval. (195)

In certain cases, RTX can be used for local palliation of metastatic soft-tissue sarcomas. (192) Especially for brain metastases, whole-brain radiotherapy is the standard treatment. Furthermore, external beam RTX is a successful and efficient treatment for pain palliation and to prevent morbidity associated with bone metastases. (197,198) However, the mainstay of therapy for disseminated metastatic disease of soft-tissue sarcoma is currently chemotherapy. For patients with limited disease-related burden, multimodality treatment schedules have beneficial effects on survival. (199,200)

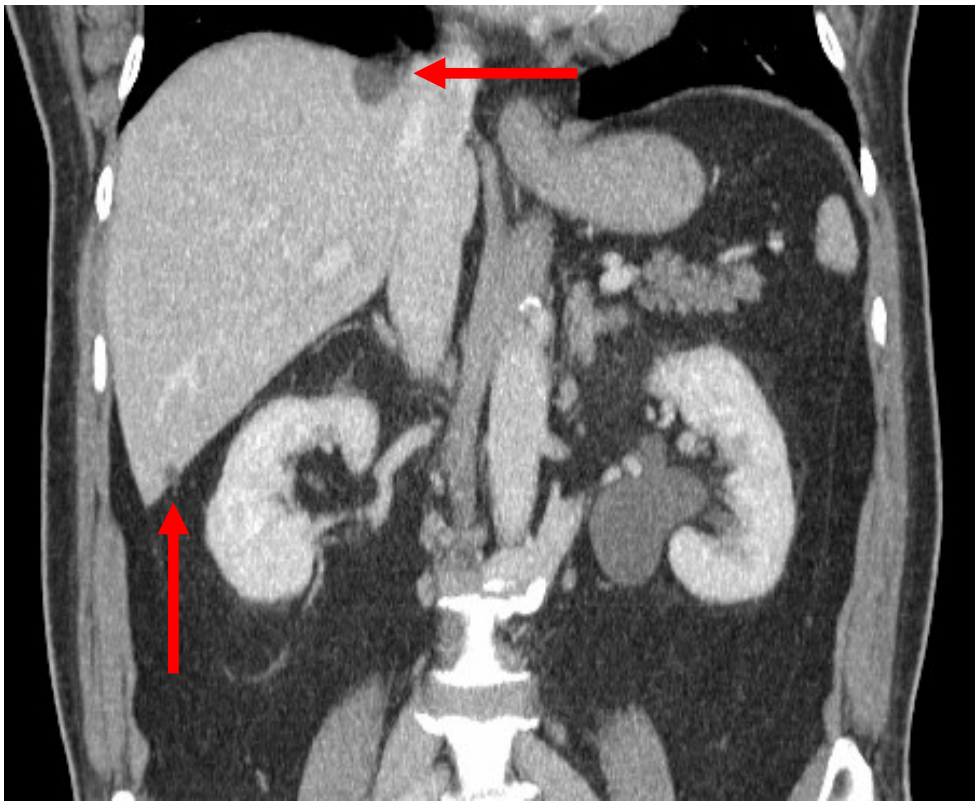
2.7.1. Intra-abdominal and retroperitoneal metastatic disease

In the natural history of extremity soft-tissue sarcoma, intra-abdominal or retroperitoneal metastases are relatively rare. When it occurs, it is commonly late in the course of disease and often after the sarcoma cells have spread to other locations, especially to the lungs. (10,11,3) The incidence of isolated abdominal metastatic disease is rather low, and varies between 2.9% and 5%. (12,13) Several studies showed that intra-abdominal or retroperitoneal metastases were diagnosed after a mean interval of 23 to 45 months after primary diagnosis. (11,14-17)

Certain histological subtypes - like the myxoid liposarcoma and the leiomyosarcoma - tend to initially develop intra-abdominal or retroperitoneal metastases. (12,13,16) A common site of these intra-abdominal metastases is the liver, whereas pancreatic metastases are relatively rare. (14,15,201,202) A study by De Witt et al. compared primary pancreatic lesions and pancreatic metastases with endoscopic ultrasound and observed that metastatic lesions tend to be well-defined, whereas primary tumours show irregular margins.(203)

The diagnosis of intra-abdominal or retroperitoneal metastases is difficult, as symptoms are vague and unspecific. Further, they manifest only when the disease is already at an advanced stage. Possible complaints are intestinal obstruction, abdominal pain, gastrointestinal bleeding, anorexia or abdominal distension.

Patients with symptoms should undergo examination and investigation for metastases. (10,11) As symptoms of intra-abdominal metastases occur relatively late, several authors recommend imaging of the abdominal cavity in regular intervals. However, no consensus has been established, whether diagnostic imaging should be preformed for all histological subtypes and whether ultrasound or CT-scan should be used during the follow-up.



Figur 3. Liver metastases of 64 year-old patient with myxoid liposarcoma

Generally, treatment must be adapted to the extent of metastatic disease. Surgical resection for isolated solitary or multiple metastatic lesions is considered as the only curative therapy, whereas all other treatment modalities are seen as palliative. (204) For the maximal clinical benefit of metastasectomy and for the reduction of treatment-associated morbidity, patient selection is crucial. However, due to the curative potential of surgical resection, all patients should be evaluated for metastasectomy. (10,11,15,205) To achieve complete resection en bloc excision of adjacent structures (e.g. colectomy, nephrectomy splenectomy) may be necessary.

In case of disseminated and non-resectable metastatic disease, systemic chemotherapy is the treatment of choice. The most commonly used multiagent regimes include doxorubicin in combination with ifosfamid, but a statistically significant improvement of survival could not be observed, compared to doxorubicin alone. (206-208) Other regimes comprehend gemcitabine with docetaxel (209) or ifosfamid with etoposid. (210)

2.8. Follow-up

Follow-up regimes aim to detect LR or metastatic disease at an early stage, when therapy is feasible and still effective. Consequently, an efficient, well-established risk-adapted follow-up schedule may prolong patient survival. (211-214) Generally, these protocols are based upon the predicted risk for local and systemic relapse. Since histological grade, subtype, tumour size, depth and localization are seen as major risk factors, they must be considered as an integral aspect in developing an efficient protocol. (215-218)

Given that the majority (>95%) of soft-tissue sarcomas relapse during the first five years after treatment, as well as about 80% of pulmonary metastases and around 70% of LR develop during the first 2-3 years of follow-up, regular examinations within this period are crucial. Follow-up for low-grade lesions should involve at least history-taking and physical examination, whereas for high-grade tumours additional imaging with chest X-ray/CT is recommended. Generally, for routine follow-up imaging, X-ray is sufficient, given that it has a higher specificity. However, in case of suspect findings and in high-risk STSs, CT scans are highly commended. (1,216) Concerning LR, especially patients' self-examination, history and physical examination, - particularly of the primary tumour site - are essential. For the early detection of LR, ultrasound or MRI are recommended by certain experts, although there remains a lack of consensus concerning the use of MRI. (219-222)

At present, only the NCCN guidelines recommend abdomen and pelvis CT scans for certain subtypes (MLS, leiomyosarcoma, epithelioid sarcoma, angiosarcoma) during follow-up. (12,13,18) Despite several authors suggesting regular abdominal CT scans, abdominal imaging is currently not part of the follow-up recommendations of ESMO. (1,6,21) At present, no consistent follow-up protocol is established and no reliable data has been published suggesting specific intervals. The ESMO clinical practice guidelines recommend examinations every 2-3 months in the first two years, every 2-4 months for years 3-4 and every 6 months for years 5-10. Subsequently, regular checks every 6-12 months are suggested, depending on the center's practice and tumour-specific factors.

As late advanced disease can even arise after more than 10 years, no generally-accepted time for stopping the follow-up has been established. Further secondary radiation-associated (angiosarcoma) or independent (acute myeloid leukemia) cancers could develop after treatment. (1)

2.9. Prognosis and new predictive factors

The prognosis of soft-tissue sarcomas depends on several well-known factors, such as age at diagnosis, tumour size, histological grade and subtype, as well as the tumour depth and primary localization. (76,130) Another evaluated factor that has a negative impact on prognosis is being aged older than 60, as such patients are more likely to have multiple comorbidities and are frequently treated with a less aggressive therapy. (223,224) Therefore, overall 5-year survival rates may vary between 50% and 75%. (21,225)

Several recent studies aim to identify new predictive factors for the clinical course and outcome of patients with STS. Given that DNA repair mechanisms are an essential factor for cancer growth, a recent study has evaluated the association of certain genes for DNA repair pathways with oncological outcome. However, no correlation between the genes RAD51, XRCC2 and XPD and the overall survival or LR could be shown. (226)

By contrast, another study observed a high risk of tumour-related death if there is a co-expression of survivin, an inhibitor of apoptosis and human telomerase reverse transcriptase. (227)

A study published in 2014 was first able to show that higher preoperative uric acid levels are associated with superior tumour-specific survival for patients with soft-tissue sarcomas treated with curative intent. (228) Furthermore, a correlation between elevated c-reactive protein (CRP) levels and tumour aggressiveness as well as inferior cancer-specific survival has been observed. (229,230) Moreover, it has been shown that a preoperatively low lymphocyte/monocyt ratio, elevated plasma fibrinogen level and a high neutrophil/lymphocyte ratio are associated with inferior prognosis. (231-233)

3. Material & Methods

For this study, the files of patients with soft tissue sarcomas that have been treated at the department of Orthopaedics and Orthopaedic surgery at the Medical University of Graz Austria and at the Department of Orthopaedic Oncology at the Sarcoma Center Berlin-Brandenburg in Berlin, Germany were evaluated in a retrospective analysis.

3.1. Dataset

The basis for our retrospective analysis is a dataset that includes STS patients that underwent surgical treatment with a curative intent between 2000 and 2009 at the institutions mentioned above. Patient demographics such as age, gender, time of diagnosis and other disease-related information like histological subtype, treatment regimes as well as metastatic related information have been included in this dataset.

3.2. Completion of dataset

For a more detailed evaluation of these STS cases, a completion of this dataset was preformed. The files of those patients were reviewed, patient histories were evaluated and surgical as well as pathological reports of biopsies and later definitive surgery were analysed. Further data about neo-adjuvant and adjuvant therapy as well as information about metastatic disease have been collected.

The analysed dataset included data for the age and gender of the patients, tumour characteristics like histological subtype, size, depth, grade and primary localization. Further information about the treatment regimes comprehended surgery, resection margin status, administration of radiotherapy and chemotherapy. The final endpoints were the occurrence of intra-abdominal metastases, overall survival or the patients' death.

3.3. Patients and definition of characteristics

From 2000 to 2009 558 patients who fulfilled the inclusion criteria, underwent surgical treatment in our institutions and their data was analysed retrospectively in our study. Patients with an intra-abdominal or retroperitoneal soft tissue sarcoma were excluded, as they are more likely to develop local recurrence or metastases in these localizations. (15,234) Further, patients younger than 18 years were not included, because they are usually treated more aggressively, often with neoadjuvant and adjuvant CTX. Moreover, surviving patients with an event-free follow-up of less than 24 months and those with primary metastatic disease were excluded, due to poor prognosis. The follow-ups were performed until December 2012. If patients did not come to follow-up examinations, they or their general medical doctor were called to obtain necessary information on the patient status.

Before we had excluded these patients we collected the data of 753 patients. Four of them could not be included as the primary sarcoma was located intra-abdominal or retroperitoneal. 92 patients were excluded due to an event-free follow-up of less than 24 months and 48 patients, as they had had obtained prior therapy with a non curative intent. Further, 50 patients with primary metastases were excluded. In these 50 patients 57 locations of metastatic lesions were detected. The exact distribution is seen in table 5.

	Absolute count (n)	**Percent (%)**
Total cohort	608	100.00
Lungs	36	5.9
Lymphatic nodes	16	2.6
Bones	2	0.3
Pleura	1	0.2
Liver	1	0.2
Suprarenal gland	1	0.2

Table 5. Distribution of primary metastases in 608 patients

Patients were referred to the departments with STS suspicious tumours (n=231), after external biopsy (n=101) or after resection at peripheral hospitals with diagnosis of a sarcoma in the pathologists' reports (n=226). In the majority of cases, limb-sparing surgery was feasible and performed by specialized surgeons in our centers. In the case of initial external resection, re-resection was performed when possible. The main aim of surgery was to achieve a wide resection with macro- and microscopically negative resection margins. Exceptions to the intent of surgery were made for the atypical and well differentiated liposarcoma (low-grade sarcoma) according to modern recommendations and guidelines. (1) Especially in the second half of the evaluated period, marginal resection was performed in most of these sarcomas, due to a low tendency for local recurrence in the extremities. (1)

As a multidisciplinary approach is standard of care in our institutions, high-risk patients were treated with adjuvant radiation therapy. In case of high-grade tumours, large size and adverse events such as tumour violation during surgery adjuvant radiotherapy was preformed. The main criteria for the administration of adjuvant chemotherapy were a high risk of systemic disease in accordance with nomograms and multidisciplinary. (1) The follow-up schedules in both centers included regular checks of the patient every two or three months in the first three years, and then every six months until the fifth year, and thereafter annually.

The follow-up examination included the taking of the patient's history, clinical examination, MRI of the tumour site, CT and alternating plain radiography of the lungs. Further regular abdominal ultrasound examinations were performed at the department of Orthopaedics and Orthopaedic surgery at the Medical University of Graz, whereas routine imaging of the abdomen was not part of the follow-up at the Sarcoma center Berlin-Brandenburg. In the case of abdomen-related symptoms, such as pain, bloating or obstipation, a CT-scan of the abdomen was additionally preformed additionally in both centers. The above-described factors underwent univariate and multivariate evaluation for statistical analysis and were characterized as follows.

Patient characteristics were defined as male versus female and age under or above 65 years. Seventeen histological subtypes were defined, namely liposarcoma, not otherwise specified, myxoid liposarcoma, pleomorph liposarcoma, fibrosarcoma, myxofibrosarcoma, leiomyosarcoma, rhabdomyosarcoma malignant peripheral nerve sheath tumour (MPNST), angiosarcoma, synovial sarcoma, not otherwise specified sarcoma, clear-cell sarcoma, epitheloid sarcoma, extraskeletal Ewing-Sarcoma, extraskeletal chondrosarcoma, extraskeletal osteosarcoma and alveolar soft-part sarcoma. Size was evaluated with a cut-off at five centimeters. The tumour depth factor was analysed by its relation to the fascia, in regard to whether it was profound or superficial. Further, the primary tumour was classified according to the TNM-Classification for Soft tissue sarcoma, namely T1a, T1b, T2a, and T2b.

The grading of STS was evaluated according to the FNCLCC grading system, namely G1, G2, G3. As especially for epithelioid sarcoma, clear cell sarcoma, angiosarcoma, and extraskeletal Ewing-sarcoma grade provides lesser information than histological typing, and therefore grading was not applied for these subtypes and they were classified as high grade tumours. (91,94) Moreover, grading was analysed with the dichotomous pattern of low grade versus high grade. Low grade included G1 and high grade all others. The localization of the primary STS was divided into four categories, namely lower and upper extremity, thoracic/trunk as well as head/neck. The extremity categories also comprehended the upper and lower girdles.

The biopsy and resection specimens were examined and diagnosed by five specialized pathologists; in certain cases, other reference STS pathologist was consulted. In order to classify the resection margins, we applied the R-classification, to the extent that the information from the pathology reports allowed it.

Additional treatment modalities such as radiation therapy and chemotherapy were classified in neoadjuvant, adjuvant and both therapies in combination.

Local recurrence was registered from the day when it was first diagnosed. The treatment modalities for the LR were divided into four categories (watch and wait, surgical resection, radiotherapy, chemotherapy).

The end point metastatic disease is initially divided in dichotomous categories and then in localization (lungs, lymphatic node, bone, pleura, mediastinum, pericardium, brain). Further, symptoms, the diagnostic method, how it was diagnosed (follow-up, trauma, or other) and the date, when the metastatic disease was diagnosed have been filed. The same goes for the end point data, which most importantly concerns intra-abdominal metastases. The follow-up period of patients was registered as months between the date of first presentation in our centers and the date of last presentation or the date of the patient's death.

For all statistical analyses, the Statistical Package of Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA) was used. A $p < 0.05$ was considered statistically significant. For the comparison of unrelated samples, Fisher's exact test was used. Non-parametric analyses were performed with the Mann-Whitney U test and survival curves were calculated with the Kaplan-Meier method and finally compared with the long-rank test.

The study has been approved by the Institutional Review Board of the Medical University of Graz (24-573ex 11/12).

4. Results

4.1. Presentation of patients and clinical data

In our study, 558 patients that were treated in the mentioned institutions between 2000 and 2009 could be included. Overall, 52.5% (n=293) were male patients and 47.5% (n=265) were female patients, who all had extra-abdominal and extra-retroperitoneal soft tissue sarcoma. The mean age at diagnosis was 57 years (range: 18-96 years). With a count of 221 patients, 39.6% of patients were older than 65 years. The median follow-up time was 58.3 months with a range between 4 to 148 months.

86.9% of all tumours were initially located at the extremities. The most frequent primary tumour site was the lower extremity with 70.6% (n=394), followed by the upper extremity with 18.6% (n=104), the trunk with 9.9% (n=55) and 0.9% (n=5) of all sarcomas were at the head or neck.

In the total cohort, 17 subtypes have been identified. The 558 patients were histologically classified as follows: 15.2% liposarcoma (round-cell, well differentiated), 14.7% myxofibrosarcoma, 9.9% leiomyosarcoma, 9.7% myxoid liposarcoma, 9.3% synovial sarcoma. The category of otherwise diagnosed STS comprised of 25.8% of all patients, the highest percentage.

As 74.7% of all sarcoma were classified as G2 or G3, the study concentrates mainly on high-grade tumours. Grading was not applicable for 25 sarcomas, including clear-cell sarcomas, angiosarcomas, epitheloid sarcomas and Ewing-sarcomas.

The tumour depth was defined as superficial in 36 patients, in 483 patients the primary sarcomas was located deep in the fascia, and this corresponds with 86.56% of the total cohort. For 39 sarcomas, the tumour depth was unknown. In 69.4%, the primary tumour was classified as T2b, in 17.2% as T1b, in 3.9% T1a and just 2.5% as T2a.

The evaluated sarcomas were mainly large tumours. The mean tumour size was 8.9cm with a range of 1 to 33 centimeters. In 401 patients the primary STS was larger than 5 centimeters in the pathology report.

More exact information on clinical data is provided in table 6.

	Absolute count (n)	Percent (%)
Eligible patients	558	100.0
Sex		
Male	293	52.5
Female	265	47.5
Primary tumour site		
Lower extremity	394	70.6
Upper extremity	104	18.6
Trunk	55	9.9
Head/ Neck	5	0.9
Histology		
Undifferentiated/unclassified sarcomas	144	25.8
Liposarcoma	85	15.2
Myxofibrosarcoma	82	14.7
Leiomyosarcoma	55	9.9
Myxoid liposarcoma	54	9.7
Synovial sarcoma	52	9.3
Fibrosarcoma	14	2.5
MPNST	13	2.3
Chondrosarcoma	12	2.2
Rhabdomyosarcoma	11	2.0
Angiosarcoma	9	1.6
Angiosarcoma	9	1.6
Clear-cell sarcoma	6	1.08
Pleomorphic liposarcoma	5	0.9
Ewing-sarcoma	5	0.9
Extrask. osteosarcoma	3	0.5
Alveolar soft-part sarcoma	2	0.4

	Absolute count (n)	Percent (%)
Tumour grade (FNCLCC)		
G1	124	22.2
G2	143	25.6
G3	249	44.6
not applicable	25	4.5
unknown	17	3.1
TNM-Classification		
T1a	22	3.9
T1b	96	17.2
T2a	14	2.5
T2b	387	69.4
unknown	39	7.0
Tumour depth		
superficial	36	6.4
profound	483	86.6
unknown	39	7.0
Tumour size		
< 5 cm	114	20.4
≥ 5 cm	401	71.9
unknown	43	7.7

Table 6. Clinical and patient related data.

The results of surgery were classified by resection margin status after definitive surgery. 89.1% of all the patients had negative resection margins according to the R-classification. In 39 patients, only an R1 resection could be achieved. 20 of these patients received adjuvant RTX, 11 patients had a G1 liposarcoma, and therefore the R1 resection was sufficient according to the ESMO guidelines. (1) Seven of the 39 patients did not obtain additional treatment after surgery.

4.2. **Treatment modalities and end point data**

In table 7, the counts of treatment modalities that were additionally preformed to surgery are listed. In 85 cases (15.2%) isolated limb perfusion (ILP) was applied.

In total, 43.0% (n=221) of the cohort received additional radiation therapy; in 3.4% neoadjuvant radiotherapy and in 39.6% adjuvant radiotherapy was applied. 221 patients underwent additional postoperative radiotherapy, due to a high-grade sarcoma or in cases STS with unclear resection margin status. 52.3% of all high-grade sarcoma received additional radiotherapy.

All in all, in 20.6% (n=115) of all patients, some kind of chemotherapy was preformed. 64 patients received only neoadjuvant CTX, 51 patients received only adjuvant chemotherapy and 20 patients both. 26.6% of all high-grade tumours and 22.4% of all sarcomas larger than 5 centimeters were treated with chemotherapy.

	Absolute count (n)	Percent (%)
Isolated limb perfusion (ILP)		
No ILP	473	84.8
ILP	85	15.2
Radiation therapy (RTX)		
No RTX	319	57.0
RTX	240	43.0
Neoadj. RTX	19	3.4
Adj.RTX	221	39.6
Chemotherapy (CTX)		
No CTX	443	79.4
CTX	115	20.6
Neoadj. CTX	64	11.5
Adj.CTX	51	9.1
Neoadj. + adj. CTX	20	3.6

Table 7. Additional treatment modalities

193 patients had an event during follow-up, which means that 34.6% of the total cohort developed either metastatic disease, local recurrence or both. Distant metastatic diseases were seen in 148 patients, comprising of up to 26.5% of the total cohort. All of them were secondary metastases of soft tissue sarcomas. For intra-abdominal metastases that represents the primary end point and the greatest interest of our study with a percentage of 5.0% (n=28) has been observed. The time to diagnosis of the abdominal metastatic disease was 32.7 months with a range between 1 and 100 months. 17.9% (n=100) of all patients developed a local recurrence, after a mean follow-up of 22.3 months (range: 1.6 - 94.5 months). At last follow-up 54 patients (9.7%) were dead of disease, making up 9.7% and 55 patients (9.9%) dead of other cause. The mentioned counts and percentages are shown in detail in table 8.

	Absolute count (n)	**Percent (%)**
Total cohort	558	100.00
Distant metastases		
No	410	73.5
Yes	148	26.5
Abdomen/Retroperitoneum met.		
No	530	95.0
Yes	28	5.0
Local recurrence		
No	458	82.1
Yes	100	17.9
Overall survival		
No death	449	80.5
Death of disease	54	9.7
Death of other cause	55	9.9

Table 8. End point data

4.2. Metastatic disease

148 patients developed distant metastases after a mean follow-up of 20.5 months (range: 1 – 107.2 months), resulting in 26.5% of the total cohort. 8.4% (n=47) of all patients had a local relapse in addition to the metastatic disease. 27 of these 47 patients developed the local relapse prior to distant metastases. The mean age at the time of diagnosis of the primary tumour of patients who were diagnosed with metastases was 57 years (range: 18 – 88 years). 80 male and 68 female patients developed distant metastases.

4.2.1. Extra-abdominal metastases

21.5% (n=120) of all patients developed only extra-abdominal or extra-retroperitoneal metastases. In all 148 patients with distant metastases, 223 extra-abdominal metastatic sites have been identified. The most frequent site of all metastatic lesions was the lung, as 19.5% (n=109) of the total cohort developed pulmonary metastases, followed by bones with 5.9% (n=33), lymph nodes with 4.8% (n=27) and pleura with 2.9% (n=16). More detailed information about the affected sites is presented in Table 9. 10.0% (n=56) of all patients had isolated pulmonary metastases.

	Absolute count (n)	**Percent (%)**
Total cohort	558	100.00
Lungs	109	19.5
Bones	33	5.9
Lymphatic nodes	27	4.8
Pleura	16	2.9
Soft tissue	15	2.7
Mediastinum	5	0.9
Brain	5	0.9
Subcutan tissue	4	0.7
Pericardium/ Endocardium	3	0.5
Skin	3	0.5
Others	2	0.4
Meninges	1	0.2

Table 9. Distribution of metastases

15 of all histological subtypes developed extra-abdominal metastases. The most common entities were undifferentiated/unclassified sarcomas (24.2%), leiomyosarcoma (15.0%) and myxofibrosarcoma (10.8%). The exact percentages are listed in Table 10. Similar to the total cohort, a great amount of high-grade sarcomas were observed. 92.5% (n=111) of all STS that developed only extra-abdominal metastases were classified as high-grade tumours. The most common primary tumour site was the lower extremity with 72.5% (n=87). 75% (n=90) of the primary tumours that developed extra-abdominal metastases were ≥ 5 cm and in 89.2% (n=107) the primary sarcoma was located deep to the fascia.

With 68.3% (n=82), most of the extra-abdominal metastatic lesions were detected with CT-scans of the thorax during regular follow-up examinations. In 61.6% of all patients with just extra-abdominal metastatic disease palliative chemotherapy was applied. In 50% of isolated metastatic lesions to the lung or lymphatic nodes were resected. In 16 cases, resulting in 13.3% of patients with these metastases, radiation therapy was preformed for symptom palliation.

	Absolute count (n)	**Percent (%)**
Extra-abdominal metastases	120	100.00
Histology		
Undifferentiated/unclassified sarcomas	29	24.2
Leiomyosarcoma	18	15.0
Myxofibrosarcoma	13	10.8
Synovialsarcoma	12	10.0
Liposarcoma	6	5.0
Rhabdomyosarcoma	6	5.0
MPNST	6	5.0
Angiosarcoma	6	5.0
Myxoid liposaroma	5	4.2
Fibrosarcoma	6	5.0
Clear- cell sacoma	5	4.2
Epitheloidsarcoma	3	2.5
Extrask. Chondrosarckoma	2	1.7
Alv. soft-part-sarcoma	2	1.7
Extrask. Ewing-sarcoma	1	0.8

Table 10. Histological subtypes of extra-abdominal metastases

4.2.2. Intra-abdominal metastases

After a mean follow-up of 32.7 months (range, 1 - 100 months) 5.0% (n=28) of the total cohort developed intra-abdominal metastases. The mean age at diagnosis of the primary tumour was 58 years (range: 18 – 76). With 46.4% (n=13) of male patients and 53.6% (n=15) of female patients, no statistically significant gender preference had been observed for these metastatic lesions.

5 (17.9%) of these 28 patients had isolated abdominal metastatic lesions. 3 (10.7%) patients had abdominal metastatses and other non-pulmonary metastases. 20 (71.4%) of all patients with intra-abdominal metastases developed metastases to the lung in combination of other metastatic lesions.

In 14 of these 20 patients metastases to the lung were diagnosed before abdominal lesions, in four cases they were diagnosed at the same time in the CT-scan and in 2 patients abdominal metastases were diagnosed prior to lung metastases.

The most common intra-abdominal site was the liver with 2.9% (n=16) of the total cohort, followed by the intestine with 0.7% (n=4) and the pancreas with 0.5% (n=3) and peritoneum with 0.5% (n=3). More detailed information is shown in Table 11.

	Absolute count (n)	**Percent (%)**
Total cohort	558	100.00
Liver	16	2.9
Intestine	4	0.7
Peritoneum	3	0.5
Pankreas	3	0.5
Abdomen	2	0.4
Diaphragma	2	0.4
Omentum	1	0.2
Suprarenal gland	1	0.2

Table 11. Distribution of intra-abdominal metastases

4.2.2.1. Clinical features, detection and therapy

Just 11 (39.3%) of all patients who developed abdominal/retroperitoneal metastases suffered from symptoms. The most frequent complaint was abdominal or side pain with 21.4% (n=6) of all 28 patients. Further symptoms are listed in table 11. In all other cases, the abdominal metastatic disease was discovered prior to symptoms during regular follow-up imaging.

In 7 patients an abdominal metastatic lesion was detected with an ultrasound and in a further 7 patients with an abdominal CT-scan. The other detection modalities are listed in table 11.

22 of these patient received palliative chemotherapy alone, in 2 patients additionally to CTX resection and in one patient laser ablation was performed. More detailed information on palliative therapy concept is shown in table 12.

	Absolute count (n)	Percent (%)
Patients with abd. /retrop. Met.	28	100.00
Symptoms		
Abdominal/side pain	6	21.4
Abdominal sensation of pressure	3	10.7
Ileus/ perforation	2	7.1
Anorexia	2	7.1
Obstipation	1	3.6
Detection modalities		
Ultrasound	7	25.0
Abdominal CT-scan	7	25.0
Abdominal/thoracal CT-scan	6	21.4
Thoracal CT-scan	4	14.3
MRI	2	7.1
unknown	2	7.1
Therapy		
Resection	3	10.7
Resection + CTX	2	7.1
CTX	22	78.6
CTX + Laser	1	3.6

Table 12. Clinical features, detection and therapy concepts

4.2.2.2. Characteristics of primary tumour of patients with abdominal metastases

The most frequent histological subtype metastazing intra-abdominal was the NOS with 8 patients, followed by the myxoid liposarcoma with 6. The percentages of other subtypes are listed in table 12. 12.5% of all myxoid liposarcoma developed intra-abdominal metastases, compared to just 4.6% of all other subtypes (p=0.044). Therefore, the myxoid liposarcoma has a significant risk to develop abdominal metastases. More detailed information is presented in table 13.

	Absolute count (n)	Percent (%)
Patients with abd. Met.	28	100.00
Histology		
Undifferentiated/unclassified sarcomas	8	28.6
myxoid liposarcoma	6	21.4
Leiomyosarcoma	5	17.9
Liposarcoma	4	14.3
Angiosarcoma	2	7.1
pleomorphic liposarcoma	1	3.6
Myxofibrosarcoma	1	3.6
MPNST	1	3.6

Table 13. Histological subtypes of intra-abdominal metastases

Further, the effect of grading on the development of abdominal metastases was evaluated and a significant difference between low and high-grade sarcoma concerning the abdominal metastatic potential has been observed (p=0.039). No significant difference was seen in tumour depth (p=0.711), in patients <65 years or ≥65 years (p=0.693) or concerning gender (p=0.563). Detailed information on counts and p-values is presented in table 14.

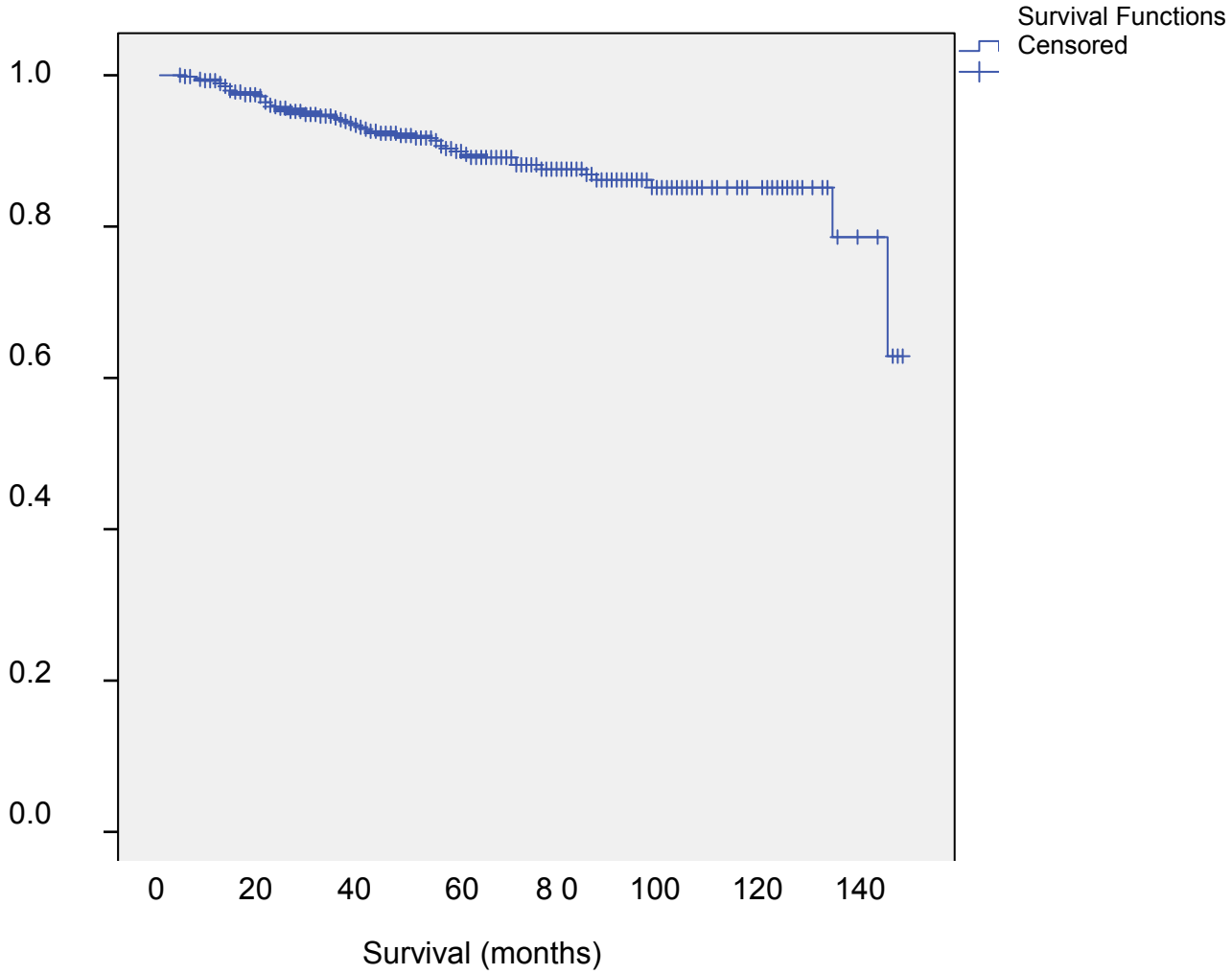
	n	Secundary Met./ p-value	n	Abdominal Met. p-value
Ages				
< 65	101	0.196	19	0.693
> 65	47		9	
Gender				
Male	81	0.565	13	0.563
Female	67		15	
Tumour depth				
Superficial	6	0.176	1	0.711
Profound	134		27	
Histology				
Myx.Liposarcoma	11	0.332	6	0.044
Non myx. Liposarcoma	137		22	
Grading				
High grade	137	*)	26	0.039
Low grade	8		1	

Table 14. Chi-Square-Tests for characteristics of patients and primary tumour.
*) was not calculable, due to missing data

The mean primary tumour size of patients with abdominal metastases was 9.5 cm (range: 3 – 20 cm) and was not statistically different to the mean tumour size of patients who did not develop these metastases (p=0.177), as on average they were measured as 8.9 cm (range: 1 – 33 cm).

4.4. Patient survival

For the survival analysis 558 of extra-abdominal, at diagnosis non-metastatic STS patients with a mean follow-up time of 58.3 months (range: 4 - 148 months) were evaluated. The five-year overall survival estimated Kaplan-Meier was 89% and at 10 years 84%. In figure 4 the Kaplan-Meier curves presents the survival of the total cohort.



Firgure 4. Kaplan-Meier survival curve for all 558 STS patients

Further we analysed the post-metastatic survival of patients with extra-abdominal and of those with intra-abdominal metastases with the Kaplan-Meier curve. The 5-year overall survival for patients with extra-abdominal metastases was 48% and for patients with intra-abdominal metastases 22%. These results were compared by the Log-Rank test that did show a difference between both results, but not with a statistical significance (p=0.092). The Kaplan-Meier survival curves of both groups are shown in figure 5.

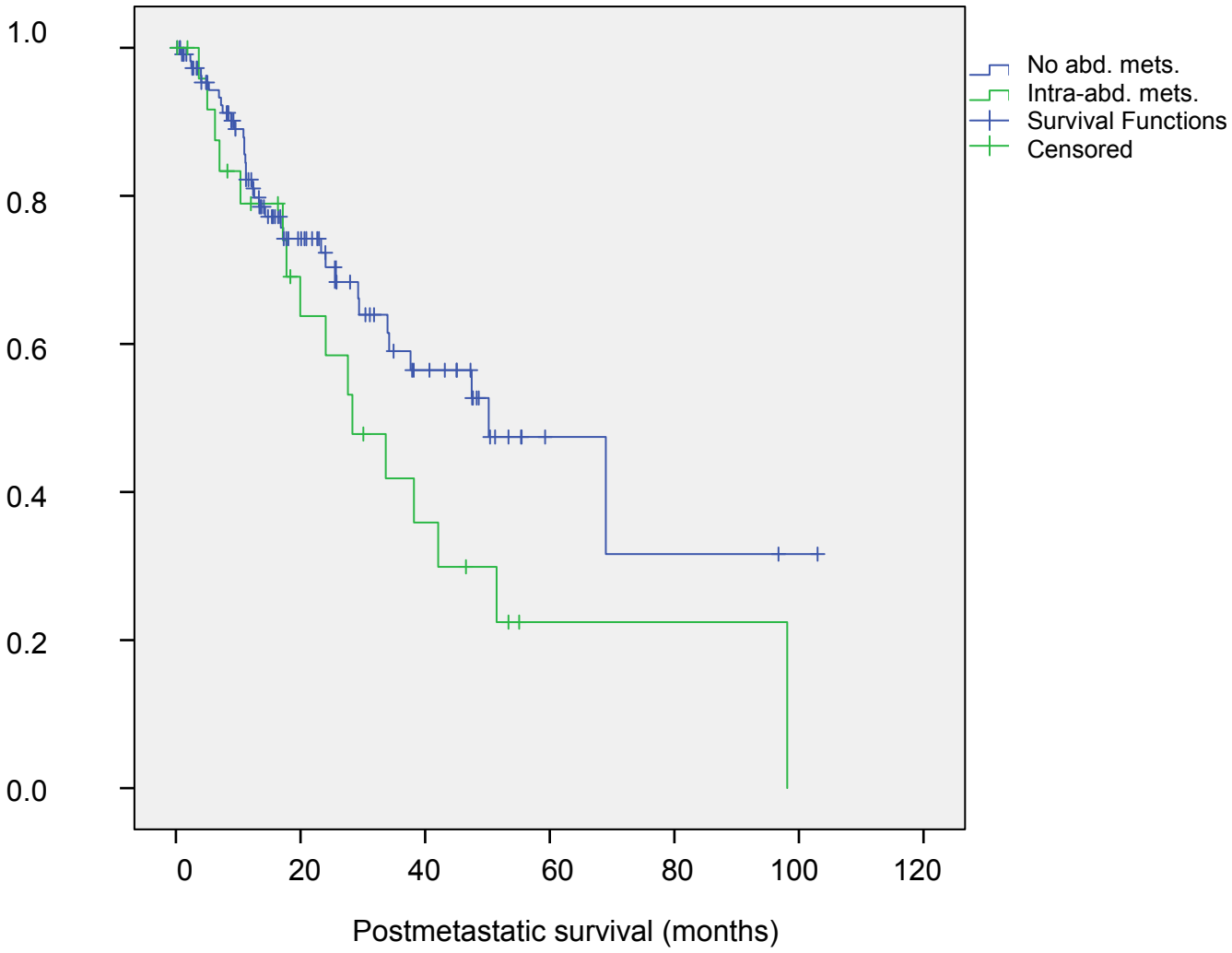


Figure 5. Kaplan-Meier curve of post-metastatic survival

5. Discussion

5.1. Incidence and distribution of abdominal metastases

It is generally well known that extremity soft tissue sarcomas especially spread hematogenously and that the event of distant metastatic disease is related to an inferior OS. (3,4) The most frequent location is the lung. In contrast to this metastatic site, abdominal metastases are relatively rare. (12,13,191) In the current study, an overall incidence of distant metastases of 26.5% has been observed, if primary metastases were excluded, but even if patients with primary metastases were included the pertentage amounts for just 32.6%. In contrast to that prior reports provide a higher incidence of 40% to 50%. (5-7) These difference is probably due to the fact that 22.2% of the included patient in our study were diagnosed with a low-grade soft tissue sarcoma.

In the analysed cohort, 5% of the total cohort experienced abdominal metastatic disease after a mean follow-up of 32.7 months (range: 1-100 months), and similar results have been published. (11,14-17) As the majority of abdominal metastases develop within the first 2 years, imaging during this period is especially crucial. In our study we observed for patient with abdominal metastases a mean post-metastatic survival of 25.5 months, whereas the study by Behranwala et al showed for patients who underwent surgery a mean post-metastatic survival of 33 months and 8 months for those who were not treated with surgery. (10)

In the analysed cohort, eight different locations of abdominal metastases have been identified. The most frequent sites were the liver, intestine, peritoneum and the pancreas. In contrast to the findings of Jaques et al., who observed in their analysed cohort a high incident of hepatic metastases of 7%, in our study only 2.9% of all patients with STS of the trunk or the extremities experienced metastatic disease of the liver. (15)

5.2. Detection modalities and therapy

Further, due to a lack of guidelines in respect to the detection of abdominal or retroperitoneal metastases and the increasing concerns regarding the radiation exposure, we questioned the current standard at our institutions. (20) Current literature provides no justification for additional abdomen imaging during the follow-up. The Society of Surgical Oncology recommend in their practice guidelines published last in 1997 to have CT scans of the chest for high grade lesions <5cm and thoracic and abdominal CT scans for patients with >5 cm myxoid liposarcoma as initial staging. (7) The NCCN as well endorses abdominal/pelvic CT imaging for myxoid liposarcoma, and in addition a scan should be considered for leiomyosarcoma, epitheliod sarcoma and angiosarcoma. (18) Conversely, in the recently published recommendations of ESMO routine CT scan of the abdominal cavity is not part of follow-up schedules. (1)

As already mentioned, about 70% to 80% of the metastatic diseases are located in the lungs, and thus several authors recommend routine imaging of the chest, although further imaging is required depending on clinical presentation. (8,187) However, several institutions include regular abdominal imaging in their follow-up schedules, even if isolated abdominal or retroperitoneal metastases are infrequent.

In the current study, 5 patients, which accounts for 0.8% of the total cohort, experienced isolated metastatic disease to the abdominal cavity. Thompson et al. reported a higher incidence of 2.8%, even if patients with primary metastases were excluded, the higher percentage might be due to the fact that children were included. (12) Further, in the study by Kings et al. an even higher with 5% has been observed, this higher result maybe based on the inclusion of patients with primary metastases. (13) Similar to literature, in the majority of cases, lung metastases were usually diagnosed prior to abdominal metastatic lesions, whereas abdominal lesions were never diagnosed prior to other locations. In an equal number of cases, the abdominal metastatic disease was identified through a CT scan or ultrasound of the abdominal cavity. In 4 patients, the lesions were detected during thoracic routine CT scans. According to our results and due to the retrospective study design, we could not evaluate whether CT or ultrasound is more beneficial and efficient for the detection of these metastatic lesions.

The detection of abdominal metastases is often difficult as symptoms manifest only when the disease is already at an advanced stage. Behranwala et al. reviewed the clinical features of 19 patients and observed that just 2 patients were asymptomatic. (10) Contrary to their findings, in our cohort just 11 of all 28 patients with abdominal metastases had symptoms. As the majority of these metastases have been diagnosed during follow-up imaging prior to symptoms, routine-imaging procedures may be considered even in absence of clinical symptoms.

In regard to the treatment of metastatic lesions in the abdominal cavity, several authors recommend resection, as a complete tumour removal is associated with better clinical outcome. (10,11,15,210) However, in our study most of the patients with abdominal metastases were treated only with CTX, as they occurred at an advanced stage. Resection was performed in only 5 patients. Due to the small number of patients who underwent surgery, reliable statistical analysis concerning overall survival regarding different treatment modalities could not be preformed.

5.3. Risk factors for abdominal metastases

The identification of risk factors for development of abdominal metastases would be favorable, as the determination of what patient should be followed-up with abdominal CT scan, would be eased. Further, low-risk patients would not be exposed to excessive radiation and would be saved from potential morbidity from the wrong findings. Moreover, we questioned if certain histological subtypes would show an increased spread to intra-abdominal or retroperitoneal sites to justify additional abdominal imaging during follow-up examinations. However, clear information cannot be obtained from the currently available literature.

In our current study, we evaluated several clinical features of patients with soft tissue sarcomas and the sarcoma itself such as age, sex distribution, tumour size and depth as well as to the histological subtype and grading, concerning their prognostic value for the genesis of abdominal metastases. What was especially interesting was that to the best of our knowledge, these factors have not yet been analysed. Patient related information like age older than 65 years or gender did not show a relevant impact.

Further, tumour specific factors like primary tumour size or tumour depth did not vary significantly between sarcomas that did or did not develop consecutively, such as a metastatic disease. In contrast to these results, according to our data, high-grade sarcomas are significantly more likely to metastasize in the abdominal cavity or in the retroperitoneum.

Moreover, we analysed the data to determine, if certain histological types would show a higher incidence of abdominal metastases. 8 of the 17 STS types developed such a metastatic disease. The most frequent entities were undifferentiated/unclassified sarcomas, myxoid liposarcomas, leiomyosarcomas and high-grade liposarcomas; similar results were reported in previous studies. (14-17) However, just for the myxoid liposarcoma, a significantly higher tendency for abdominal metastases has been observed, as 6 of all 54 myxoid liposarcomas metastasize at these locations. Similar results were published by Spillane et al., Cheng et al., as well as by Zanarini et al. (16, 235,236).

In contrast to these findings, King et al. did not observe any myxoid liposarcoma and Thompson et al. just one that developed metastatic disease in the abdominal cavity or retroperitoneum. (12,13)

Due to a small sample size, statistical analysis in these studies are less confidable, and therefore, prospective studies with a standardized follow-up schedule and a large number of patients are essential to provide more reliable results on this matter.

6. Limitations

Due to the retrospective study design, our study is prone to certain limitations. However, we do not believe that the findings and results were influenced substantially by the retrospective design itself, as the data was collected prospectively. A limitations that might be considered, is the fact that no standardized follow-up schedule concerning abdominal imaging was established prospectively. In the center in Graz regular examinations of the abdominal cavity were preformed with ultrasound or with a CT scan. While in the Sarcoma center Berlin-Brandenburg abdominal imaging was not part of the routine follow-up.

However, a sampling bias may occur as the hypothesis that certain subtypes are more likely to develop such a metastatic disease could influence the decision of whether an ultrasound or CT-scan should be preformed. Further, the tendency to perform chest imaging more often may negatively influence the observed rate of isolated abdominal metastases.

Even if we analysed the files of 558 patients, the sample size of 28 patients with abdominal metastases was not sufficient to conduct further differential statistical analyses concerning therapy success or the ideal diagnostic imaging modality. Although these limitations may slightly influence the results, the strength of the study lies definitely in the large number of patients that has been evaluated with a relatively long mean follow-up of 58.3 months.

7. Conclusion

Soft tissue sarcomas rank among the rarest malignant tumours. Therefore, it is essential that their treatment follows regularly updated guidelines and is preformed at specialized reference centers. The occurrence of metastatic lesions to the abdominal cavity indicates an advanced stage. Further, in the majority of cases, these metastatic lesions are identified prior to symptoms. However, our data did not confirm a significant difference in post-metastatic survival for patients with or without abdominal metastatic lesions. Even though the identification of certain risk factors for these metastases and the early detection are essential, as the resection of singular metastases can improves overall survival. In our study, only higher grade and the histological subtype myxoid liposarcoma were significantly associated with an increased incidence of abdominal metastases. These findings correspond to previous findings in literature. Therefore, we suggest routine imaging of the abdominal cavity during follow-up examinations in addition to CT scans of the chest for these patients. However, as insufficient data is provided by our study, we are unable to decide which is the most efficient and beneficial imaging modality. Thus, radiation exposure's additional costs and potential consequences of false positives findings must be considered.

References

(1) ESMO Guidelines Working Group, Soft tissue and visceral sarcomas: ESMO clinical Practice Guidelines for diagnosis, treatment and follow-up; Ann Oncol 2014; 25 (Supplement 3) iii102-iiii112.

(2) Van Dyck P, Gielen J, Van Hoenacker FM, De Schepper AM, Parizel PM. Imaging of soft tissue tumors: general imaging strategy and technical considerations. JBR-BTR. 2006 Jul-Aug;89(4):204-6.

(3) Van Geel AN, Pastorino U, Jauch KW, etal. Surgical treatment of lung metastases: the European Organization for Research and Treatmentof Cancer-Soft Tissue and Bone Sarcoma Groupstudy of 255 patients. Cancer. 1996 Feb 15;77(4):675-82.

(4) Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg. 1999 May; 229(5): 602.

(5) Stojadinovic A, Leung DH, Allen P, Lewis JJ, Jaques DP, Brennan MF. Primary adult soft tissue sarcoma: time-dependent influence of prognostic variables. J Clin Oncol. 2002 Nov 1;20(21):4344-52.

(6) Whooley BP, Gibbs JF, Mooney MM, McGrath BE, Kraybill WG. Primary extremity sarcoma: what is the appropriate follow-up? Ann Surg Oncol. 2000 Jan-Feb;7(1):9-14.

(7) Pollack R, Brennan M, Lawrence W Jr.Society of Surgical Oncology practice guidelines. Soft-tissue sarcoma surgical practice guidelines. Oncology (Williston Park). 1997 Sep;11(9):1327-32.

(8) Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005 Aug 18;353(7):701-11.

(9) Riad S, Griffin AM, Liberman B, et al. Lymph node metastasis in soft tissue sarcoma in an extremity. ClinOrthopRelat Res. 2004 Sep;(426):129-34.

(10) Behranwala KA, Roy P, Giblin V, A'hern R, Fisher C, Thomas JM. Intra-abdominal metastases from soft tissue sarcoma. J Surg Oncol. 2004 Sep 1;87(3):116-20.

(11) Lev-Chelouche D, Nakache R, Soffer D, Merimsky O, Klausner MJ, Gutman M. Metastases to the retroperitoneum in patients with extremity soft tissue sarcoma: an unusual metastatic pattern. Cancer. 2000 Jan 15;88(2):364-8.

(12) Thompson MJ, Ross J, Domson G, Foster W. Screening and surveillance CT abdomen/pelvis for metastases in patients with soft-tissue sarcoma of the extremity. Bone Joint Res. 2015 Mar;4(3):45-9.

(13) King DM, Hackbarth DA, Kilian CM, Carrera GF. Soft-tissue Sarcoma Metastases Identified on Abdomen and Pelvis CT Imaging. Clinical Orthopaedics and Related Research. 2009;467(11):2838-2844.

(14) Hafner GH, Rao U, Karakousis CP. Liver metastases from soft tissue sarcomas. J Surg Oncol. 1995 Jan;58(1):12-6.

(15) Jaques DP, Coit DG, Casper ES, Brennan MF. Hepatic metastases from soft-tissue sarcoma. Ann Surg. 1995 Apr; 221(4): 392–397.

(16) Spillane AJ, Fisher C, Thomas JM. Myxoidliposarcoma--the frequency and the natural history of nonpulmonary soft tissue metastases. Ann Surg Oncol. 1999 Jun;6(4):389-94.

(17) Pearlstone DB, Pisters PW, Bold RJ, et al. Patterns of recurrence in extremity liposarcoma: implications for staging and follow-up. Cancer. 1999 Jan 1;85(1):85-92.

(18) No authors listed. Soft Tissue Sarcoma – NCCN Clinical Practice Guidelines in Oncology Version 2. www.nccn.org (data last accessed 21 August 2015).

(19) Smith-Bindman R, Lipson J, Marcus R, et al. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med. 2009 Dec 14;169(22):2078-86.

(20) Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med. 2007 Nov 29;357(22):2277-84.

(21) Cormier JN, Pollock RE. Soft tissue sarcomas. CA Cancer J Clin. 2004 Mar-Apr 54(2):94-109.

(22) Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis developmentin the main histologic types of adult soft tissuesarcomas: a study of 1240 patients from theFrench Federation of Cancer Centers Sarcoma Group. Cancer 2001 May 15; 91(10):1914-1926.

(23) Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004 Jan-Feb;54(1):8-29.

(24) Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. World Health Organization Classification of tumours of soft tissue and bone, 4th, IARC Press, Lyon 2013.

(25) Gutierrez JC, Perez EA, Franceschi d, Moffat FL, Jr, Livingstone AS; Koniaris LG. Outcomes for soft-tissue sarcoma in 8249 cases from a large state cancer registry. J Surg Res. 2007 Jul;141(1):105-114.

(26) Gatta G, van der Zwan JM, Casali PG et al.Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011 Nov;47(17):2493-511.

(27) Gustafson P. Soft tissue sarcoma. Epideiology and prognosis in 508 patients. Acta Orthop Scand Suppl. 1994 Jun;259:1-31.

(28) Wibmer C, Leithner A, Zielonke N, et al. Increasing incidence rates of soft tissue sarcomas? A population-based epidemiologic study and literature review. Ann Oncol. 2010 May;21(5):1106-11.

(29) Burningham Z, Hashibe M, Spector L, Schiffman JD. The Epidemiology of Sarcoma. Clinical Sarcoma Research. 2012;2:14.

(30) Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996. CA Cancer J Clin. 1996 Jan-Feb;46(1):5-27.

(31) Brady M, Gaynor JJ, Brennan MF. Radiation-Associated Sarcoma of Bone and Soft Tissue. Arch Surg. 1992 Dec;27(12): 1379-1385.

(32) Karlsson P, Holmberg E, Johansson KA, et al. Soft tissue sarcoma after treatment for breast cancer. Ratiother Oncol.1996 Jan;38(1):25-31.

(33) Evans HL, Baser ME, McGaughra J et al. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet. 2002 May; 39(5):311-314.

(34) Leroy K, Dumas V, Martin-Garcia N, et al. Malignant Peripheral Nerve Sheath Tumors Associated With Neurofibromatosis Type 1: A Clinicopathologic and Molecular Study of 17 Patients. Arch Dermatol. 2001 Jul;137(7):908-13.

(35) Widemann BC. Current status of sporadic and neurofibromatosis typ 1-associated malignant peripheral nerve sheath tumors. Curr Oncol Rep. 2009 Ju;11(4):322-328.

(36) Ognjanovic S, Olivier M, Bergemann TL, et al. Sarcomas in TP53 germline mutation carriers: A review of the IARC TP53 database. Cancer. 2012 Mar 1;118(5):1387-96.

(37) Sharif S, Ferner R, Birch JM, et al. Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. J Clin Oncol. 2006 Jun 1;24(16):2570-2575.

(38) Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome, J Natal Cancer Inst. 1998 Apr 15;90: 606-611.

(39) Heymann S, Delaloge S, Rahal A, et al.. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. Radiat Oncol. 2010 Nov;8;5:104.

(40) Pansuriya TC, Kroon HM, Bovee JV. Enchondromatoisis: insights on the different subtypes. Int J Clin Exp Pathol.2010;3(6):557-569.

(41) Davidson TI, Kissin MW, Bradish CF, Westbury G. Angiosarcoma arising in a patient with Maffucci syndrome. European Journal of Surgical Oncology : the Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.1985;11(4):381-384.

(42) Eriksson M, Hardell L, Adami HO. Exposure to Dioxins as a risk factor for soft tissue sarcoma: a population-based case-control study. J Natl Cancer Inst. 1990 Mar 21;82(6):486-90.

(43) Hardell L, Eriksson M. The association between soft tissue sarcomas and exposure to phenoxyacetic acids. A new case-referent study. Cancer. 1988 Aug; 62(3):652-656.

(44) Deyrup AT, Lee VK, Hill CE et al. Epstein-Barr virus associated smooth muscle tumors are distinctive mesenchymal tumors reflecting multiple infection events: a clinic-pathologic and molecular analysis of 29 tumors from 19 patients. Am J Surg Pathol. 2006 Jan;30(1):75-82.

(45) Kirkpatrick CJ, Alves A, Kohler H et al. Biomaterial-induced sarcoma: A novel model to study preneoplastic change. Am J Pathol. 2000 Apr;156(4):1455-67.

(46) Flechter CD. Undifferentiated sarcomas: what to do? And does it matter? A surgical pathology perspective. Ultrastruct Pathol. 2008 Mar-Apr;32(2):31-6.

(47) Gomez P, Morcuende J. High-Grade Sarcomas Mimicking Traumatic Intramuscular Hematomas: A Report of Three Cases. The Iowa Orthopaedic Journal. 2004;24:106-110.v

(48) Johnson CJ, Pynsent PB, Grimer RJ. Clinical features of soft tissue sarcomas. Ann R Coll Surg Engl. 2001 May; 83(3): 203–205.

(49) Pike J, Clarkson PW, Masri BA. Soft tissue sarcomas of the extremities: How to stay out of trouble. BCMJ, 50(6): 310-317.

(50) Smolle MA, Leithner A, Grimer RJ. Evaluating the British sarcoma referral form. Ann R Coll Surg Engl. 2015 Sep;97(6):434-8.

(51) Gielen J, CeulemansR. Ultrasound of Soft Tissue Tumors. In: De Schepper AM, editors.Imaging of Soft Tissue Tumors. Springer-Verlag Berlin Heidelberg 2006; 3rd edition; page 3-18.

(52) Lakkaraju A, Sinha R, Garikipati R, Edward S, Robinson P. Ultrasound for initial evaluation and triage of clinically suspicious soft tissue masses. Clin Radiol. 2009 Jun;64(6):615-21.

(53) Hung EH, Pinto CH, Doyle AJ. Pitfalls in ultrasonography of soft tissue tumors. Semin Musculoskelet Radiol. 2014 Feb;18(1):79-85.

(54) Kwok HC, Pinto CH, Doyle AJ. The pitfalls of ultrasonography in the evaluation of soft tissue masses. J Med Imaging Radiat Oncol. 2012 Oct;56(5):519-524.

(55) Brodowicz T, Amann G, Leithner A,et al. Konsensus Diagnose und Therapie von Weichteilsarkomen. Wien Klein Wochenschr. 2012;124:85-99.German.

(56) Lo HH, Kalisher L, Faix JD. Epithelioid sarcoma: radiologic and pathologic manifestations. AJR Am J Roentgenol. 1977 Jun;128(6):1017–1020.

(57) Lorigan JG, O'Keeffe FN, Evans HL, Wallace S. The radiologic manifestations of alveolar soft-part sarcoma. AJR. 1989 Aug;153(2):335–339.

(58) Murray JA. Synovial sarcoma. Orthop Clin North Am. 1977 Oct;8(4):963–972.

(59) De Schepper AM, De Beuckeleer L, Vandevenne J, Somville J. Magnetic resonance imaging of soft tissue tumors. Eur Radiol. 2000 Jan;10(2):213-23.

(60) Heslin MJ, Smith JK. Imaging of soft tissue sarcomas. Surg Oncol Clin N Am. 1999 Jan;8(1):91-107.

(61) Amini B, Jessop AC, Ganeshan DM, Tseng WW, Madewell JE. Contemporary imaging of soft tissue sarcomas. J Surg Oncol 2015 Apr; 111(5):496-503.

(62) Elias DA, White LM, Simpson DJ. Osseous invasion by soft-tissue sarcoma: assessment with MR imaging. Radiology. 2003 Oct;229(1):145–152.

(63) Aga P, Singh R, Parihar A, Parashari U. Imaging Spectrum in Soft Tissue Sarcomas. Indian Journal of Surgical Oncology 2011 Dec;2(4):271-279

(64) Dominietto M, Rudin M. Could magnetic resonance provide histology? Front Genet. 2014 Jan;13;4:298

(65) Charest M, Hickeson M, Lisbona R, et al. FDG PET/CT imaging in primary osseous and soft tissue sarcomas: a retrospective review of 212 cases. Eur J Nucl Med Mol Imaging. 2009 Dec;36(12):1944-1951.

(66) Bastiaannet E, Groen H, Jager PL, et al. The value of FDG-PET in the detection, grading and response to therapy of soft tissue and bone sarcomas; a systematic review and meta-analysis. Cancer Treat Rev. 2004 Feb;30(1):83-101.

(67) Windhager R, Hovy L, Prietzel T von Salis-Soglio G: AWMF Leitlinien Weichteilsarkome der Deutschen Gesellschaft für Orthopädie und Orthopädische Chirurgie (DGOOC) und des Berufsverbandes der Ärzte für Orthopädie. 2002.German.

(68) Leithner A, Windhager R. Leitlinien der Biopsie von Knochen – und Weichteiltumoren. Orthopäde. 2007 Feb; 36(2):167-74. German.

(69) Domanski HA, Akermann M, Carlen B, et al. Core-needle biopsy performed by the cytopathologist: a technique to complement fine-needle aspiration of soft tissue and bone lesions. Cancer. 2005 Aug 25;105(4):229-239.

(70) Pohlig F, Kirchhoff C, Lenze U, Schauwecker J, Burggkart R, Rechl H, et a. Percutaneous core needle biopsy versus open biopsy in diagnostics of bone and soft tissue sarcoma: a retrospective study. Eur J Med Res. 2012 Nov 1; 17:29.

(71) Heslin MJ, Lewis JJ, Woodruff JM, Brennan MF. Core needle biopsy for diagnosis of extremity soft tissue sarcoma. Ann SurgOncol. 1997 Jul-Aug;4(5):425-31.

(72) Depuy DE, Roseenberg AE, Punyaratabandhu T, et al. Accuracy of CT-guided needle biopsy of musculoskeletal neoplasms. AJR Am J Roentgenol. 1998 Sept;171(3):759-762.

(73) Jones C, Liu K, Hirschowitz S, Klipfel N, Layfield LJ. Concordance of histopathologic and cytologic grading in musculoskeletal sarcomas: can grades obtained from analysis of the fine-needle aspirates serve as the basis for therapeutic decisions? Cancer. 2002 Apr 25;96(2):83-91.

(74) Singh HK, Kilpatrick SE, Silverman JF. Fne needle aspiration biopsy of soft tissue sarcomas: utility and diagnostic challenges. Adv Anat Pathol. 2004 Jan;11(1):24-37.

(75) Tunn PU, Gebauer B, Fritzmann J, Hunrebein M, et al. Soft tissue sarcoma [in German]. Chirurg. 2004 Dec;75(12):1165-1173. (73)

(76) Maretty-Nielsen K. Prognostic factors in soft tissue sarcoma. Dan Med J. 2014 Nov;61(11):B4957.

(77) Delattre O, Zucman J, Melot T, et al. The Ewing family of tumors—a subgroup of small-round-cell. tumors defined by specific chimeric transcripts. N Engl J Med. 1994 Aug;331(5):294-299.

(78) Doyle LA. Sarcoma classification: an update based on the 2013 World Health Organization Classification of Tumors of Soft Tissue and Bone. Cancer. 2014 Jun15;120(12):1763-1774.

(79) Watanabe K, Kusakabe T, Hoshi N, Saito A, Suzuki T. h-Caldesmon in leiomyosarcoma and tumors with smooth muscle cell-like differentiation:

its specific expression in the smooth muscle cell tumor. Hum Pathol. 1999 Apr;30(4):392-396.

(80) Van de Rijn M, Barr FG, Xiong QB, Hedges M, Shipley J, Fisher C. Poorly differentiated synovial sarcoma: an analysis of clinical, pathologic, and molecular genetic features. Am J Surg Pathol. 1999 Jan;23(1):106-112.

(81) Miettinen M. Immunohistochemistry of soft tissue tumours – review with emphasis on 10 markers. Histopathology. 2014 Jan; 64(1):101-18.

(82) Wardelmann E, Schildhaus HU, Merkelbach-Bruse S, et al. Soft tissue sarcoma: from molecular diagnosis to selection of treatment. Pathological diagnosis of soft tissue sarcoma mid molecular biology and targeted therapies. Ann Oncol. 2010 Oct;21(7):265-269.

(83) Mertens F, Panagopoulos I, Manda N. Genomic characteristics of soft tissue sarcomas. Virchows Arch. 2010 Feb;456(2):129-139.

(84) Brooks JS, Lee S. Contemporary diagnostics: sarcoma pathology update. Contemporary diagnostics: sarcoma pathology update. J SurgOncol. 2015 Apr;111(5):513-9.

(85) Liegl-Atzwanger B, Hofmann G, Leithner A, Beham A. Undifferentiated high-grade pleomorphic sarcoma (UHPS): Diagnostic criteria, differential diagnosis, and treatment. An attempt to erasure the misnomer "MFH". European Surgery. 2009 Aug:41(4):143-149

(86) Brooks JJ. The significance of double phenotypic patterns and markers in human sarcomas. A new model of mesenchymal differentiation. Am J Pathol. 1986 Oct;125(1):113-123.

(87) Bertoni F, Capanna R, Biagini R, Bacchini P, Guerra A, Ruggieri P, et al. Malignant fibrous histiocytoma of soft tissue. An analysis of 78 cases located and deeply seated in the extremities. Cancer.1985 Jul; 56(2):356-67.

(88) Russell WO, Cohen J, Enzinger F, Hajdu SI, Heise H, Martin RG, et al. A clinical and pathological staging system for soft tissue sarcomas. Cancer. 1977 Oct;40(4):1562-1570.

(89) Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer. 1984 Jan 15;33(1):37-42.

(90) Costa J, Wesley RA, Glatstein E et al. The grading of soft tissue sarcomas. Results of a clinicohistopathologic correlation in a series of 163 cases. Cancer. 1984 Feb 1;53(3):530-41.

(91) Deyrup AT, Weiss SW. Grading of soft tissue sarcomas: the challenge of providing precise information in an imprecise world. Histopathology. 2006 Jan;48(1):42-50.

(92) Guillou L, Coindre JM, Bonichon F, Nguyen BB, Terrier P, Collin F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol. 1997 Jan;15(1):350-362.

(93) Coindre JM, Trojani M, Contesso G, et al. Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer. 1986 Jul; 58(2):306-309.

(94) Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer. 2001 May 15; 91(10):1914–1926.

(95) Khoja H, Griffin A, Dickson B, et al. Sampling modality influences the predictive value of grading in adult soft tissue extremity sarcomas. Arch Pathol Lab Med. 2013 Dec;137(12):1774-9.

(96) Hoeber I, Spillane AJ, Fisher C, et al. Accuracy of biopsy techniques for limb and limb girdle soft tissue tumors. Ann SurgOncol. 2001 Jan-Feb;8(1):80-7.

(97) Edge SB, Byrd DR, Compton CC, et al. AJCC (American Joint Committee on Cancer). Cancer Staging Manual, 7th edition. New York: Springer; 2010.

(98) Kneisl JS, Coleman MM, Raut CP. Outcomes in the management of adult soft tissue sarcomas. J SurgOncol. 2014 Oct;110(5):527-538.

(99) Boffa DJ, Greene FL. Reacting to changes in staging designations in the 7th edition of the AJCC staging manual. Ann Surg Oncol. 2011 Jan;18(1):1-3. (93) ESMO/European Sarcoma Network Working Group. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25(3):102-12.

(100) Maki RG, Moraco N, Antonescu CR, Hameed M, Pinkhasik A, Singer S, et al. Toward better soft tissue sarcoma staging: building on american joint committee on cancer staging systems versions 6 and 7. Ann Surg Oncol. 2013 Oct;20(11):3377-3383.

(101) Ramanathan RC, A'Hern R, Fisher C, Thomas JM. Modified staging system for extremity soft tissue sarcomas. Ann Surg Oncol. 1999 Jan-Feb;6(1):57-69.

(102) Salas S, Stoeckle E, Collin F, Bui B, Terrier P, Guillou L, et al. Superficial soft tissue sarcomas (S-STS): a study of 367 patients from the French Sarcoma Group (FSG) database. Eur J Cancer. 2009 Aug;45(12):2091-2102.

(103) Kattan MW, Leung DH, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol. 2002 Feb 1;20(3):791-6.

(104) Dalal KM, Kattan MW, Antonescu CR, Brennan MF, Singer S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. Ann Surg. 2006 Sep; 244(3):381-391.

(105) No authors listed. Adult Soft Tissue Sarcoma Treatment–for health professionals (PDQ®). http://www.cancer.gov/types/soft-tissue-sarcoma/hp/adult-soft-tissue-treatment-pdq#section/_277 (data last accessed 14.10.2015).

(106) Chen Y, Hao J, Yang Y, Yang J, Hao X. Tumor rupture predicts early metastasis and poor prognosis in stage III soft tissue sarcomas. World J Surg. 2011 May;35(5):1002-1009.

(107) Enneking WF, Maale GE. The effect of inadvertent tumor contamination of wounds during the surgical resection of musculoskeletal neoplasms. Cancer. 1988 Oct1;62(7):1251-1256.

(108) Virkus WW, Marshall D, Enneking WF, Scarborough MT. The effect of contaminated surgical margins revisited. Clin Orthop Relat Res. 2002 Apr;(397)(397):89-94.

(109) Sommerville SM, Patton JT, Luscombe JC et al.Clinical outcomes of deep atypical lipomas (well-differentiated lipoma-like-liposarcomas) oft he extremities. ANZ J Surg. 2005 Sep;75(9):803-6.

(110) Gortzak Y, Lockwood GA, Mahendra A, Wang Y, Chung PW, Catton CN, et al. Prediction of pathologic fracture risk of the femur after combined modality treatment of soft tissue sarcoma of the thigh. Cancer. 2010 Mar 15;116(6):1553-1559.

(111) Holt GE, Griffin AM, Pintilie M, et al. Fractures following radiotherapy and limb-salvage surgery for lower extremity soft-tissue sarcomas. A comparison of high-dose and low-dose radiotherapy. J Bone Joint Surg Am. 2005 Feb;87(2):315-9.

(112) Mercurio AD, Motta T, Green E, Noble G, Hart RT, Allen MJ. Effects of extensive circumferential periosteal stripping on the microstructure and mechanical properties of the murine femoral cortex. J Orthop Res. 2012 Apr;30(4):561-568.

(113) Brooks AD, Gold JS, Graham D, Boland P, Lewis JJ, Brennan MF, et al. Resection of the sciatic, peroneal, or tibial nerves: assessment of functional status. Ann Surg Oncol. 2002 Jan-Feb;9(1):41-47.

(114) Bickels J, Wittig JC, Kollender Y, Kellar-Graney K, Malawer MM, Meller I. Sciatic nerve resection: is that truly an indication for amputation? Clin Orthop Relat Res. 2002 Jun;(399):201-204.

(115) Chao AH, Mayerson JL, Chandawarkar R, Scharschmidt TJ. Surgical management of soft tissue sarcomas: Extremity sarcomas. J Surg Oncol. 2015 Apr 1;111(5):540-545.

(116) Clarkson PW, Griffin AM, Catton CN, O'Sullivan B, Ferguson PC, Wunder JS, et al. Epineural dissection is a safe technique that facilitates limb salvage surgery. Clin Orthop Relat Res. 2005 Sep;438:92-96.

(117) Ferguson PC, Kulidjian AA, Jones KB, Deheshi BM, Wunder JS. Peripheral nerve considerations in the management of extremity soft tissue sarcomas. Recent Results Cancer Res. 2009;179:243-256.

(118) Lee GW, Mackinnon SE, Brandt K, Bell RS. A technique for nerve reconstruction following resection of soft-tissue sarcoma. J Reconstr Microsurg. 1993 Mar;9(2):139-44.

(119) Fischer S, Soimaru S, Hirsch T et al. Local tendon transfer for knee extensor mechanism reconstruction after soft tissue sarcoma resection. J Plast Reconstr Aesthet Surg. 2015 May;68(5):729-35.

(120) Gerrand CH, Wunder JS, Kandel RA, O'Sullivan B, Catton CN, Bell RS, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br 2001 Nov;83(8):1149-1155.

(121) Gerrand CH, Wunder JS, Kandel RA, et al. Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br. 2001 Nov;83(8):1149-55.

(122) Hohenberger P, Allenberg JR, Schlag PM, Reichardt P. Results of surgery and multimodal therapy for patients with soft tissue sarcoma invading to vascular structures. Cancer. 1999 Jan 15;85(2):396-408.

(123) Barner-Rasmussen I, Popov P, Böhling T, Tarkkanen M, Sampo M, Tukiainen E. Microvascular reconstruction after resection of soft tissue sarcoma of the leg. Br J Surg. 2009 May;96(5):482-9.

(124) Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous Vein Versus PTFE for above-knee femoropopliteal bypass: A review of the literature. Eur J Vasc Endovasc Surg. 2004;27:357–62.

(125) Mahendra A, Gortzak Y, Ferguson PC, Deheshi BM, Lindsay TF, Wunder JS. Management of vascular involvement in extremity soft tissue sarcoma. Recent Results Cancer Res. 2009;179:285-99.

(126) Schwartz A, Rebecca A, Smith A, Casey W, Ashman J, Gunderson L, et al. Risk factors for significant wound complications following wide resection of extremity soft tissue sarcomas. Clin Orthop Relat Res. 2013 Nov;471(11):3612-3617.

(127) Schwarzbach MH, Hormann Y, Hinz U, et al. Results of limb-sparing surgery with vascular replacement for soft tissue sarcoma in the lower extremity. J Vasc Surg. 2005 Jul;42(1):88-97.

(128) Ghert MA, Davis AM, Griffin AM, Alyami AH, White L, Kandel RA, et al. The surgical and functional outcome of limb-salvage surgery with vascular reconstruction for soft tissue sarcoma of the extremity. Ann Surg Oncol. 2005 Dec; 12(12):1102-1110.

(129) Hohenberger P, Allenberg JR, Schlag PM, Reichardt P. Results of surgery and multimodal therapy for patients with soft tissue sarcoma invading to vascular structures. Cancer. 1999 Jan 15;85(2):396-408.

(130) Coindre JM, Terrier P, Bui NB, et al. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group J Clin Oncol. 1996;14(3):869-877.

(131) Gronchi A, Casali PG, Mariani L, et al. Status of surgical margins and prognosis in adult soft tissue sarcomas of the extremities: a series of patients treated at a single institution. J Clin Oncol. 2005 Jan 1;23(1):96-104.

(132) McKee MD, Liu DF, Brooks JJ, Gibbs JF, Driscoll DL, Kraybill WG. The prognostic significance of margin width for extremity and trunk sarcoma. J Surg Oncol. 2004 Feb;85(2):68-76.

(133) Enneking WF, Spanier SS, Malawer MM. The effect of the Anatomic setting on the results of surgical procedures for soft parts sarcoma of the thigh. Cancer. 1981 Mar 1;47(5):1005-1022.

(134) Kandel R, Coakley N, Werier J, Engel J, Ghert M, Verma S, et al. Surgical margins and handling of soft-tissue sarcoma in extremities: a clinical practice guideline. Current Oncol. 2013 Jun;20(3):e247-54.

(135) Kawaguchi N, Matumoto S, Manabe J New method of evaluating the surgical margin and safety margin for musculoskeletal sarcoma, analysed on the basis of 457 surgical cases. J Cancer Res Clin Oncol. 1995;121(9-10):555-63.

(136) Kawaguchi N, Ahmed AR, Matsumoto S, Manabe J, Matsushita Y. The concept of curative margin in surgery for bone and soft tissue sarcoma. Clin Orthop Relat Res. 2004 Feb;(419):165-172.

(137) Potter BK, Hwang PF, Forsberg JA, Hampton CB, Graybill JC, Peoples GE, et al. Impact of margin status and local recurrence on soft-tissue sarcoma outcomes. J Bone Joint Surg Am. 2013 Oct 16;95(20):e151.

(138) Lintz F, Moreau A, Odri GA, Waast D, Maillard O, Gouin F. Critical study of resection margins in adult soft-tissue sarcoma surgery. Orthop Traumatol Surg Res. 2012 Jun;98(4):9-18.

(139) Tunn PU, Kettelhack C, Durr HR. Standardized approach to the treatment of adult soft tissue sarcoma of the extremities. Recent Results Cancer Res. 2009;179:211-228.

(140) Dickinson IC, Whitwell DJ, Battistuta D, Thompson B, Strobel N, Duggal A, et al. Surgical margin and its influence on survival in soft tissue sarcoma. ANZ J Surg. 2006 Mar;76(3):104-109.

(141) Von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Casper ES, et al. Soft tissue sarcoma, version 2.2014. J Natl Compr Canc Netw. 2014 Apr; 12(4):473-483.

(142) Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. Cancer. 2002 May 1;94(9):2511-2516.

(143) Wittekind C. TNM supplement: a commentary on uniform use, 4th Edition. John Wiley & Sons. 2012.

(144) Lewis JJ, Leung D, Heslin M, Woodruff JM, Brennan MF. Association of local recurrence with subsequent survival in extremity soft tissue sarcoma. J Clin Oncol. 1997 Feb;15(2):646-652.

(145) Novais EN, Demiralp B, Alderete J, Larson MC, Rose PS, Sim FH. Do surgical margin and local recurrence influence survival in soft tissue sarcomas? Clin Orthop Relat Res. 2010 Nov;468(11):3003-3011.

(146) Maretty-Nielsen K, Aggerholm-Pedersen N, Safwat A, Jorgensen PH, Hansen BH, Baerentzen S, et al. Prognostic factors for local recurrence and mortality in adult soft tissue sarcoma of the extremities and trunk wall: a cohort study of 922 consecutive patients. Acta Orthop. 2014 Jun;85(3):323-332.

(147) O'Donnell PW, Griffin AM, Eward WC, Sternheim A, Catton CN, Chung PW, et al. The effect of the setting of a positive surgical margin in soft tissue sarcoma. Cancer. 2014 Sep 15;120(18):2866-2875.

(148) Alamanda VK, Crosby SN, Archer KR, Song Y, Schwartz HS, Holt GE. Primary excision compared with re-excision of extremity soft tissue sarcomas--is anything new? J Surg Oncol. 2012 Jun 1;105(7):662-667.

(149) Bhangu AA, Beard JAS, Grimer RJ. Should Soft Tissue Sarcomas be Treated at a Specialist Centre? Sarcoma. 2004;8(1):1-6.

(150) Zacherl M, Kastner N, Glehr M, Scheipl S, Schwantzer G, Koch H, et al. Influence of prereferral surgery in soft tissue sarcoma: 10 years' experience in a single institution. Orthopedics. 2012 Aug 1;35(8):e1214-20.

(151) Jonathan J. Lewis JJ,Leug D, Espat J, et al. Effect of Reresection in Extremity Soft Tissue Sarcoma. Annals of Surgery. 2000 May;231(5):655-663.

(152) Rehders A, Stoecklein NH, Poremba C, Alexander A, Knoefel WT, Peiper M. Reexcision of soft tissue sarcoma: sufficient local control but increased rate of metastasis. World J Surg. 2009 Dec;33(12):2599-2605.

(153) Manoso MW, Frassica DA, Deune EG, Frassica FJ. Outcomes of re-excision after unplanned excisions of soft-tissue sarcomas. J Surg Oncol. 2005 Sep 1;91(3):153-158.

(154) Zacherl M, Giessauf C, Glehr G, Gruber G, Maurer-Ertl W, Schwantzer G, et al. Revision of inadequately treated soft-tissue sarcoma is associated with increased need for plastic or reconstructive surgery. Eur Surg. 2009 Aug;41(4):155-162.

(155) Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS. Preoperative vs. postoperative radiation therapy for soft tissue sarcoma: a retrospective comparative evaluation of disease outcome. Int J Radiat Oncol Biol Phys. 2003 Jun1;56(2):482-488.

(156) O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002 Jun 29;359(9325):2235-2241.

(157) Kim B, Chen YL, Kirsch DG, Goldberg SI, Kobayashi W, Kung JH, et al. An effective preoperative three-dimensional radiotherapy target volume for extremity soft tissue sarcoma and the effect of margin width on local control. Int J Radiat Oncol Biol Phys. 2010 Jul 1;77(3):843-850.

(158) Haas RL, Delaney TF, O'Sullivan B, Keus RB, Le Pechoux C, Olmi P, et al. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys. 2012 Nov 1;84(3):572-580.

(159) Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998 Jan;16(1):197-203.

(160) Strander H, Turesson I, Cavallin-Stahl E. A systematic overview of radiation therapy effects in soft tissue sarcomas. Acta Oncol. 2003;42(5-6):516-531.

(161) Beane JD, Yang JC, White D, et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol. 2014 Aug;21(8):2484-9.

(162) Alektiar KM, Velasco J, Zelefsky MJ, Woodruff JM, Lewis JJ, Brennan MF. Adjuvant radiotherapy for margin-positive high-grade soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys. 2000 Nov 1;48(4):1051-1058.

(163) Stinson SF, DeLaney TF, Greenberg J, et al. Acute and long-term effects on limb function of combined modality limb sparing therapy for extremity soft tissue sarcoma. Int J RadiatOncolBiol Phys. 1991 Nov;21(6):1493-9.

(164) Cahlon O, Brennan MF, Jia X, Qin LX, Singer S, Alektiar KM. A postoperative nomogram for local recurrence risk in extremity soft tissue sarcomas after limb-sparing surgery without adjuvant radiation. Ann Surg. 2012 Feb;255(2):343-347.

(165) Green CM, Nguyen N, Wylie J, et al. The treatment of periarticular soft tissue sarcoma following neo-adjuvant radiotherapy: a cohort study. World J Surg Oncol. 2015 Mar 14;13:108.

(166) Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma. 2010; 2010: 506182.

(167) Edland RW. Liposarcoma. A retrospective study of fifteen cases, a review of the literature and a discussion of radiosensitivity. Am J Roentgenol Radium Ther Nucl Med. 1968 Aug; 103(3): 778-791.

(168) Shiu MH, Chu F, Castro EB, Hajdu SI, Fortner JH. Results of surgical and radiation therapy in the treatment of liposarcoma arising in an extremity. Am J Roentgenol Radium Ther Nucl Med. 1975; 123(3): 577-582.

(169) Chung PW, Deheshi BM, Ferguson PC, et al. Radiosensitivity translates into excellent local control in extremity myxoidliposarcoma: a comparison with other soft tissue sarcomas. Cancer. 2009 Jul 15;115(14):3254-61.

(170) Pitson G, Robinson P, Wilke D, et al. Radiation response: an additional unique signature of myxoidliposarcoma. Int J RadiatOncolBiol Phys.2004 Oct; 60(2): 522-526.

(171) Eriksson M. Histology-driven chemotherapy of soft-tissue sarcoma. Ann Oncol. 2010 Oct;21(7):270-6.

(172) Anderson P, Aguilera D, Pearson M, Woo S. Outpatient chemotherapy plus radiotherapy in sarcomas: improving cancer control with radiosensitizing agents. Cancer Control. 2008 Jan;15(1):38-46.

(173) Grobmyer SR, Maki RG, Demetri GD, et al. Neo-adjuvant chemotherapy for primary high-grade extremity soft tissue sarcoma. Ann Oncol. 2004 Nov;15(11):1667-72.

(174) Craft A, Cotterill S, Malcolm A, et al. Ifosfamide-containing chemotherapy in Ewing's sarcoma: The Second United Kingdom Children's Cancer Study Group and the Medical Research Council Ewing's Tumor Study. J Clin Oncol. 1998 Nov;16(11):3628-33.

(175) Thacker MM, Temple HT, Scully SP. Current treatment for Ewing's sarcoma. Expert Rev Anticancer Ther. 2005 Apr;5 (2):319-31.

(176) Esnaola NF, Rubin BP, Baldini EH, et al. Response to Chemotherapy and Predictors of Survival in Adult Rhabdomyosarcoma. Ann Surg. 2001 Aug; 234(2): 215–223.

(177) Jones RL, Fisher C, Al-Muderis O, et al. Differential sensitivity of liposarcoma subtypes to chemotherapy. European Journal of Cancer. 2005 Dec;41(18):2853–2860.

(178) Spurrell EL, Fisher C, Thomas JM, et al. Prognostic factors in advanced synovial sarcoma: an analysis of 104 patients treated at the Royal Marsden Hospital. Annals of Oncology. 2005 Mar;16(3):437–444.

(179) Karavasilis V, Seddon BM, Ashley S, et al. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. Cancer. 2008 Apr 1;112(7):1585-91.

(180) Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008 Aug 1;113(3):573-81.

(181) Woll PJ, Reichardt P, Le CesneA,et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentrerandomised controlled trial. Lancet Oncol. 2012 Oct;13(10):1045-54.

(182) Italiano A, Delva F, Mathoulin-Pelissier S, Le Cesne A, Bonvalot S, Terrier P, Trassard M, Michels JJ, Blay JY, Coindre JM, Bui B. Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. Ann Oncol. 2010 Dec;21(12):2436-41.

(183) Creech O, Krementz ET, Ryan RF, Winblad JN. Chemotherapy of Cancer: Regional Perfusion Utilizing an Extracorporeal Circuit. Annals of Surgery. 1958;148(4):616-632.

(184) Deroose JP, van Geel AN, Burger JW, Eggermont AM, Verhoef C. Isolated limb perfusion with TNF-alpha and melphalan for distal parts of the limb in soft tissue sarcoma patients. J Surg Oncol. 2012 May;105(6):563-9.

(185) Eggermont AM, Schraffordt Koops H, Klausner JM, et al. Isolated limb perfusion with tumor necrosis factor and melphalan for limb salvage in 186 patients with locally advanced soft tissue extremity sarcomas. The cumulative multicenter European experience. Annals of Surgery. 1996;224(6):756-765.

(186) Jakob J, Tunn PU, Hayes AJ, Pilz LR, Nowak K, Hohenberger P. Oncological outcome of primary non-metastatic soft tissue sarcoma treated by neoadjuvant isolated limb perfusion and tumor resection. J Surg Oncol. 2014 Jun;109(8):786-90.

(187) Brennan MF. Lessons learned from the study of soft tissue sarcoma. Int J Surg. 2013 Dec;11(1):8-10.

(188) Singer S, Corson JM, Gonin R, Labow B, Eberlein TJ. Prognostic factors predictive of survival and local recurrence for extremity soft tissue sarcoma. Ann Surg. 1994 Feb;219(2):165-173.

(189) Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. Ann Surg. 2002 Mar;235(3):424-434.

(190) Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol. 1996 May;14(5):1679-89.

(191) Carter RJ, Qin LX, Downey RJ, et al. Perioperative chemotherapy in patients undergoing pulmonary resection for metastatic soft-tissue sarcoma of the extremity. Cancer. 2007Nov 1;110(9):2050-60.

(192) Billingsley KG, Lewis JJ, Leung DH, Casper ES, Woodruff JM, Brennan MF.Multifactorial analysis of the survival of patients with distant metastasis arising from primary extremity sarcoma. Cancer. 1999 Jan 15;85(2):389-95.

(193) García Francoa CE, Algarrab SM, Ezcurra AT, et al. Long-term results after resection for soft tissue sarcoma pulmonary metastases. Interact Cardiovasc Thorac Surg. 2009 Aug;9(2):223-6.

(194) Casson AG, Putnam JB, Natarajan G, et al. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. Cancer. 1992 Feb 1;69(3):662-8.

(195) Rehders A, Hosch SB, Scheunemann P, et al. Benefit of surgical treatment of lung metastasis in soft tissue sarcoma. Arch Surg. 2007 Jan;142(1):70-5; discussion 76.

(196) Sardenberg RA, Figueiredo LP, Haddad FJ, et al. Pulmonary metastasectomy from soft tissue sarcomas. Clinics (Sao Paulo). 2010 Sep; 65(9): 871–876.

(197) Behranwala KA, A'Hern R, Omar AM, Thomas JM. Prognosis of lymph node metastasis in soft tissue sarcoma. Ann Surg Oncol. 2004 Jul;11(7):714-9.

(198) Estourgie SH, Nielsen GP, Ott MJ. Metastatic patterns of extremity myxoidliposarcoma and their outcome. J Surg Oncol. 2002 Jun;80(2):89-93.

(199) Sibly E, Sumathi VP, Grimer RJ, et al. Patterns of metastasis and outcome for patients with myxoidliposarcoma. J Bone Joint Surg Br. 2006;88(2):298

(200) Van Glabbeke M, van Oosterom AT, Oosterhuis JW, et al. Prognostic factors for the out-come of chemotherapy in advanced soft tissuesarcoma: an analysis of 2,185 patients treated with anthracycline-containing first-line regimens – a European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Study. J Clin Oncol. 1999 Jan;17(1):150-7.

(201) Soyfer V, Corn BW, Kollender Y, Tempelhoff H, Meller I, Merimsky O. Radiation Therapy for Palliation of Sarcoma Metastases: A Unique and Uniform Hypofractionation Experience. Sarcoma. 2010;2010:927972.

(202) Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol. 2007 Apr 10;25(11):1423-36.

(203) Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys. 2011 Mar 15;79(4):965-76.

(204) Bedi M, King DM, Charlson J, Whitfield R, Hackbarth DA, Zambrano EV, et al. Multimodality management of metastatic patients with soft tissue sarcomas may prolong survival. Am J ClinOncol. 2014 Jun;37(3):272.

(205) Bedi M, King DM, Saeed H, e t al. Localized Management of Soft Tissue Sarcoma Metastasis:A Review of a MultidisciplinaryApproach. Cancer Research Frontiers. 2015 Apr; 1(2): 162-171.

(206) Bedre G, Gupta T, Rajasekharan P, Munshi A, Jalali R. Cerebellar, pancreatic, and paraspinal metastases in soft tissue sarcomas: unusual sites or changing patterns? JOP. 2007 Jul 9;8(4):444-9.

(207) Adsay NV, Andea A, Basturk O, et al. Secondary tumors of the pancreas: an analysis of a surgical and autopsy database and review of the literature. Virchows Arch. 2004 Jun;444(6):527-35.

(208) DeWitt J, Jowell P, Leblanc J, et al. EUS-guided FNA of pancreatic metastases: a multicenter experience. Gastrointest Endosc. 2005 May;61(6):689-96.

(209) Abdalla EK, Pisters PW. Metastasectomy for limited metastases from soft tissue sarcoma. Curr Treat Options Oncol. 2002 Dec;3(6):497-505.

(210) Yamamoto H, Watanabe K, Nagata M, et al. Surgical treatment for pancreatic metastasis from soft-tissue sarcoma: report of two cases. Am J Clin Oncol. 2001 Apr;24(2):198-200.

(211) Santoro A, Tursz T, Mouridsen H, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995;13(7):1537.

(212) Le Cesne A, Judson I, Crowther D, et al. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 2000;18(14):2676.

(213) Grenader T, Goldberg A, Hadas-Halperin I, Gabizon A. Long-term response to pegylated liposomal doxorubicin in patients with metastatic soft tissue sarcomas. Anticancer Drugs. 2009 Jan;20(1):15-20.

(214) Yousaf N, Harris S, Martin-Liberal J, et al. First line palliative chemotherapy in elderly patients with advanced soft tissue sarcoma. Clin Sarcoma Res. 2015 Mar 24;5:10.

(215) Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002 [corrected]. J Clin Oncol. 2007 Jul 1;25(19):2755-63.

(216) Verma S, Younus J, Stys–Norman D, et al. . Ifosfamide-based combination chemotherapy in advanced soft-tissue sarcoma: a practice guideline. Curr Oncol. 2007 Aug; 14(4): 144–148.

(217) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Soft Tissue Sarcomas, Version 1.2013.

(218) Ruka W, Rutkowski P, Krzakowski M, Grzesiakowska U, Ptaszyński K, Jeziorski A, Polkowski W, Ryś J, Słuszniak J, Dziewirski W, Morysiński T, Świtaj T, Bębenek M, Siedlecki JA, Limon J, Nowecki ZI. Soft tissue sarcomas in adult patients –guidelines for diagnosis and treatment. Nowotwory – Journal of Oncology. 2010;60:55–65.

(219) Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. Sarcoma. 2010;2010:506182.

(220) Patel SR, Zagars GK, Pisters PW. The follow-up of adult soft-tissue sarcomas. SeminOncol. 2003 Jun;30(3):413-6.

(221) Labarre D, Aziza R, Filleron T, Delannes M, Delaunay F, Marques B, Ferron G, Chevreau C. Detection of local recurrences of limb soft tissue sarcomas: Is magnetic resonance imaging (MRI) relevant?Eur J Radiol. 2009 Oct;72(1):50-3.

(222) Vanel D, Shapeero LG, De Baere T. MR imaging in the follow-up of malignant and aggressive soft-tissue tumors: results of 511 examinations. Radiology. 1994 Jan;190(1):263-8.

(223) Rutkowski P, Ługowska I. Follow-up in soft tissue sarcomas. Memo. 2014; 7(2): 92–96.

(224) Cool P, Grimer R, Rees R. Surveillance in patients with sarcoma of the extremities. Eur J SurgOncol. 2005 Nov;31(9):1020-4.

(225) Chou YS, Liu CY, Chen WM, et al. Follow-up after primary treatment of soft tissue sarcoma of extremities: impact of frequency of follow-up imaging on disease-specific survival. J SurgOncol. 2012 Aug 1;106(2):155-61.

(226) Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Gerger S, et al. Common gene variants in RAD51, XRCC2 and XPD are not associated with clinical outcome in soft-tissue sarcoma patients. Cancer Epidemiol 2013 Dec;37(6):1003-1009.

(227) Würl P, Kappler M, Meye A, et al. Co-expression of survivin and TERT and risk of tumour-related death in patients with soft-tissue sarcoma. Lancet. 2002 Mar 16;359(9310):943-5.

(228) Szkandera J, Gerger A, Liegl-Atzwanger B, Stotz M, Samonigg H, Ploner F, et al. Uric acid levels in blood are associated with clinical outcome in soft-tissue sarcoma patients. ClinChem Lab Med 2014 Oct 15.

(229) Nakamura T, Matsumine A, Matsubara T, et al. Clinical significance of pretreatment serum C-reactive protein level in soft tissue sarcoma. Cancer. 2012 Feb 15;118(4):1055-61.

(230) Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Samonigg H, et al. Validation of the prognostic relevance of plasma C-reactive protein levels in soft-tissue sarcoma patients. Br J Cancer 2013 Oct 29;109(9):2316-2322.

(231) Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Friesenbichler J, et al. The lymphocyte/monocyte ratio predicts poor clinical outcome and improves the predictive accuracy in patients with soft tissue sarcomas. Int J Cancer 2014 Jul15;135(2):362-370.

(232) Szkandera J, Pichler M, Liegl-Atzwanger B, Absenger G, Stotz M, Ploner F, et al. The elevated pre-operative plasma fibrinogen level is an independent negative prognostic factor for cancer-specific, disease-free and overall survival in soft-tissue sarcoma patients. J SurgOncol 2013 Oct 7.

(233) Szkandera J, Absenger G, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer 2013 Apr 30;108(8):1677-1683.

(234) Potter DA, Glenn J, Kinsella T, et al. Patterns of recurrence in patients with high-grade soft-tissue sarcomas. J Clin Oncol. 1985;3:353-366.

(235) Zanarini D, Sugarbaker PH. Extremity soft tissue sarcoma with metastases to abdominopelvic surfaces. J Surg Oncol. 1997 Jan;64(1):68-72; discussion 72-3.

(236) Cheng EY, Springfield DS, Mankin HJ. Frequent incidence of extrapulmonary sites of initial metastasis in patients with liposarcoma. Cancer. 1995 Mar 1;75(5):1120-7.