Dissertation

Follow-up and outcome of patients with soft tissue sarcoma.

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the "Guidelines of the Medical University of Graz on Good Scientific Practice".

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Disclosures

The current dissertation has been published as the following articles:

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- *Smolle MA, Schaffler A et al.* **Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study.** J Surg Oncol. 2020;121(4):605-11.

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- *Smolle MA, van Praag V et al.* **Surgery for metachronous metastasis of soft tissue sarcoma – A magnitude of benefit analysis using propensity score methods.** European Journal of Surgical Oncology. 2019 Feb;45(2):242-248.

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***Referring publications**

1. *Smolle MA, Andreou D et al.* Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk. EFORT Open Rev. 2017;2(10):421-31.

2. *Smolle MA, Schaffler A et al.* Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study. J Surg Oncol. 2020;121(4):605-11.

3. *Smolle MA, van Praag V et al.* Surgery for metachronous metastasis of soft tissue sarcoma – A magnitude of benefit analysis using propensity score methods. European Journal of Surgical Oncology. 2019 Feb;45(2):242-248.

4. *Smolle MA, Sande MV et al.* Individualizing Follow-Up Strategies in High-Grade Soft Tissue Sarcoma with Flexible Parametric Competing Risk Regression Models. Cancers (Basel). 2019;12(1).

All co-authors of every article have given their written permission to have the papers presented and discussed within the current thesis. Notably, the written permission of Prof. Sander Dijkstra could not be obtained due his current medical condition.

The written permission for reproduction of the herein presented articles, their contents, tables and figures, has been obtained from the respective publishers (*The British Editorial Society of Bone & Joint Surgery, Elsevier, Wiley, MDPI*).

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Table of Contents

Abbreviations and Definitions

Abbreviation	Description
AM	Abdominal metastasis
ANNOUNCE	Docorubicin Plus Oralatumab vs. Doxorubicin Plus Placebo in Patients with Advanced Soft Tissue Sarcomas
BSC	Best supportive care
CI	Confidence interval
CT	Computed Tomography
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CTX	Chemotherapy
DM	Distant metastasis
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ESMO	European Society for Medical Oncology
eSTS	Extremity soft tissue sarcoma
GIST	Gastrointestinal stromal tumour
HR	Hazard ratio
IPTW	Inverse probability of treatment weight
IQR	Interquartile range
LR	Local recurrence
MPNST	Malignant peripheral nerve sheath tumour
MRI	Magnetic resonance imaging
NOS	Not otherwise specified
OS	Overall Survival
PALETTE	Pazopanib expLorEd in SofT Tissue Sarcoma
PD-1	Programmed death-1
PDGFRa	Platelet Derived Growth Factor Receptor Alpha
PERSARC	Personalised Sarcoma Care
R0/R1/R2	Resection margin status 0/1/2
REGOSARC	Regorafenib in patients with advanced Soft Tissue Sarcoma

RTX	Radiotherapy
SEER	Surveillance, Epidemiology, and End Results
STS	Soft tissue sarcoma
TRK	Tropomyosin receptor kinase
UPS	Undifferentiated pleomorphic sarcoma
WTS	Weichteilsarkom

Zusammenfassung

Weichteilsarkome (WTS) stellen eine seltene Tumorentität dar, mit einer geschätzten Inzidenz von 4 bis 6 Fällen pro 100.000 Patienten pro Jahr. Das primäre Therapieziel bei lokalisiertem WTS ist die operative Entfernung mit tumorfreien Resektionsrändern. Im Falle von Metastasen, welche 20-30% der Patienten mit primär lokalisierten WTS entwickeln, sind die Therapieoptionen allerdings limitiert, nicht zuletzt wegen mäßiger Ansprechraten auf derzeit erhältliche systemische Therapeutika.

In dieser kumulativen Dissertation werden vier Arbeiten zusammengefasst und präsentiert, die seit dem Jahr 2017 über die Diagnostik, Therapie, und die Nachsorge von Patienten mit WTS publiziert wurden.

Der erste Artikel stellt eine Übersichtsarbeit zur klinischen Präsentation, Diagnostik, Therapie, und der Prognose von WTS-Patienten dar. Aufgrund unspezifischer klinischer Symptome (Schwellung, Schmerzen, an Größe zunehmende Läsion), ist eine Bildgebung mit Ultraschall und – vorzugsweise – Magnetresonanztomographie mit Kontrastmittel notwendig, um die weiteren Therapieschritte einzuleiten. Eine Biopsie, welche nach speziellen onko-chirurgischen Gesichtspunkten durchgeführt werden sollte, und die Verdachtsdiagnose bestätigt, wird gefolgt von einer weiten Resektion. Optional werden (neo)adjuvante Radiotherapie und Chemotherapie angewandt.

Die Inzidenz, Behandlung und Prognose von WTS-Patienten mit abdominellen Metastasen (AM) wird im zweiten Artikel diskutiert. Von 769 Patienten mit WTS, die in die multizentrische Studie eingeschlossen wurden, entwickelten 202 sekundäre Metastasen (26.3%), von denen sich 24 mit AM präsentierten (3.1%). Patienten mit Liposarkomen hatten ein höheres AM-Risiko, hinweisend auf das unterschiedliche biologische Verhalten der über 50 verschiedenen WTS-Subtypen. Das Post-Metastasen-Überleben von Patienten mit AM war schlecht, wobei Patienten mit Metastasektomie eine bessere Prognose aufwiesen als Patienten, die mit Radiotherapie, Chemotherapie oder Best Supportive Care (BSC) behandelt wurden.

In Zusammenhang hiermit diskutiert die dritte Arbeit den unabhängigen Einfluss von Metastasektomien auf das Überleben von WTS-Patienten mit metachronen Metastasen. Von 135 Patienten, welche in die bi-zentrische Studie eingeschlossen wurden, erhielten 68 eine Metastasektomie, während 67 Patienten mit Chemotherapie, Radiotherapie, oder BSC behandelt worden waren. Unter Verwendung von „Inverse-Probability-of-Treatment-

Weight“, um den „Behandlungs-Auswahl“ Bias hinsichtlich Metastasektomie vs. nicht-operative Behandlung zu kompensieren, konnte ein unabhängiger Vorteil von Metastasektomie auf das Patientenüberleben festgestellt werden, mit 1- und 10-Jahres Überlebensraten von 86% und 17% für operativ behandelte Patienten, verglichen mit 39% und 3% für konservativ therapierte WTS-Patienten mit metachronen Metastasen.

In der vierten Publikation wurde ein individuelles Nachsorgeschema für Patienten mit WTS der Extremitäten im Rahmen einer Multicenterstudie erstellt. Die statistischen Modelle (flexible parametrische competing-risk Regressions-Analysen), entwickelt an einer Testkohorte von 1913 Patienten mit intermediären oder hochgradigen WTS, und validiert an einer unabhängigen Kohorte von 1085 WTS-Patienten, ermöglichen eine Abschätzung des individuellen Risikos von Patienten hinsichtlich Lokalzrezidiven und Fernmetastasen. Die Resultate dieser Modelle wurden in die PERSARC App integriert, die nicht nur die Berechnung des kumulativen Lokalrezidiv- und Fernmetastasen-Risikos ermöglicht, sondern auch das konditionelle Risiko lokalen und systemischen Befalls von einem Nachsorgezeitpunkt zu dem nächsten in 3 bis 6 Monaten.

Internationale Kollaborationen ermöglichen ein besseres Verständnis von Diagnose, Behandlung und Outcome von WTS-Patienten, um schlussendlich das Gesamtergebnis von Patienten, die von dieser seltenen und heterogenen malignen Erkrankung betroffen sind, zu verbessern.

Abstract

Soft tissue sarcomas constitute a rare tumour entity, with an estimated incidence of 4 to 6 cases per 100.000 patients per year. The primary treatment goal in localised STS consists of surgical resections with tumour-free margins. In case of metastatic disease, developing in 20-30% of patients with initially localised disease, however, treatment options are limited, owing to the moderate response to systemic anti-tumour agents currently available.

In the current cumulative thesis, four articles published since 2017 about diagnosis, treatment, or follow-up of patients with STS will be summarised and presented.

The first article constitutes a review about the clinical presentation, diagnosis, therapeutic management, and outcome of STS-patients. Due to unspecific clinical signs (swelling, pain, lump increasing in size over time), imaging with ultrasound and – preferably – magnetic resonance imaging with contrast agent is required to initiate further treatment. A biopsy adhering to specific onco-surgical rules confirming the suspected diagnosis is followed by wide surgical resection. Optionally, (neo)adjuvant radiotherapy and chemotherapy may be administered.

The incidence, treatment and prognosis of STS-patients with abdominal metastases (AM) is discussed in the second article. Of 769 patients with STS included in a multi-centre study, 202 developed secondary metastases (26.3%), of whom 24 presented with abdominal metastases (3.1%). Patients with liposarcoma had a significantly higher AM-risk, already highlighting differences in biological behaviour of the over 50 STS subtypes. Post-metastasis survival of patients with AM was poor, although patients undergoing metastasectomy had a better prognosis than those treated with radiotherapy, chemotherapy, or best supportive care (BSC).

Related to this, the third study discusses the independent impact of metastasectomy on survival of STS patients with metachronous metastases. Of 135 patients included in a bi-centre study, 68 underwent metastasectomy, whilst the remaining 67 patients had been treated by radiotherapy, chemotherapy, or BSC. Using inverse-probability-weighting to account for "treatment-selection" bias regarding metastasectomy vs. non-operative treatment, an independent benefit of metastasectomy on patients' survival was observed, with 1- and 10-year survival rates of 86% and 17%, respectively, for surgically treated patients as compared with 39% and 3% for non-operatively managed STS patients with metachronous metastasis.

In the fourth article, an individual follow-up protocol for patients with extremity STS was developed within a multicentre study. The statistical models (flexible parametric competing

risk regression models) developed on a test cohort of 1913 patients with intermediate or high-grade STS, and validated on an independent cohort of 1085 STS-patients, allow for assessment of patients' individual risk for local recurrence and distant metastasis. The results of these models have been implemented in the PERSARC app that does not only enable prediction of cumulative local recurrence and distant metastasis risk, but also estimation of conditional risks for local and systemic spread from one follow-up appointment to the subsequent one in 3 or 6 months.

International collaborations allow for better understanding of diagnosis, management, outcome, and follow-up of STS patients, eventually improving the overall outcome of patients affected by this rare and heterogeneous malignancy.

Introduction

With over 50 different histological subtypes, soft tissue sarcomas of the extremities (eSTS) form a heterogeneous group of malignant mesenchymal neoplasms differing from haematological or other solid malignancies in various ways. First, eSTS are relatively rare, with an incidence of 4 to 6 per 100.000 patients per year in Europe (1, 2). In comparison, the estimated incidence of lung and colon cancer, respectively, is 65 and 30 per 100.000 inhabitants per year (3). Second, the aetiology of eSTS remains to be clarified in the majority of cases, whilst in rare circumstances, genetic syndromes as *Neurofibromatosis Type I*, *Retinoblastoma syndrome* and *Bloom's syndrome* or history of previous irradiation are associated with development of eSTS (4). On the other hand, solid tumours as colon cancer, lung cancer and hepatocellular carcinoma have several known lifestyle-related (e.g. smoking, meat-rich nutrition) and health-related (e.g. hepatitis-B-virus infection) risk factors. Third, eSTS frequently cause scarce to no specific symptoms, thus potentially delaying correct diagnosis. In comparison, most solid or haematological malignancies present with specific symptoms (e.g. lung cancer – haemoptysis; haematological diseases – fever, involuntary weight-loss, night-sweat, fatigue; colon cancer – constipation, haematorrhoea). Fourth, distinct laboratory abnormalities indicative of eSTS are to date still missing, whilst some solid tumours and the majority of haematological malignancies can be assumed or even detected on the basis of body-fluid-based markers (e.g. prostate cancer – prostate specific antigen [PSA]; multiple myeloma – M-protein) (5-7). Fifth, eSTS have an extraordinarily high risk of developing local recurrence in case of residual tumour cells upon definite surgery in comparison to other solid tumours, wherefore wide resection with clear surgical margins is inevitable (8-10). Sixth, therapeutic options apart from surgery and local radiotherapy are limited, as standard chemotherapeutic agents as *doxorubicin* and *ifosfamide* are of limited effectiveness and novel anti-tumour drugs as immune-checkpoint-inhibitors have not nearly reached success rates seen in lung cancer, melanoma or renal cell cancer (11-13).

The following cumulative thesis comprises four articles published since 2017 dealing with diagnosis, treatment, follow-up and outcome of eSTS-patients. The first publication is a comprehensive review article summarising diagnosis and treatment of STS.

The second publication is an original article analysing the incidence and outcome of STS-patients with metachronous abdominal metastases. It is based on a retrospective cohort of 769 patients with STS, treated at three tertiary sarcoma centres.

The third publication constitutes an original article retrospectively investigating the effect of metastasectomy (i.e. surgical removal of metastases) on the prognosis of 135 patients with different STS-metastases, of whom 68 had undergone metastasectomy, and 67 had been treated by radiotherapy, chemotherapy, or best supportive care.

The fourth article is and an original article describing the development of a prediction model for individual local recurrence- and distant metastasis-risk in 3016 patients who have undergone surgery for primary localised STS at 7 tertiary sarcoma centres. All these publications are appended to the general introduction and discussion.

Results

The following section is briefly summarising the key findings of three original articles and the most important points of one review article being:

- *Smolle MA, Schaffler A et al.* **Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study.** J Surg Oncol. 2020;121(4):605-11. (Original Article)

- *Smolle MA, van Praag V et al.* **Surgery for metachronous metastasis of soft tissue sarcoma – A magnitude of benefit analysis using propensity score methods.** European Journal of Surgical Oncology. 2019 Feb;45(2):242-248. (Original Article)

- *Smolle MA, Sande MV et al.* **Individualizing Follow-Up Strategies in High-Grade Soft Tissue Sarcoma with Flexible Parametric Competing Risk Regression Models**. Cancers (Basel). 2019;12(1). (Original Article)

- *Smolle MA, Andreou D et al.* **Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk**. EFORT Open Rev. 2017;2(10):421-31. (Review Article; introduction to the dissertation topic)

In the first original article of this dissertation ("Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study"), 769 patients with STS who had been treated at three tertiary sarcoma centres (A*: Department of Orthopaedic Surgery, Leiden University Medical Centre, The Netherlands; B: HELIOS Klinikum Berlin-Buch, Germany; C: Department of Orthopaedics and Trauma, Medical University of Graz*) were analysed for development of abdominal metastases. Of the 769 patients, 202 developed secondary metastases (26.3%). The most common location was the lung (n=114), followed by bone (n=32) and lymph nodes (n=27) (14). DM developed after a median of 15 months following surgery (Interquartile Range [IQR]: 10-29 months). Of the 202 patients with DM, 24 presented with metastases to the abdomen, involving the liver (n=13), intestines

(n=3), pancreas (n=2), peritoneum (n=2), and multiple abdominal organs (n=4) (14). The overall incidence of abdominal metastases thus was 3.1%. Abdominal metastases were further divided into first and late abdominal metastases, defined as abdominal lesions occurring as the first metastases or following known metastases to other body parts, respectively. Fourteen patients had late abdominal metastases that had developed within a mean of 2.0 years after diagnosis of initial secondary lesions. The remaining 10 patients presented with first abdominal metastases, occurring after a mean of 2.4 years following surgery (14). According to this study, patients with liposarcoma as the underlying histological subtype were at a significantly higher risk to develop abdominal metastases in comparison to other subtypes (hazard ratio [HR] for liposarcoma: 6.589; 95% confidence interval [CI]: 1.668-26.026; p=0.007), irrespective of tumour grading. Regarding post-metastasis survival, no significant difference between patients with abdominal metastases and those with metastases to other sites was found (p=0.585). Notably, patients undergoing surgery for metastases had a significantly better post-metastasis survival than patients treated by radiotherapy, chemotherapy, or best supportive care (p=0.018). However, this association was only analysed in the univariate setting, as the main purpose of the study was to investigate incidence, risk factors and outcome of patients with abdominal metastases (14).

The second original article of this dissertation ("Surgery for metachronous metastasis of soft tissue sarcoma – A magnitude of benefit analysis using propensity score methods"), identified 135 patients with metachronous metastases out of a cohort of 1578 patients with primary localised STS who had undergone surgery with curative intent at two centres (A*: Department of Orthopaedic Surgery, Leiden University Medical Centre, The Netherlands; B: Department of Orthopaedics and Trauma, Medical University of Graz*) (15). Median age of patients at diagnosis of secondary metastases was 65 years (IQR: 50 – 75 years). The most common location of metastases were the lungs (n=99; 74%), followed by soft tissues and lymph nodes (n=21; 16%), bones (n=7; 5%), skip lesions (n=5; 4%), and organs (n=2; 1%) (15). Of the 135 patients, 67 had been treated by radiotherapy, chemotherapy, or best supportive care, whereas 68 patients had undergone metastasectomy. In order to independently assess the potential effect of metastasectomy on patients' outcome, inverse probability of treatment weight (IPTW) was performed, including variables at baseline that were associated with an increased likelihood for patients to undergo metastasectomy (15). These included singular

metastases (p<0.001), a prolonged time interval from surgery to development of first metastasis (p=0.020), location of metastases other than the lungs (p=0.039), a good ECOG performance status (p=0.019), as well as high haemoglobin (p=0.006) and albumin levels (p=0.002) at time of treatment decision (15). All these variables were included in the propensity score that was subsequently used to generate the IPTW, for whom the data was weighted for. In the naïve survival analysis, patients undergoing metastasectomy had a significantly better overall survival (OS) than patients treated by non-invasive measures (10-year OS: 23% vs. 4%; p<0.0001). After weighting for the IPTW, this association prevailed (adjusted 10-year OS: 17% vs. 3%; p<0.0001) (15). Thus, it was concluded that metastasectomy is beneficial for STS patients with metachronous metastases, even after adjustment for favourable prognostic factors as low number of metastases, good general condition, and time interval to secondary lesions (15).

The aim of the third original article of this cumulative dissertation ("Individualizing Follow-Up Strategies in High-Grade Soft Tissue Sarcoma with Flexible Parametric Competing Risk Regression Models") was to develop a more individualised follow-up protocol for patients with STS, based on a multi-centre study involving 7 tertiary sarcoma centres (*A: Department of Surgery, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom; B: Department of Orthopaedics and Trauma, Medical University of Graz, Austria; C: Department of Orthopaedic Surgery, Leiden University Medical Centre, The Netherlands; D: Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori Milano, Italy; E: Sarcoma Centre HELIOS Klinikum Berlin-Buch; Germany; F: University Musculoskeletal Oncology Unit, Mount Sinai Hospital, University of Toronto*) (16-18). Altogether, 3016 patients with G2 or G3 STS of the extremities were retrospectively included, of whom 1931 were analysed as the test cohort, and 1085 as the validation cohort (19). Flexible parametric competing risk regression models were calculated to estimate risk for LR and DM, taking into account varying incidences of events over time. In the multivariate flexible parametric competing risk regression model for LR, gender, grading, tumour size, margins, histology (divided into 9 subtypes), neoadjuvant radiotherapy, adjuvant radiotherapy, and adjuvant chemotherapy were included (19). Furthermore, for the flexible parametric competing risk regression model for DM, gender, grading, tumour size, margins, histological subtype and neoadjuvant radiotherapy were used (19). From the models, subdistribution hazard functions and cumulative incidence functions

for LR and DM were created, allowing visualisation of varying and overall event-risks, respectively. Internal and external validation of the two models with C-statistics was performed to assess model calibration. Harrell's C-index for internal and external validation of LR was 0.705 and 0.683, respectively. For DM, Harrell's C-index was 0.723 for internal and 0.772 for external validation (19). The herein developed models were subsequently included in the PERSARC app for individualised soft tissue sarcoma aftercare that is available in the Apple and Android store (16-18).

In the review about diagnosis and treatment of patients with soft tissue sarcoma ("Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk"), it is outlined that early and accurate diagnosis of STS is impaired by their rarity, unspecific symptoms and resemblance to benign soft tissue lesions (20). Yet, a worrisome feature described by patients is a noticed increase in size of any soft tissue lump, even if it had been present for several years (20, 21). During physical examination, the mobility of the lump within the soft tissues should be assessed; any lesion attached to surrounding structures points towards an infiltrative process and should prompt further investigation (20, 22). Magnetic resonance imaging (MRI) with contrast agent can be considered as "gold-standard" in diagnosis of STS, not only allowing assessment of the lesion's actual extent, but also involvement of important anatomical structures as nerves or vessels (20, 23). MRI may be preceded by sonography in case the soft tissue lump appears small, and patient history as well as clinical examination are inconspicuous (i.e. no increase in size, lump easily movable within soft tissues). Should sonography reveal any suspicious findings, MRI with contrast agent is recommended prior to incisional or excisional biopsy. The difference between these procedures is defined by their purpose; whilst upon excisional biopsy, the entire lesion is removed in one procedure, during incisional biopsy only a representative amount of tissue is obtained for histological analysis. Depending on the diagnosis, marginal or wide resection of the benign or malignant tumour, respectively, ensues. Thereafter, follow-up appointments are scheduled, aiming at detecting any LRs or DMs at early stages, thus allowing sufficient and aggressive treatment.

Discussion

Soft tissue sarcomas constitute rare and aggressive neoplasms, with diagnosis, treatment, follow-up and prognosis largely differing from common malignancies as lung, prostate, breast, and colon cancer. In the current thesis, three original articles and one literature review on soft tissue sarcomas, covering topics from incidence and outcome of abdominal STS-metastases, over the impact of metastasectomy, to a more individualised follow-up regimen in STS patients, will be discussed in further detail.

In the herein presented study analysing the incidence, treatment and outcome of abdominal metastases in STS, the overall incidence of metastases to the abdomen was 3.1% (14). This rate is lower than reported by *Thompson et al*. with 5.0% (24) and *King et al.* with 5.6% (25), both analysing various STS subtypes, including epithelioid sarcoma, liposarcoma, synovial sarcoma, MPNST, and pleomorphic sarcoma (24, 25). On the other hand, in the study by *Behranwala et al.,* the incidence of abdominal metastases was 0.9% only, although they also included histological subtypes with higher metastatic potential to the abdomen as myxoid liposarcoma (26). As a comparison, *Ogose et al.* and *Sheah et al.,* both analysing patients with different liposarcoma subtypes, estimated the incidence for abdominal metastases at 8.5% (27) and 12.1% (28), respectively.

According to our study, liposarcoma as histological subtype constituted an independent risk factor for early development of primary abdominal metastasis in comparison to all other histological subtypes, independent from original tumour grading (14). Also, patients with myxoid liposarcoma were at higher risk for development of abdominal metastases as compared to all other histological subtypes, albeit this was only confirmed in the univariate analysis (14). Notably, the risk for abdominal metastases did not significantly vary between liposarcoma sub-entities myxoid, pleomorphic, and NOS, indicating that any STS with liposarcomatous differentiation have a greater tendency to set abdominal metastases (14). This observation has also been made previously; according to *Fuglo et al.*, of 45 patients with myxoid liposarcoma, two patients presented with primary metastatic disease, and 5 with secondary metastases, all of whom developed at extrapulmonary sites, including two cases of abdominal metastases (29). Furthermore, *Cheng et al.* reported on extrapulmonary metastases in 13 of 22 patients with liposarcoma treated at a single institution, with soft tissues, bone and liver being the most common extrapulmonary sites for metastases (30).

Similar observations were made by *Pearlstone et al.* in their study involving 122 patients with liposarcoma, of whom 102 had a myxoid subtype (31). Extrapulmonary metastases developed in 34 of 43 patients (79.1%) with distant spread, being significantly more common in case of liposarcoma as the underlying histological subtype (31). Intra-abdominal lesions occurred in 22 patients (51.2%), involving intestines, abdominal wall, kidney and adrenal, bowel serosa and omentum (31). Similarly, we observed hepatic, intestinal, pancreatic, peritoneal, and multiple intestinal metastases in our study, although the overall incidence of abdominal lesions was lower at 11.9% (14). This can be explained by the fact that the overall percentage of patients with liposarcoma was 25.5%, as compared with 83.6% myxoid liposarcoma cases in the study by *Pearlstone et al.* (31).

Apart from histological subtypes, one also has to consider the follow-up regimen implemented. For example, *Behranwala et al.* only performed radiological investigation of the abdomen in case patients presented with symptoms pointing towards presence of abdominal metastases (26), whereas in the herein presented study, as well as in other previously published studies (14, 24, 25), abdominal CT-scan or ultrasound was routinely performed during follow-up. Moreover, symptoms of patients with abdominal metastases may be vague, with 20.8% of patients with abdominal metastases in our study reporting unspecific abdominal pain (14). Therefore, the actual incidence of abdominal metastases may be underestimated in case symptomatic patients only are screened for secondary lesions to the abdomen. Yet, it remains to be clarified whether (earlier) detection of STS-metastases to the abdomen result in any survival benefit. When addressing this question, one should take into consideration the study published by *Puri et al.* in 2018 (32). The authors initiated a prospective, randomised study including 500 patients with sarcoma, of whom 141 had been diagnosed with STS, and 359 with bone sarcoma (32). After surgery, patients were randomly assigned to either undergo 3-monthly follow-ups for two years and 6-monthly follow-ups for three years, or 6-monthly follow-ups for all 5 years. Furthermore, patients were randomised to either receiving regular CT-scans or chest x-rays (32). During follow-up, unsurprisingly, pulmonary metastases were detected in follow-up arms involving CT scans significantly earlier than in those arms with chest x-rays. Yet, this did not result in a survival benefit, with a 5-year OS rate of 53% and 56% for CT- and X-ray-arms, respectively (32). Even more strikingly, OS did not significantly differ between the “prolonged interval” and “short interval” follow-up regimen, with a 5-year OS rate of 54% vs. 55% (32). Based on these observations, one may

thus consider a less stringent and dense follow-up regimen advantageous. Yet, also with a follow-up protocol consisting of longer inter-appointment intervals, individual patient risks for local or systemic relapse would not be compensated for. One attempt to approach this issue will be discussed further on in this thesis. Moreover, the majority of patients included in the study by *Puri et al.* had underlying bone sarcoma, behaving slightly differently to STS, wherefore the results reported may not be transferable to patient cohorts with STS only. Nevertheless, at least in our study, patients undergoing surgery for abdominal metastases had a significantly better post-metastasis-survival in comparison to patients treated by CTX, RTX, or BSC (14). Of note, these results have to be interpreted with caution, as obtained from a retrospective, heterogeneously treated patient cohort, and has only been analysed in the univariate setting. Our observations are supported by published literature, though. In the study by *Grimme et al.,* analysing the outcome of 38 patients undergoing metastasectomy for hepatic STS metastases (of whom 5 had primary extremity STS), median OS was 46 months (33). Similarly, *Rehders et al.* reported on a median OS of 44 months in patients undergoing surgical resection of STS-metastases to the liver (34). On the other hand, non-surgical approaches seem to be associated with reduced survival rates, ranging between a mean OS of 4.6 months for exclusively "non-invasively" treated patients (27), to a median OS of 12 months in cohorts of patients undergoing metastasectomy or being treated by non-invasive measures (26).

Still, metastatic disease remains the major factor limiting life expectancy of patients with STS. Other than in many haematological and solid malignancies as leukaemia, colorectal cancer, non-small cell lung cancer, colon cancer, and renal cell cancer, effective systemic treatment approaches, be it conventional CTX or targeted therapy, are of limited efficacy in STS. This lack of powerful anti-tumour agents for STS is in part due to the fact that STS have – in comparison to other malignant diseases – a rather low incidence. For example, the annual incidence of colon cancer and lung cancer is 19.5 and 22.4 cases per 100.000 patients (35), respectively, whereas the yearly incidence of any STS is estimated at 4.7 cases per 100.000 patients per year (36, 37). Moreover, the term "soft tissue sarcoma" summarises a heterogeneous group of over 50 different histological subtypes, with varying biological behaviour, aggressiveness, treatment responses, and metastatic potential – as already outlined for liposarcomas and their increased tendency for abdominal metastases (38). Yet, over the last few years, novel

therapeutic agents for STS have been investigated in multicentre trials, with partially promising results. In the REGOSARC (Regorafenib in patients with advanced Soft Tissue Sarcoma) and PALETTE (Pazopanib expLorEd in SofT Tissue Sarcoma) trials, two multitarget tyrosine kinase inhibitors showed encouraging effects in patients with metastatic non-adipocytic STS (39, 40). Also, the programmed death-1 (PD-1) inhibitor pembrolizumab achieves partially promising anti-tumour effects in advanced STS, especially in dedifferentiated liposarcoma and UPS (11). Likewise, combination immunotherapy of PD-1 inhibitor nivolumab with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab leads to encouraging response rates in different advanced STS (41). One of the most recently developed agents with promising treatment effects in advanced tropomyosin receptor kinase (TRK)-positive STS is the inhibitor of TRK, *larotrectinib* (42). First therapeutic attempts with this TRK-inhibitor resulted in 75% overall response rates in patients with pre-treated TRK fusion-positive tumours, including STS (42, 43). Notably, however, TRK-fusions are seen in less than 5% of non-gastrointestinal stromal tumour (GIST) STS except for infantile fibrosarcoma (44, 45), wherefore this powerful therapeutic agent may be administered in a minority of patients only. This limitation likewise applies to the protein kinase inhibitor sunitinib, showing encouraging antitumour effects in advanced alveolar soft part sarcoma, a rare and aggressive STS subtype, whilst being only moderately effective in significantly more frequently occurring undifferentiated pleomorphic sarcomas (46, 47). Even more, other novel agents achieved no better antitumour effects in metastatic STS than conventional CTX with doxorubicin, as reported in the ANNOUNCE (*Doxorubicin* Plus *Oralatumab* vs. *Doxorubicin* Plus Placebo in Patients with Advanced Soft Tissue Sarcomas) phase III trial for the monoclonal antibody olaratumab inhibiting platelet derived growth factor receptor alpha (PDGFRa) (48).

Therefore, apart from systemic treatments, surgical resection of metastases may be performed in order to reduce tumour burden and thus eventually improve patients' prognosis. Different retrospective studies already revealed a positive impact of metastasectomy on survival of patients with metastasised STS (49-53). In a large retrospective analysis of 3149 STS patients treated at a single institution, pulmonary metastases occurred in 719, of whom 403 were primary, and 316 secondary metastases (49). Histological subtypes liposarcoma and MPNST were identified as independent negative predictors of post-metastasis survival, whereas a disease-free interval of > 12 months, low-grade tumours, and complete

tumour/metastasis resection were revealed as positive prognostic factors (49). In the study by *Mizuno et al.,* ≤ 2 metastatic nodules and complete tumour removal were identified as positive prognostic factors for OS in 52 patients with pulmonary metastases undergoing metastasectomy (50). Median OS of these patients was 33 months (50). This rate is comparable to the 33 months reported by *Billingsley et al.* in patients undergoing pulmonary metastasectomy, whilst patients treated conservatively had a median survival of 11 months only (49). Likewise, in our study, patients undergoing metastasectomy had a median post-metastasis survival of 32.4 months, as compared to 9.6 months for patients receiving CTX and/or RTX or BSC (54).

One may argue that patients undergoing surgery for metastases are in a better general condition and present with factors being associated with a better prognosis, as low number of metastases. Indeed, this "treatment-selection" bias cannot be ruled out with complete certainty in any retrospective analysis, as patients are not randomly assigned to one or the other treatment approach. On the other hand, a prospective trial aiming at randomly assigning patients to metastasectomy or non-operative treatment may be difficult to conduct owing to two major reasons: First, it is ethically questionable to subject patients to a surgery with associated risks and complications, or on the other hand withhold potentially effective treatment measures. Second, the low incidence of STS would require not only a multicentric setup, but also long-term studies in order to include a sufficient patient number. In light of these difficulties, we sought to compensate for "treatment-selection" bias in our retrospective study by applying advanced statistical models. Propensity score methods constitute tools to reduce bias in observational studies based on covariates at baseline that may have influenced decision towards one or the other treatment approach (55). In this context, a propensity score is defined as the likelihood of a patient to being assigned to a specific treatment based on selected covariates (56). In our study, we used inverse probability of treatment weighting (IPTW) – being one of four ways to use the propensity score in observational studies (56, 57) – to analyse the independent effect of metastasectomy. At baseline, patients undergoing metastasectomy in our cohort rather had singular than multiple metastases, presented with a longer time interval from diagnosis to development of first metastasis, had higher haemoglobin and albumin levels prior to metastasectomy, and presented with a better ECOG performance status than patients treated by non-operative measures (54). Notably, all these factors may significantly contribute to patient's survival, wherefore the naive analysis of the

prognostic impact of metastasectomy would be influenced by the abovementioned "treatment-selection" bias. Thus, the propensity score was calculated including all these variables, together with other baseline parameters. Consecutively, the IPTW was generated, defined as the inverse probability of patients to have received the treatment they actually received (58). In the weighted multivariate Cox-regression model for OS, surgery for metastases was independently associated with a better outcome, irrespective of ECOG performance status (significant negative predictor), number of metastases, haemoglobin levels, and albumin levels (all not significant) (54). This result is particularly encouraging considering that both haemoglobin and albumin levels are known prognostic factors in cancer. Low pre-treatment haemoglobin levels are associated with reduced survival in bone sarcoma in general (59), Ewing sarcoma (60), and STS (61). Moreover, low albumin levels constitute a negative prognostic parameter for survival in myofibroblastic and fibroblastic sarcomas (62), as well as liposarcomas (63). Additionally, the number of metastatic lesions has been identified as a negative prognostic factor in STS patients with distant spread (53). In the study by *Dossett et al.* (53), multiple pulmonary nodules, old patient age, and synchronous rather than metachronous metastasis were associated with reduced survival in STS patients. Also, *Billingsley et al.* identified age over 50 years and a disease-free interval of less than 12 months as negative prognostic factors (49). In one of the largest retrospective studies published thus far on this topic including 539 patients undergoing pulmonary metastasectomy for STS with therapeutic intent, *Chudgar et al.* discovered a positive prognostic impact of leiomyosarcoma as the underlying histological subtype, a prolonged disease-free interval, minimally invasive surgery, solitary pulmonary lesions and small initial tumour size on OS (64). Median OS was 33.2 months, again being comparable to the median OS of 39.6 months in our study (54, 64). Taken together, or analysis supports the theory of a more "aggressive", operative approach in patients with metastatic STS, even in case of a seemingly unfavourable prognosis, as long as surgical benefits outweigh the associated risks.

In light of the potential benefit observed for surgical resection of metastatic lesions, detection of secondary metastases at an early stage is essential to not only minimise the risk of complications depending on the extent of surgery necessary to remove all metastatic nodules, but also to initiate any treatment at a low systemic tumour burden. Therefore, postoperative follow-up regimens have been implemented in the past, aiming at detecting LR or DM at early

stages. The follow-up regimen applied by many tumour centres adheres to a heuristic approach proposed by the European Society of Medical Oncology (ESMO) (65). It consists of clinical and radiological appointments with thoracic x-rays or CT-scans and MRI-scans of the primary tumour site every 3 months for the first three postoperative years, then every 6 months until the end of the fifth postoperative year, and every 12 months thereafter (65). Although the higher risk of local or systemic relapse within the early postoperative period is taken into consideration within this follow-up protocol, the individual risks of patients depending on specific features, be it demographic variables as patient age and gender, tumour-related parameters as grading, size and histology, or treatment-associated features as margin status and RTX, is largely disregarded.

Based on preceding projects aiming at improving aftercare of patients with STS (18, 66), we aimed at individualising follow-up regimens in patients with intermediate or high-grade STS of the extremities (19).

One of the first attempts to further individualise follow-up strategies in STS by individually assessing overall patient survival was published by *Kattan et al.* in 2002 (67). Including retrospective data of 2136 STS patients treated at the *Memorial Sloan-Kettering Cancer Center* in New York, the authors developed a nomogram based on a Cox regression model by including variables tumour size, histological grade, patient age, histological subtype, and tumour site (i.e. upper limb, lower limb, visceral, thoracic/trunk, retro- or intraabdominal, head/neck region) (67). With the nomogram deriving from this model, the 12-year sarcoma-specific survival can be calculated for each patient (67). Furthermore, in an online version of the model, 4- and 8-year OS rates can be likewise accessed (68). However, this nomogram is not specific for extremity STS as including primary intra- and retroperitoneal STS, as well as those of the trunk and head/neck region as well. Its validation on a cohort of 962 patients with extremity STS by *Mariani et al.* resulted in a concordance index of 0.75, indicative of a good model calibration (69). Another validation of the nomogram developed by *Kattan et al.* using the Surveillance, Epidemiology, and End Results (SEER) database likewise achieved a concordance index above 0.7, indicating a good calibration of the nomogram (68, 70).

Regarding LR-risk, a nomogram was developed by *Cahlon et al.* in 2012, again using data from STS patients treated the *Memorial Sloan-Kettering Cancer Center (71)*. This time, the authors focused on extremity location only, and performed a competing risk regression analysis with death as the competing event to estimate individual LR-risk (71). In view of variables included,

the model by *Cahlon et al.* was quite similar to our flexible parametric competing risk regression model for LR. Their multivariate model was based on margin status, grading, tumour size, histology, and patient age (71), whilst we used gender, grading, tumour size, margins, histology, adjuvant CTX, and neoadjuvant as well as adjuvant RTX (19). Of note, since *Cahlon et al.* had only included patients without adjuvant RTX, the resulting model is merely transferable to STS patients undergoing surgery only, whilst our flexible parametric competing risk regression model was based on a cohort of patients with extremity STS who may have received any neoadjuvant or adjuvant treatment (19).

Regarding assessment of individual DM-risk, a retrospective, multicentre study was published by *Callegaro et al*. (66) including data of 3752 STS-patients altogether, of whom 1452 were included in the test cohort, and 2300 in the validation cohort. The authors developed two different nomograms, allowing for graphical assessment of patients' individual DM-risk, and OS probability (66). Similar to our study, they developed statistical models on a test cohort, and validated their results on an independent cohort of STS patients with almost similar variable distribution (66). The variables tumour size, grading and histological subtype were included in their multivariate competing risk-regression model for DM. We likewise compiled a statistical model including histology, grading, and tumour size. Based on the backward stepwise selection process to identify parameters to be include in the multivariate model, patient gender, margin status, and neoadjuvant RTX were included as well (19). Corresponding with the findings of *Callegaro et al.*, tumour grading and size, as well as histological subtypes, were significant predictors for DM (19, 66). Notably, we additionally discovered a protective impact of female gender and negative tumour margins on risk for DM (19). Although female gender has been associated with a better OS in STS patients (72, 73), a significant association between gender and altered risk for LR or distant spread had not been reported until now. The underlying reason for this prognostic discrepancy that was also apparent when analysing LR, remains to be determined, though.

Regarding the prognostic impact of histology, we made similar observations to the one reported by *Callegaro et al*.; a significantly higher risk for DM was present for MPNST, synovial sarcoma, leiomyosarcoma, and vascular sarcoma in comparison to myxoid liposarcoma (19, 66). In detail, the subhazard ratio for DM was 1.825, 1.986, 2.016, and 2.589 in patients with MPNST, synovial sarcoma, vascular sarcoma, and leiomyosarcoma in comparison to liposarcoma. Only slightly different from our results, the subhazard ratios for DM reported by

Callegaro et al. were 1.53 for MPNST, 2.10 for synovial sarcoma, 3.16 for vascular sarcoma, and 2.93 for leiomyosarcoma, as compared with myxoid liposarcoma (66).

Histological subtypes leiomyosarcoma, MPNST, and synovial sarcoma were also associated with a higher LR risk in comparison to myxoid liposarcoma based on our multivariate flexible competing risk regression model (19). Furthermore, gender, grading, tumour size, margins, neo- and adjuvant RTX, as well as adjuvant CTX were included based on a stepwise backward procedure. In the study by *van Praag et al.,* tumour size, histology, margins, and RTX were likewise included in their Fine & Gray competing risk regression model for LR, based on a cohort of 766 STS patients (18). In comparison to conventional competing risk regression models, the advantage of flexible parametric competing risk regression models is the possibility to account for time-varying event-risks, i.e. the known higher risk for local and systemic relapse during the first few years after surgery for STS (74). This is reflected by the subdistribution hazard functions originating from the two flexible parametric competing risk regression models for LR and DM in our study (19). A peak in LR-risk was observed at 12 months following surgery, whilst risk constantly decreased thereafter (19). For DM, the subdistribution hazard function revealed two peaks; one within the first year following surgery, and another less prominent one in the second postoperative year (19). Apart from this variance in event-risk over time, significant differences in inter-individual risks depending on demographic, tumour- and treatment-related variables were observed. As the ultimate aim of the study was to incorporate the results of the statistical models in an app for smartphones, ten clinical examples how risks for LR and DM differ depending on distinct constellations of variables were provided in the original publication (19). The combination of male gender, 10 cm-sized grade 2 myxofibrosarcoma with R1/2 resection margins and no neoadjuvant or adjuvant treatment served as a clinical example with a high risk for LR, reaching a cumulative risk for local relapse of over 20% and 40% 12 and 24 months following surgery, respectively (19). As a comparison, a male patient having undergone resection with clear (R0) margins for a 6 cm-sized synovial sarcoma, again without neoadjuvant or adjuvant treatment would have a cumulative LR-risk of about 10% and 20% one and two years after surgery (19). On the other hand, DM-risks in these two examples behave differently – here, the patient with myxofibrosarcoma would have a cumulative DM-risk of less than 10% at 12 months, and about 15% at 24 months following surgery, whilst for the patient with synovial sarcoma, risk of DM would be nearly as high as 20% and 30% at 12 and 24 months (19). As the development of the

two flexible parametric competing risk regression models on a single patient cohort can result in model overfitting, we validated the model on an independent cohort of patients with extremity STS and used the Harrell C-index to assess internal and external calibration. Similar to previous studies, the C-index for both flexible parametric competing risk regression models, was between 0.683 (i.e. external validation of model for LR) and 0.772 (i.e. external validation of model for DM) (66, 67, 69).

In order to allow for individual LR- and DM-risk assessment depending on innumerable combination of parameters, the herein presented statistical models have been incorporated in the PERSARC (Personalised Sarcoma Care) app that is freely available for Android and Apple devices. With this app, different questions can be answered; the cumulative risk for LR and DM; the conditional risk for LR and DM for the next three and six months depending on the time from surgery, the 5-year OS, as well as the OS in case an event (LR or DM or both) had occurred. The first two outcome parameters (i.e. cumulative and relative LR and DM-risk) are based on the study presented in the current thesis (19). Furthermore, crude OS rates as well as OS rates after development of LR or DM derive from models published by *Rueten-Budde et al.* (16).

The SARCULATOR is another app-based prediction tool to allow for individual assessment of 5- and 10-year OS in patients with extremity STS, as well as cumulative incidence for DM. It contains data from the models developed by *Callegaro et al.*, as already discussed above (66). This nomogram has also been successfully used to post-hoc stratify STS patients enrolled in a prospective controlled clinical trial into different risk groups (75). Of note, all patients initially included in the trial were regarded as “high risk” and were either assigned to three cycles of preoperative CTX only, or three cycles of preoperative CTX followed by two cycles of postoperative CTX (76). By applying the SARCULATOR, three risk groups could be stratified from the randomised cohort, with 10-year OS rates in the high-, intermediate- and low-survival probability groups being 78%, 63%, and 42%, respectively (75). This study once more highlights the importance of individual risk assessment in STS patients, and eventually promotes the use of prognostic tools prior to enrolment in clinical studies to further improve overall patient outcome.

Notably, neither the SARCULATOR nor the PERSARC app are meant to be a tool substituting clinical experience, but may on the other hand aid physicians to assess the risk of patients for

local or systemic relapse individually at baseline. Even more, the PERSARC app allows for comprehensible depiction of conditional risks, i.e. the possibility of a patient to experience LR or DM as calculated from the day the appointment is scheduled during the next three to six months. In specific cases, a very low conditional risk for local or systemic relapse at three and six months may subsequently facilitate scheduling the next appointment in half a year rather than three months later. On the one hand, patients would be spared from repeated irradiation caused by thoracic CT-scans and time exposure due to MRI scans. On the other hand, health-care costs could be reduced by adhering to follow-up regimens developed individually for each patient, based on their risk for local or systemic relapse.

In conclusion, despite the rarity of STS in general as well as their heterogeneous clinical, histological, treatment- and outcome-specific behaviour, combined efforts by performing multicentre studies and using advanced statistical tools allow for more in-depth research and production of results more generalisable to this large and diverse group of malignant neoplasms. Eventually, all these research efforts will enable multidisciplinary teams to further enhance management of patients with STS, thus improving their overall outcome.

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Appendix

The following publications are appended (in order of appearance):

Smolle MA, Andreou D et al. **Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk**. EFORT Open Rev. 2017;2(10):421-31.

Smolle MA, Schaffler A et al. **Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study.** J Surg Oncol. 2020;121(4):605-11.

Smolle MA, van Praag V et al. **Surgery for metachronous metastasis of soft tissue sarcoma – A magnitude of benefit analysis using propensity score methods.** European Journal of Surgical Oncology. 2019 Feb;45(2):242-248.

Smolle MA, Sande MV et al. **Individualizing Follow-Up Strategies in High-Grade Soft Tissue Sarcoma with Flexible Parametric Competing Risk Regression Models**. Cancers (Basel). 2019;12(1).

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EFORT open reviews

Diagnosis and treatment of soft-tissue sarcomas of the extremities and trunk

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- The relatively low incidence and often atypical clinical presentation of soft-tissue sarcomas (STS) impedes early and adequate diagnosis. Patients may report on recently enlarged soft-tissue swellings, infrequently complain of painful lesions, or even have no symptoms at all.
- A thorough diagnostic work-up is essential in order to distinguish between benign soft-tissue tumours and STSs. Patient history, clinical features and radiological findings all help in assessing the underlying pathology. 'Worrying' features such as recent increase in size, deep location relative to the fascia, a tumour exceeding 4 cm in size, and invasive growth patterns seen on imaging should prompt verification by biopsy.
- Even though acquisition of biopsy material may be incomplete, one should bear in mind some essential rules. Regardless of the biopsy technique applied, the most direct route to the lump in question should be identified, contamination of adjacent structures should be avoided and a sufficient amount of tissue acquired.
- Treatment of STS is best planned by a multidisciplinary team, involving experts from various medical specialities. The benchmark therapy consists of *en bloc* resection of the tumour, covered by a safety margin of healthy tissue. Depending on tumour histology, grade, local extent and anatomical stage, radiotherapy, chemotherapy and isolated hyperthermic limb perfusion may be employed.
- Due to the complexity of treatment, any soft-tissue swelling suspected of malignancy is best referred directly to a sarcoma centre, where therapeutic management is carefully planned by an experienced multidisciplinary team.

Keywords: soft-tissue sarcoma; diagnostic pathway; therapeutic management

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Soft-tissue swellings, lumps and bumps are frequently seen in routine clinical practice. However, with an estimated annual incidence of five cases per 100 000 people in Europe, soft-tissue sarcomas (STS) are relatively rare and are outnumbered by benign soft-tissue tumours a hundred times over.[1-3] Consequently, the majority of patients consulting their physician because of soft-tissue swellings will be diagnosed with a benign lesion. On the other hand, the early identification of patients with possible STS and prompt referral to a sarcoma centre is essential in order to avoid unnecessary delays in diagnosis and to ensure optimal multidisciplinary treatment.[4,5]

Contrary to most primary bone tumours, STSs mainly develop in the elderly population, with a peak incidence in the 6th decade of life.[6] Exceptions are rhabdomyosarcoma and synovial sarcoma, distinct histological subtypes mainly arising in children and young adults.[7] STSs are predominantly located in the lower limbs, followed by the upper limbs and trunk.[8] Further common locations include the head/neck region and retroperitoneal space.[9] As these STSs are usually seen by Ear-Nose-Throat physicians and Gastrointestinal surgeons, they will not be analysed in this article.

The following report will give an overview of the clinical, radiological and histological findings in patients with STS. Treatment options, outcomes and future perspectives will also be discussed.

Patient history and clinical examination

The diagnostic pathway should always start with a thorough documentation of the patient's history. Lumps that have not changed in size or shape over the years are most likely benign, whereas recently noticed, constantly-enlarging swellings should urge caution.[10] In cases of recently-emerged soft-tissue swellings, a preceding trauma is sometimes described.[11] Especially in elderly

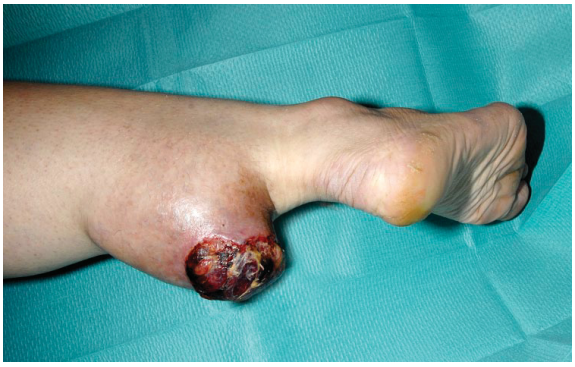

Fig. 1 Large, ulcerated tumour arising from a 30-year-old female patient's right calf, later confirmed as high-grade spindle cell sarcoma.

patients under anticoagulation therapy, this could be indicative of haematoma. On the other hand, lumps quickly increasing in size in the absence of bruising should prompt further investigation.[10]

Pain assessment is important in every physician–patient consultation. In cases of STS, however, pain is a rather poor discriminator between benign and malignant lesions.[10,12] Whilst traumatic soft-tissue swellings are usually painful, even quite large STSs may be indolent (Fig. 1). Malignant peripheral nerve sheath tumours (MPNSTs) developing in patients with neurofibromatosis type 1 are an exception, typically causing radicular pain, motor weakness or paraesthesiae.[13]

The inspection and palpation of the lump in question can reveal additional crucial information. Despite an often dramatic appearance, a reddened, hyperthermic and painful tumour is more often indicative of an ongoing inflammatory process than STS. Palpating and trying to move the lump can help assess its relation to surrounding structures. A tumour located within the subcutaneous tissues is easily moveable under the skin, whilst a mass attached to or located beneath the fascia appears to be fixed. As the majority of STSs are located deep to the fascia, every deeply-situated tumour should be considered malignant until proven otherwise.[14] However, 15% of STSs develop within the subcutaneous tissue.[14] For that reason, superficial lumps with additional worrying features also need to be further examined. In this respect, a simple rule of thumb is that every growing soft-tissue mass larger than a golf ball (equivalent to about 4 cm) that has been recently noticed should be suspected of being a sarcoma.[5,10,15]

Imaging

The chief objectives of imaging are to confirm clinical findings by detecting a soft-tissue mass, to estimate its size, tissue quality and relation to adjacent structures in detail,

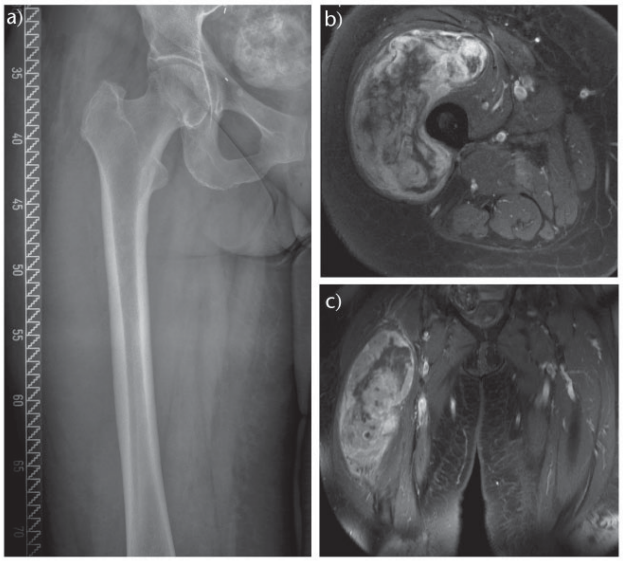

Fig. 2 Radiograph of the right hip of a 70-year-old female patient with a high-grade leiomyosarcoma showing moderate soft-tissue opacity (a). MRI scans of the same patient's leg, displaying a 25 cm × 11 cm × 9 cm partially-necrotic tumour with heterogeneous pathological contrast enhancement (b, c).

and to aid planning of the further course of action. Therefore, imaging should be carried out prior to any manipulation of the lesion, as biopsy-related artefacts may complicate image analysis.[16] More importantly, thorough imaging potentially reduces the danger of excising a tumour thought to be benign without adhering to oncological principles.

As a readily accessible and inexpensive imaging technique, ultrasound (US) is ideal for the initial evaluation of a soft-tissue mass.[17] The size of the lesion and its relation to the fascia can easily be estimated. Moreover, US can sometimes distinguish pseudotumours, such as haematomata, abscesses and cysts.[18] Assessment of the lesion's blood supply by using Doppler-US can be helpful and reveal additional information. Hypervascularity is indicative of malignancy, especially if the lesion is supplied via multiple peripheral vessels or contains large intratumoural vessels.[19]

Magnetic resonance imaging (MRI) is the method of choice to evaluate soft-tissue tumours and to distinguish benign from malignant lesions, especially if prior clinical findings and imaging were inconclusive.[20] Features indicative of malignancy include expansive and invasive growth, heterogeneous signalling on T1-weighted images and low signalling intensity on T2-weighted sequences (Figs 2 and 3).[21] Moreover, utilisation of static and dynamic gadolinium-based contrast-enhanced imaging is highly recommended to confirm the suspected pathology.[22]

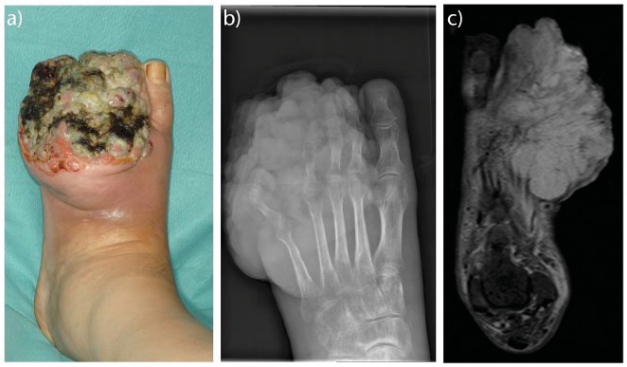

Fig. 3 Ulcerating, partially-necrotic tumour on the dorsum of the left foot of a 53-year-old male patient (a). Radiograph shows displacement of the 4th and 5th digit by the mass (b). MRI reveals the actual extent of the tumour, later confirmed as high-grade synovial sarcoma (c).

Whilst conventional radiographs are not adequate to assess soft-tissue masses, they may display calcified or ossified areas and bony involvement.[23] Particularly in children and young adults, the differential diagnosis of primary bone neoplasms with reactive soft-tissue swellings should be contemplated when osseous destruction is visible.[24] Due to overlapping features, however, even experienced radiologists are sometimes unable to distinguish between benign and malignant tumours. As an example, STSs frequently exhibit a peripheral or centripetal contrast-enhancement on MRI. However, this feature may also be seen in benign lesions with centrally-located ossification, calcification and haemorrhage (e.g. myofibromatosis).[25] Moreover, peri-tumoural oedema and ill-defined boundaries are seen both in STSs and benign tumours.[18] Consequently, imaging should always be interpreted in the context of clinical findings and should help decide whether a biopsy is necessary or not.

Biopsy

This is an essential part of the diagnostic pathway for soft-tissue tumours. In theory, acquisition of biopsy material seems uncomplicated. However, some essential rules must be considered prior to biopsy of a suspected STS. The ten simple rules listed in Table 1 aid planning a biopsy, choosing the optimal approach and obtaining sufficient tumour tissue to guide subsequent treatment (Table 1).[26] On the other hand, one must be aware of the lesion being dealt with and should consider which steps to initiate afterwards. In this case, a referral algorithm for soft-tissue lumps provides guidance (Fig. 4). As outlined above, any soft-tissue swelling larger than 4 cm or located in the deep tissues is highly indicative of a sarcoma. In case such a lesion is visible on MRI, immediate referral to a tumour centre should be initiated. For smaller lesions appearing suspect on MRI, a diagnostic biopsy may be suitable.

First, the most appropriate biopsy technique has to be decided (see rule I in Table 1), and if in doubt, this must be performed in consultation with the radiologist (minding rules II and III) and pathologist in charge (rule IV). A Tru-Cut™ (BD UK Limited) needle biopsy can be performed under local anaesthesia, hence being suitable for the out-patient setting.[27] As only a relatively small amount of tissue can be obtained, both surgeon and pathologist should be familiar with this method. Even if the skin incision is minimal when using the Tru-cut system, the entry point should be carefully planned. The needle must be directed straight down to the tumour, minimising contamination of surrounding structures (rules V and VI).

With open biopsy, sufficient and viable samples can be acquired (in compliance with rules VII and VIII), possibly enabling more precise tumour grading and sub-typing.[28] It should be noted that biopsy tracts are contaminated in up to one-third of open biopsies.[29] Therefore, liberal excision of the tract should be performed upon definitive surgery, which in turn depends on how careful and with how much foresight the biopsy has been planned (rules V and VI). However, this technique is more expensive than Tru-cut needle biopsy and necessitates hospital admission since it is performed under plexus or general anaesthesia. Another option is US- or CT-guided core needle biopsy, particularly in cases where a lesion is poorly accessible or comprises necrotic areas.[30,31] Consequently, Tru-cut biopsy

Table 1. Ten rules to aid planning and evaluation of biopsy

Rules		How to achieve?
I	Do not hurry	Take time and carefully plan your next steps
II	Do not contaminate neurovascular structures or joints	Plan your biopsy according to anatomy and eventual future surgery
III	Do adequate imaging before any operation	Arrange MRI (with contrast agent)
IV	Send biopsy specimen to a pathologist specialised in bone and soft tissues tumours	Check with your nearby pathology department whom to contact
V	Take the shortest way through one compartment only	Keeping in mind rules II, VI
VI	Plan your biopsy in view of eventual resections	Cut in longitudinal direction of the extremity
VII	Gain sufficient and representative tissue	Take samples from the peripheral area, not central necrotic regions
VIII	(If possible) store small fraction of tissue fresh frozen (-80°) for research purposes	Get in contact with the pathologist
XI	Operate as atraumatically as possible	Minimise incision or use CT-guided biopsy for deep lesions
X	Avoid any post-operative haematoma	Perform thorough haemostasis, use a drain (passed directly through skin incision) and apply compression dressing

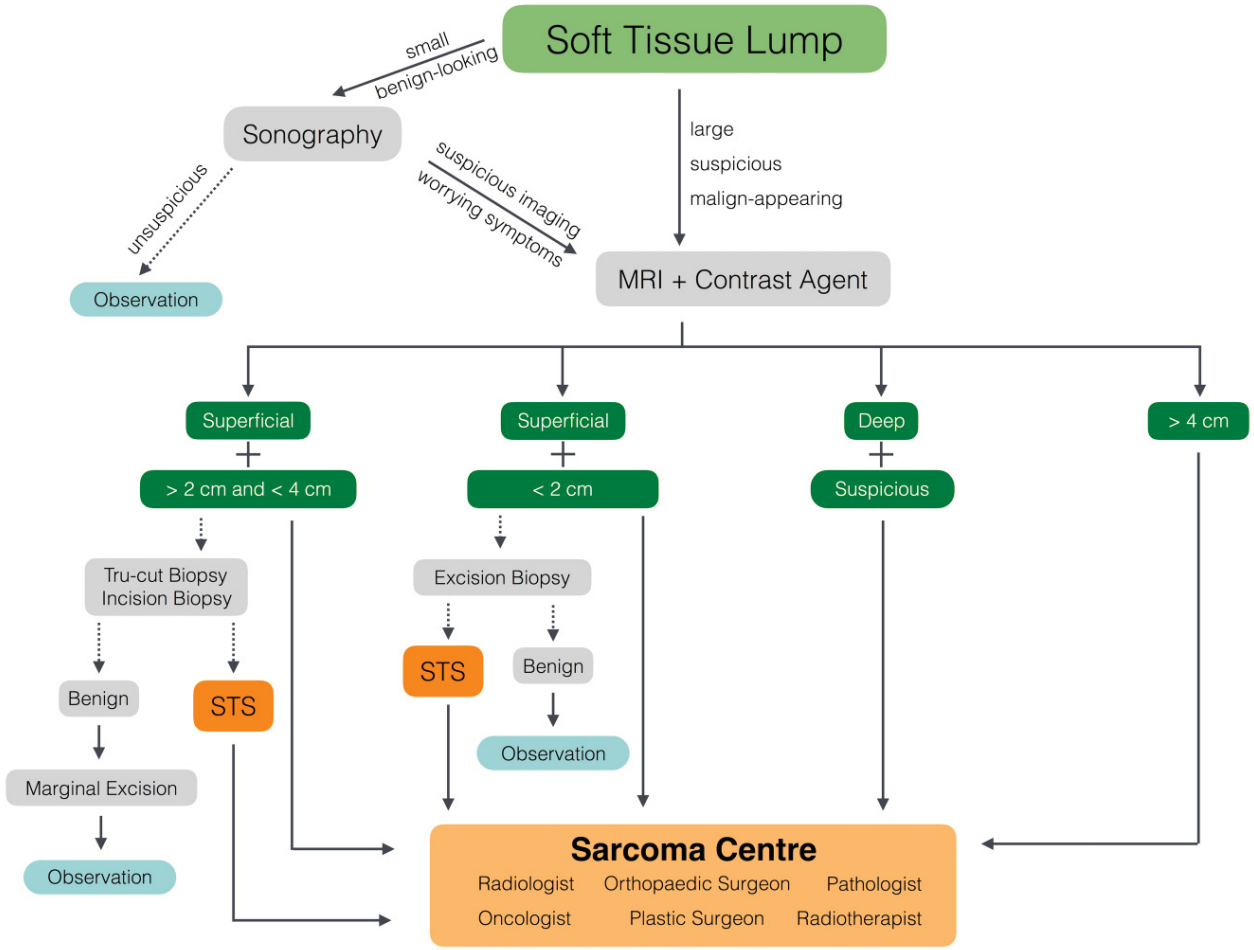

Fig. 4 Referral algorithm for soft-tissue lumps, as recommended by our department (STS, soft-tissue sarcoma).

is the method of choice for easily palpable and large tumours, whilst deeply located and/or small lesions may rather undergo incisional or image-guided biopsy. Moreover, for benign-appearing lesions smaller than 2 cm on MRI, an excision biopsy (i.e. removal of the entire lesion) may be carried out. Again, the same precautions as for Tru-cut and incisional biopsies must be taken.

Every biopsy inevitably entails opening of the tumour capsule, increasing the risk of bleeding and dispersal of malignant cells within the surgical wound. In open biopsy, a drain should therefore be inserted directly through the biopsy incision and not separately. Thorough wound closure and application of a compression dressing additionally forestalls the development of post-operative haematoma formation (bearing in mind rules IX and X).

Nevertheless, it has been demonstrated that the number of diagnostic errors and subsequent changes in treatment, as well as the risk for local recurrence (LR), are all elevated when biopsy of a musculoskeletal lesion has been carried out at institutions other than a tumour centre.[32,33] Therefore, direct referral to a specialist centre should best be initiated as soon as a malignant tumour is suspected (note solid arrows in Fig. 4).

Histology, grading and staging

The histological classification of STSs is an integral part of the diagnostic pathway. Personalised and targeted treatment approaches warrant precise sub-classification into one of more than 117 different soft-tissue tumours defined in the recent *WHO Classification of Bone and Soft Tissue Tumours*.[1]

The most common type is high-grade pleomorphic sarcoma, followed by liposarcoma – which itself comprises several sub-types – leiomyosarcoma, synovial sarcoma and MPNST.[34,35] For most STSs, histological grade is one of the most important prognostic factors in terms of LR-free, metastasis-free and disease-specific survival.[36] Distinct sub-types such as rhabdomyosarcoma and synovial sarcoma are high-grade by definition. For classification

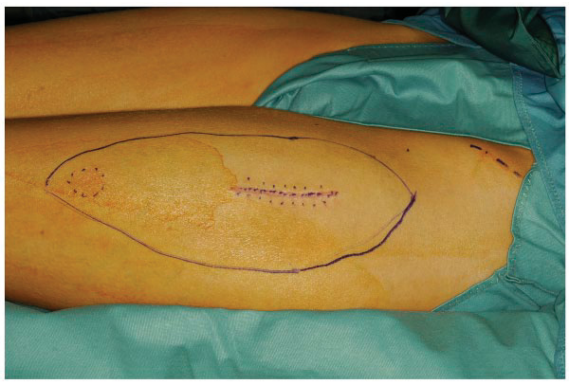

Fig. 5 Unplanned excision of a later histologically-verified alveolar soft-part sarcoma located in the left thigh of a 15-year-old female patient. Note the drain's exit point remote from the surgical wound.

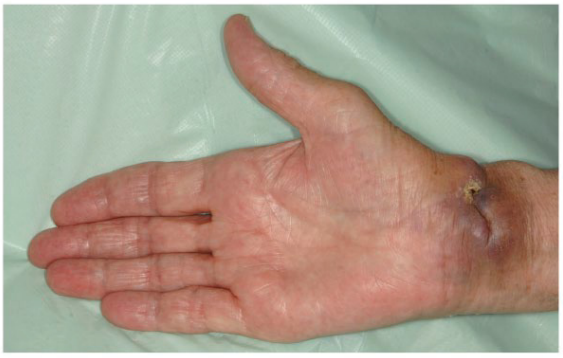

Fig. 6 Inappropriate resection of a tumour at the wrist of an 80-year-old female patient, thought to be a ganglion. Histology revealed a high-grade angiosarcoma. Consequently, a forearm amputation became necessary.

of other STS types the National Cancer Institute and the French Federation of Cancer Centres Sarcoma Group (FNCLCC) grading system are used.[37,38]

Recurrent genetic alterations are present in nearly half of STS sub-types; fusion between the SS18 gene and one of the SSX genes is pathognomonic for synovial sarcoma, whilst a PAX3-FOXO1A fusion gene is found in 80% of alveolar rhabdomyosarcomata.[39,40] In addition to conventional Haematoxylin-eosin stain and immunohistochemistry, molecular analysis with Fluorescence *in situ* hybridisation, Reverse transcription polymerase chain reaction and next generation sequencing is therefore indispensable.[41] Targetted therapies may be administered to patients based on specific genetic alterations.[42,43] However, the amount of biopsy material limits a rigorous diagnostic work-up.

Contrary to the four-part T-stage applied to most solid tumours, STSs are subdivided into two main categories only, depending on a size smaller (T1) or larger (T2) than 5 cm.[44,45] The location relative to the fascia – 'a' for superficial and 'b' for deep tumours (tumour grading according to the FNCLCC system) – and presence of lymph node or distant metastases, are taken into consideration for tumour stage according to the 7th version of the American Joint Committee on Cancer (AJCC) staging manual for STS.[44,45]

Unplanned excisions of STS

Quite frequently, patients first present to a tumour centre following an unintentional excision of a STS.[46-48] The cause for these colloquially termed 'whoops' (inadvertent)-procedures is most likely the rarity of STS, as a result of which many physicians simply do not include the possibility of sarcoma in their differential diagnosis.[49,50] A thorough diagnostic work-up notwithstanding, 'whoops'-procedures may be performed due to the often ambiguous presentation of STS. Further treatment planning of an inadvertently excised STSs can be difficult even for the experienced sarcoma specialist, as pre-operative imaging may be missing, suboptimal surgical approaches may have been chosen, healthy tissues may have been unnecessarily contaminated and resection margins may be unclear (Fig. 5).[51]

Therapeutic management following unplanned excision of STS depends on several factors; wait-and-see may be appropriate for marginally resected low-grade liposarcoma/atypical lipomatous tumours.[52,53] On the other hand, high-grade STSs undergoing unplanned excisions will most likely recur locally if left untreated.[54,55] Furthermore, limb-sparing procedures may not be feasible in cases where inappropriate surgical approaches lead to gross contamination of surrounding tissues (Fig. 6).

Nevertheless, any time delay from unplanned excision to definite surgery at a tumour centre eventually worsens prognosis.[56] Consequently, the most important step to take is urgent referral of these patients to a sarcoma centre, where further treatment will be planned and adequate re-resection or even amputation implemented.

Treatment

Treatment strategies for STSs are best planned by a multidisciplinary team including radiologists, pathologists, orthopaedic surgeons, plastic surgeons, medical oncologists, radiotherapists, thoracic surgeons and physiotherapists.[57] The standard treatment for high-grade STS is surgery, complemented by radiotherapy (RTX) and in selected cases chemotherapy (CTX).

Surgery

Over the last 30 years, amputation has progressively become less important and has been mostly replaced by

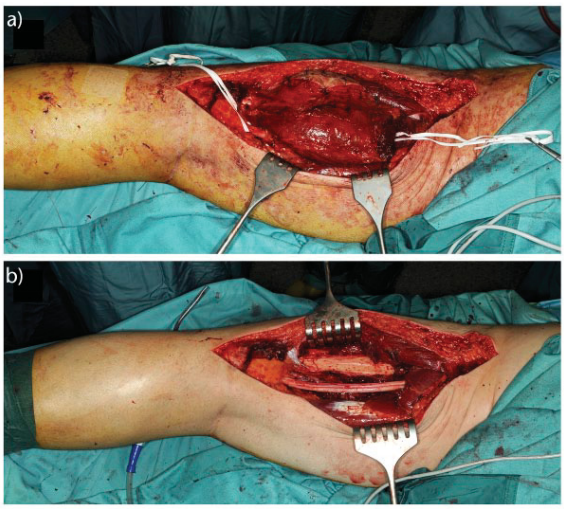

Fig. 7 Wide resection of a high-grade undifferentiated pleomorphic sarcoma arising in the dorsal aspect of the left thigh of a 50-year-old male patient (a). The sciatic nerve was dissected off the tumour and could be spared during *en bloc* resection (b).

limb-sparing procedures in the management of STS.[58] Nowadays, an extremity is only sacrificed if wide surgical tumour excision would result in severe functional impairment, due to the tumour's fixation to or infiltration of important anatomical structures, such as nerves, bone and vessels.[59]

Enneking et al[60] developed a surgical staging system for STSs, differentiating between radical, wide, marginal and intralesional resections. Intralesional resection implies that the tumour's capsule was opened upon surgery. Marginal surgery indicates that resection margins pass through a 'reactive zone' or 'pseudocapsule' surrounding the tumour. Wide resection is achieved by removing the tumour covered by a safety margin of healthy soft tissues (e.g. muscle, fascia). Radical surgery is defined as resection of an entire compartment containing the tumour. Besides this macroscopic surgical staging system, microscopic tumour margins are equally important.

However, in particular when it comes to 'clear' margins, definitions vary considerably.[58,61,62] According to the Union internationale contre le cancer (UICC) classification, wide microscopic margins (R0) are achieved when the tumour is covered by at least 1 mm of healthy tissue.[62] The R-classification, however, defines an R0-resection as microscopically-free tumour margins, irrespective of the thickness.[58] Moreover, a surgical margin built up with muscular fascia constitutes a more effective border against tumour cells than an equally thick layer of adipose tissue would do.[63-65] Therefore, an optimal margin both minimising the risk for local failure and preventing too radical resection is difficult to define precisely.

The benchmark procedure for STS is the wide *en bloc* resection of the tumour, with a reasonable safety margin.[57] As mentioned above, marginal resections may be suitable for atypical lipomatous tumours with a negligible risk of distant metastasis, even if they can recur locally.[52,53,57,66]

In order to avoid opening of the tumour capsule at surgery, major anatomical structures sometimes have to be sacrificed; the cortex of adjacent bones may be partially resected along with the specimen. Whenever possible, though, important anatomical structures such as large nerves and vessels should be spared if not directly invaded by the adjacent tumour (Fig. 7). In cases with extensive osseous involvement, total resection of the affected bone and consecutive reconstruction with a tumour prosthesis may be considered.[67] Moreover, principal veins encased by the tumour can be safely reconstructed with autologous vascular grafts following *en bloc* resection.[68] Large soft-tissue defects resulting from radical surgery may require usage of pedicled and free muscular flaps as well as split- or full-thickness skin grafts for wound closure.[69]

Isolated hyperthermic limb perfusion (ILP)

ILP with Tumour necrosis factor-alpha (TNFα) and melphalan may be applied in locally advanced STS, aiming at prevention of mutilating or ablative surgery. As TNFα selectively destroys vascular structures, the efficacy of ILP is not necessarily dependent on the tumour's histology but rather on its vasculature.[70] In a recent study, however, it was discovered that liposarcomata show the best response to ILP compared with other common histological sub-types.[71] The technique involves utilisation of a heart-lung-machine that is connected to major vessels via iliac and femoral access paths for the lower limb and transpectoral, axillary, brachial or cubital approaches for the upper limb. First, the limb is warmed to 39° ensuring optimal efficacy of the agents administered. Next, TNFα and melphalan are injected, followed by a wash-out phase with crystalloid and colloid solutions after 90 minutes. Six to ten weeks later, definite surgery may be performed. Average response rates of 72% have been reported, with complete remission achieved in 22% of patients.[72] Following ILP, limb-sparing procedures are feasible in over 80% of patients initially scheduled for amputation.[72] Notably, ILP-induced metabolic changes in the tumour already have prognostic implications; on MRI taken after ILP, tumours with a low maximum standardised uptake of 18F-Fluorodeoxyglucose significantly correlate with an improved metastasis-free survival.[73]

RTX

Radiation therapy can be administered in a neo-adjuvant setting, during surgery as intra-operative RTX or brachytherapy and in an adjuvant setting following resection.[74,75]

Depending on the treatment plan, patients may undergo irradiation of the tumour bed at several time points. Palliative RTX can be used to achieve local control in patients with inoperable tumours and/or distant metastases.

Irradiation of the operation field is strongly recommended in any high-grade (i.e. G2 and G3), deeply located tumour exceeding 5 cm in size following wide resection.[76] Based on the experience and personal preference of the multidisciplinary team, indication for RTX may be extended to high- and low-grade STSs smaller than 5 cm located beneath the fascia as well as any superficial tumour larger than 5 cm.[57]

Usually, external beam radiation therapy is applied in 1.8 to 2 Gray (Gy) fractions to the tumour bed and a surrounding safety gap, amounting to 50 Gy in total.[57] Additionally, the original tumour area is irradiated with a boost up to 66 Gy.

RTX is preferably administered post-operatively if major wound complications are anticipated.[77] On the other hand, RTX may be administered pre-operatively depending on the histological sub-type and resectability of the tumour;[78] in myxoid sarcomas and those supplied by a myxoid-like vasculature, for example, response rates to pre-operative RTX are as high as 80%.[79] However, neo-adjuvant and adjuvant RTX seem to be equally effective in terms of local disease control.[77]

CTX

The use of CTX in localised STSs of adult patients can prolong disease-free survival but is considered doubtful regarding overall survival benefits.[57,80] Neo-adjuvant CTX may be administered aiming at eliminating skip lesions or downsizing a locally advanced tumour in order to facilitate limb-sparing surgery.[81] Recent evidence suggests that the neo-adjuvant administration of epirubicin and ifosfamide improves likewise recurrence-free and overall survival in high-risk patients compared with histology-tailored regimens (e.g. gemcitabine and darcabazine in leiomyosarcoma).[82,83]

High risk patients (i.e. patients with deep, high-grade STSs of the extremities larger than 5 cm) may benefit from adjuvant CTX by deferring time to local or distant failure.[84,85] A typical regimen used in the adjuvant setting consists of anthracyclines and ifosfamide (AI-scheme).[86] Alternatively, CTX agents can be administered on the basis of histology, as gemcitabine and docetaxel for pleomorphic sarcoma and etoposide with ifosfamide for MPNST.[87,88] However, histology-driven approaches may be abandoned in future in view of the above-mentioned most recent findings.[82]

First-line treatment for advanced disease is based on anthracyclines (e.g. doxorubicin). The combination with ifosfamide may be chosen if the main goal is to palliate acute symptoms related to rapid metastatic growth.[89] Otherwise, single-agent CTX should be preferred, aiming at control of pulmonary metastases and prolongation of life.[57,89]

Apart from conventional chemotherapeutics, novel promising agents have been developed for STS over the past few years. Trabectedin is recommended as second-line treatment following failure of anthracycline-based CTX. Especially in (myxoid) liposarcoma and leiomyosarcoma, a prolongation in survival may be achieved.[90,91] In non-lipomatous STS refractory to conventional CTX, the tyrosine-kinase inhibitor pazopanib can be used, resulting in a slight prolongation of overall survival.[92]

Eribulin, a cytotoxic spindle-cell inhibitor, was the first agent showing a survival benefit in patients with advanced or metastatic liposarcoma.[93] Overall survival increased by 7.2 months under treatment with eribulin in comparison to dacarbacine. In April 2016, the European Medicines Agency approved eribulin as another second-line agent for advanced liposarcomas. Nonetheless, further multicentre trials are required to confirm the beneficial effects of novel agents in the treatment of STS.

Outcomes

Following wide resection of STSs at a sarcoma centre, the five-year LR rate ranges between 12% and 26%, depending on patient age, histological sub-type, tumour grade, anatomical location and the quality of surgical margins.[14,94] Whilst some LRs can be attributed to inadequate surgical margins or omission of adjuvant RTX, STSs sometimes recur even after an optimal primary treatment. In such cases, local failure results from a tumour's biological aggressiveness and is associated with a considerably worse prognosis.[95]

Grade 3 tumours metastasise in up to 60% of cases, as opposed to only 5% to 10% of grade 1 tumours.[96] Additionally, large tumour size and a deep location are associated with a higher risk for distant metastasis.[14] Patient prognosis is drastically reduced in cases with metastatic disease, with an expected two-year survival rate of 33% only.[97] Nevertheless, the median overall survival for patients with metastatic disease has improved over the last 20 years, due to reinforced multidisciplinary treatment approaches, development of the above-mentioned novel therapeutics and better understanding of disease dynamics.[97]

Future perspectives

The close cooperation between involved clinical specialities, from radiologists and pathologists diagnosing the tumour, through orthopaedic, plastic and thoracic surgeons performing surgical treatment, oncologists and radiotherapists responsible for (neo-) adjuvant CTX and

RTX to physiotherapists and psycho-oncologists supporting patients throughout treatment, has generally improved outcomes for patients with STS. Locally advanced STSs can be downsized by neo-adjuvant CTX alone or in combination with ILP and RTX in selected tumour types to make limb-salvage surgery possible.[98] Moreover, complex reconstructions – nowadays routinely performed following extensive tumour resection – improve patients' quality of life significantly. In the adjuvant and palliative setting, CTX can prolong disease-free survival, leads to tumour shrinkage and relieves metastasis-associated symptoms. Furthermore, recently developed agents prolong overall survival of STS patients with advanced disease.[93]

Additionally, modern analyses and technologies have found their way into management of STSs. The multi-state modelling enables prediction of outcome of patients with localised STSs.[99] With the Sarculator (Digital Forest SRL, Italy), the prognosis of patients with high-risk STSs of both the extremities and trunk undergoing peri-operative CTX can be calculated via an app.[100] Another app allowing estimation of the prognosis of patients with extremity-STS is the PERsonalised SARcoma Care (PERSARC) model that is being currently developed by sarcoma specialists.[101]

However, many questions remain to be answered, from the most appropriate width of surgical margins to the benefits of CTX in localised STS, to new treatment strategies in advanced disease. For some tumours, targeted agents, such as imatinib for gastrointestinal stromal tumours and pazopanib for non-lipomatous STS, seem to be more effective than conventional CTX.[92] The most recent discovery in this field is the human monoclonal antibody olaratumab, targeting platelet-derived growth factor receptor alpha.[102] The combination of doxorubicin with olaratumab improved median overall survival by 11.8 months in STS patients with metastatic disease in comparison with doxorubicin alone.[102]

The diagnosis of STS can be challenging. A thorough diagnostic workup is usually required to distinguish malignant from benign soft-tissue lesions. If performed only partially or inaccurately, misinterpretation of the underlying pathology at best delays ultimate diagnosis. Consequently, unplanned excisions may be performed, necessitating extensive re-resection and adjuvant therapy at tumour centres.

In order to avoid misdiagnoses, one should follow a standardised diagnostic approach, beginning with the patient history, clinical examination and appropriate imaging prior to conducting biopsy. The moment a STS is suspected – ideally prior to any invasive procedure – patients should be referred to the next sarcoma centre. Definitive treatment is best planned and performed by sarcoma specialists employing a multidisciplinary approach.

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RESEARCH ARTICLE

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Incidence, treatment and outcome of abdominal metastases in extremity soft tissue sarcoma: Results from a multi-centre study

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Abstract

Background and Objectives: Abdominal metastases (AM) from soft tissue sarcoma (STS) are rare and prognosis is poor. The aims of the study were to (a) identify risk factors for the development of AM and to (b) investigate the outcome of AM-patients.

Methods: Seven-hundred-sixty-nine STS-patients with localised disease at diagnosis treated at three tumour centres (2000-2016) were retrospectively included (409 males; mean age, 55.6 years [range, 8-96 years]; median follow-up, 4.1 years [interquartile-range, 2.5-6.6 years]).

Results: Two-hundred-two patients (26.3%) developed secondary metastases, and 24 of them AM (3.1%). Ten patients developed first AM (FAM) after a mean of 2.4 years and 14 patients late AM (LAM, after being diagnosed with metastases to other sites) after a mean of 2.0 years. Patients with liposarcoma had a significantly higher risk of developing AM ($P = .007$), irrespective of grading. There was no difference in post-metastasis-survival (PMS) between patients with AM at any time point and those with metastases to other sites ($P = .585$). Patients with LAM or FAM showed no difference in post-abdominal-metastasis-survival ($P = .884$).

Conclusions: Survival in patients with AM is poor, irrespective of whether they develop secondarily to other metastases or not. Patients at high-risk of AM (ie, liposarcoma) may be followed-up regularly by abdominal-ultrasound/CT.

KEYWORDS
abdominal metastasis, soft tissue sarcoma, survival

1 | INTRODUCTION

Soft tissue sarcomas of the extremity and trunk (STS) are rare tumours with an estimated incidence of 2.4 cases per 100 000 persons per year.[1] About 15% of STS-patients develop local recurrences and 30% distant metastases at 5 years, most commonly to the lungs.[2-5] Other metastatic sites are described (bone and lymph nodes), however abdominal metastases (AM) from STS, are very uncommon.[6,7] AM carry a poor

prognosis with 2-year survival rates of 43%.[7] Diagnosis can be difficult as AM may be asymptomatic for a long time or may only cause vague discomfort.[8] Symptoms involve intestinal obstruction, abdominal pain, or gastrointestinal bleeding.[8] Since these very symptoms can also represent side effects from chemotherapy (CTX) or pain management, they can be easily misinterpreted.[6,8] There is no clear consensus how to follow-up patients with localised STS following surgical resection, with different studies describing different follow-up regimes.[9-11] The current ESMO guidelines[12] suggest that STS-patients should be followed-up every 3 to 4 months for the first 3 years, then bi-annually for the following 2 years and thereafter annually by chest-X-rays and/or computed tomography-scan (CT-scan) of the lungs. However, the impact of regular abdominal CT-scans in follow-up remains unclear.[12]

Three studies have been published so far on the topic of AM of STS.[7,13,14] However, the number of patients with AM identified in these studies was relatively low and more importantly they did not distinguish between patients with AM as the first metastatic manifestation and those with AM developing after other metastases had occurred, therefore leaving many clinical questions unanswered.

Incidence of AM, risk factors for their development, diagnostic tools and impact on patient survival were analysed in the present retrospective multi-centre study. The aims of the study were to (a) to investigate the outcome of these patients in comparison to STS-patients with metastases to other sites and those without metastases and (b) to identify factors associated with a higher risk for developing AM.

2 | MATERIALS AND METHODS

We performed a retrospective analysis of the files of 769 patients who had been diagnosed with a primary localised extremity STS (G1-G3) between January 2000 and May 2016 at three tertiary tumour centres. Four-hundred-nine patients were male (53.2%) and 360 were female (46.8%). The mean age of all patients was 55.6 years (range, 8-96 years). Median follow-up was 4.1 years (IQR, 2.5-6.6 years).

Data was collected by reviewing medical records, such as pathology and radiology reports, outpatient records and medical charts. Time to secondary metastasis (SM) and first abdominal metastasis (FAM) was calculated from date of definite surgery to the first radiological verification of a metastatic focus (eg, MRI, CT-scan). Late abdominal metastasis (LAM) was defined as an abdominal metastasis developing after SM at another site. Follow-up intervals were calculated from the date of primary surgery to the date of last follow-up or death. Routine follow-up was performed according to the ESMO[12] and NCCN[15] guidelines in the respective years, including alternate CT-scans of the abdomen and abdominal ultrasonography, depending on the at each time valid policy.

Date of SM, as well as FAM and LAM, was documented. Overall-survival (OS) was calculated from date of primary surgery to date of last follow-up or death. Post-metastasis-survival (PMS) was defined as the interval between development of SM and last-follow-up or death. Post-abdominal-metastasis-survival (PAMS) was calculated from date of development of AM to last follow-up or death. The current study has been approved by the local institutional review board (EK-Nr. 24-573 ex 11/12) and has been performed in accordance with the Declaration of Helsinki.

2.1 | Statistical analysis

All statistical analyses were performed with the *Stata* software version *15.1* (StataCorp, TX). Means and medians were calculated for normally and non-normally distributed data using *t*-tests and Mann-Whitney-U-tests, respectively. Comparisons between groups were made using χ^2 tests. Kaplan-Meier estimates and Cox-regression models were used to estimate outcome variables, providing hazard ratios (HRs), 95% confidence intervals (95%CI) and *P* values. Considering that only two patients with AM underwent additional surgery, subgroup analysis to assess the effect of metastasectomy on PMS in this group of patients was not performed. Furthermore, the multivariate Cox-regression analysis was limited to two factors, in accordance with the 'one in ten rule'.[16] All *P* values are two-sided; a *P* value of <0.05 was considered statistically significant.

3 | RESULTS

Two-hundred-two patients (26.3%) developed SM after a median of 15 months (IQR, 10-29 months). Demographic features and tumour as well as treatment specific details of patients with and without SM are depicted in Table 1.

Taking into account all metastatic foci developing during the course of the disease, the most common location was the lung (n = 114), followed by bone (n = 32) and regional as well as distant lymph nodes (n = 27; Figure 1). Rare locations included the pericard/endocard as well as the skin in four cases, the subcutis in three and the meninges in two cases.

Twenty-four patients developed AMs during the course of disease (3.1%), including 13 hepatic, three intestinal, two pancreatic and two peritoneal metastases. Further four patients had multiple intestinal metastases, of whom two also had metastatic foci in the retroperitoneum. Ten patients presented with a FAM after a mean of 2.4 years (range, 7 months to 8.3 years) and 14 patients a LAM, after having developed a primary metastasis to another site. In the latter case, the meantime to LAM from the development of SM was 2.0 years (range, 1 month to 3.6 years). Moreover, hepatic FAM (n = 5) showed no tendency to develop earlier than FAM at other sites (n = 5; 17.1 vs 10.1 months; *t*-test *P* = .793).

3.1 | Diagnostic pathway

Nonabdominal SM was detected by CT-scan of the thorax in 76 cases, followed by chest-X-ray in 20 cases, MRI in eight cases, ultrasound in one case and other methods (abdominal CT-scan, PET-CT) in 10 patients. In nine patients, the detection method of

TABLE 1 Comparison of patient- and primary tumour characteristics with secondary metastases and those without

N = 769	No SM	SM	Missing	*P* value
Mean age	55.9 y	54.9 y	0	.230
Sex				
Female	278	85	0	.116
Male	292	117		
Histology (primary tumour)				
Liposarcoma	165	31	0	**<.001**
Myxofibrosarcoma	101	31		
Leiomyosarcoma	55	28		
Synovial sarcoma	39	9		
UPS	98	23		
Other	109	80		
Grading (primary tumour)				
G1	187	22	15	**<.001**
G2	194	79		
G3	173	99		
Location				
Upper limb	107	45	0	.552
Lower limb	410	142		
Trunk	47	13		
Head/Neck	3	2		
Proximity				
Proximal	362	124	2	.588
Distal	181	64		
Median	24	12		
Depth				
Superficial	57	22	23	.826
Deep	489	178		
Tumour size	8.2 cm	8.8 cm	30	.215
Neoadj CTX				
No	523	175	0	**.018**
Yes	44	27		
Adj CTX				
No	525	177	0	**.032**
Yes	42	25		
Neoadj. RTX				
No	530	176	0	**.005**
Yes	37	26		
Adj RTX				
No	344	90	0	**<.001**
Yes	223	112		

Abbreviations: CTX, chemotherapy; RTX, radiotherapy; SM, secondary metastasis.
P-values in bold indicate significant results.

metastasis was unclear. Most AM, irrespective of their type, were detected by CT-scan of the abdomen (n = 9) and ultrasound (n = 3).

The most common symptom reported by patients at diagnosis with AM included unspecific abdominal pain in one-fifth of patients (n = 5).

3.2 | Treatment

Primary treatment of AM included CTX in 18 patients, CTX+surgery in two patients (one for a hepatic metastasis, one for an acute ileus), CTX combined with embolization in one case and best supportive care in three patients.

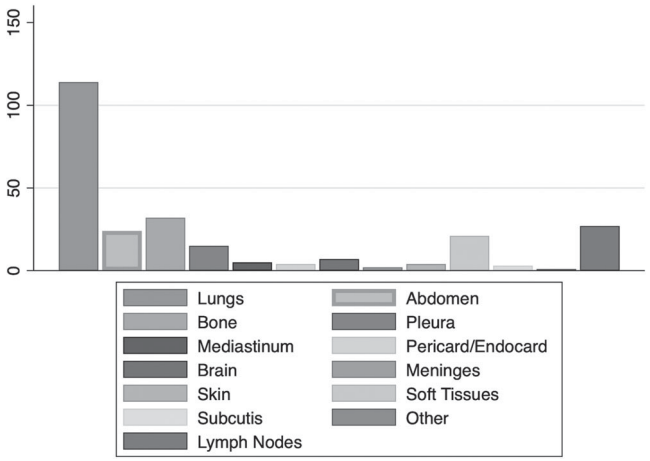

FIGURE 1 Frequency of first metastases to different body regions

There was no difference in the time interval until the development of FAM vs SM to other sites (mean time, 29.1 months vs 27.5 months; t-test *P* = .875).

3.3 | Risk factors for abdominal metastases

Of those 24 patients with AM, 11 had originally been diagnosed with liposarcoma as the underlying histological subtype, four with UPS, three with leiomyosarcoma, one with myxofibrosarcoma and five with a miscellaneous histology (χ^2 test; *P* = .178). Patients with liposarcomas developed FAM significantly more often than patients with other histologies (*P* = .016; Figure 2). Patients with myxoid liposarcoma had a significantly higher risk of developing FAM in comparison to the remaining histological subtypes pooled together

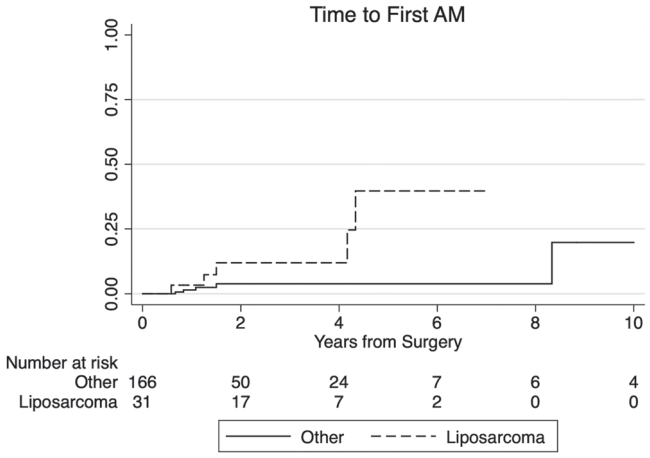

FIGURE 2 Risk of development of primary AM vs metastases to other sites from date of surgery. Patients with liposarcoma (dashed line) have a significantly higher risk of developing abdominal metastases (*P* = .016). AM, abdominal metastases

TABLE 2 Univariate Cox-regression model showing the risk for patients to develop initial AM vs SM from the date of surgery. Patients with liposarcoma have a significantly higher risk of developing AM

N = 197	Hazard ratio	Confidence interval Lower	Upper	*P* value
Mean age	0.993	0.683	0.958	.683
Sex				
Female (ref)	1			.132
Male	0.536	0.238	1.206	
Histological subtype				
Others (ref)	1			**.016**
Liposarcoma	5.072	1.357	18.955	
Liposarcoma subtype				
Liposarcoma NOS (ref)	1			
Myxoid liposarcoma	3.111	0.862	11.220	.083
Pleomorphic liposarcoma	2.647	0.272	25.798	.402
Grading				
G1 (ref)	1			
G2	1.102	0.113	9.868	.931
G3	1.578	0.183	13.566	.678
Depth				
Superficial (ref)	1			.763
Deep	1.382	0.169	11.315	
Tumour size	1.027	0.913	1.156	.655
Adjuvant CTX				
No (ref)	1			.682
Yes	1.383	0.293	6.532	
Adjuvant RTX				
No (ref)	1			.746
Yes	0.815	0.236	2.818	

Abbreviations: AM, abdominal metastases; CTX, chemotherapy; NOS, not otherwise specified; RTX, radiotherapy.
P-values in bold indicate significant results.

(HR, 7.712; 95% CI, 1.920-30.986; $P = .004$). On the other hand, there were no differences in the probability of developing AM between the different subtypes of liposarcoma (ie, NOS, pleomorphic and myxoid) in our patient cohort (Table 2).

In the multivariate analysis, histological subtype only (liposarcoma vs others; $P = .007$) could be identified as an independent

TABLE 3 Multivariate Cox-regression model showing the risk for patients to develop primary AM vs SM from date of surgery. In comparison to all other histological subtypes, patients with liposarcoma have a significantly higher risk of developing primary AM

N = 195	Hazard ratio	Confidence interval Lower	Upper	*P* value
Histological subtype				
Others (ref)	1			**.007**
Liposarcoma	6.589	1.668	26.026	
Grading				
G1 (ref)	1			
G2	1.792	0.195	16.453	.606
G3	3.422	0.372	31.457	.277

P-values in bold indicate significant results.

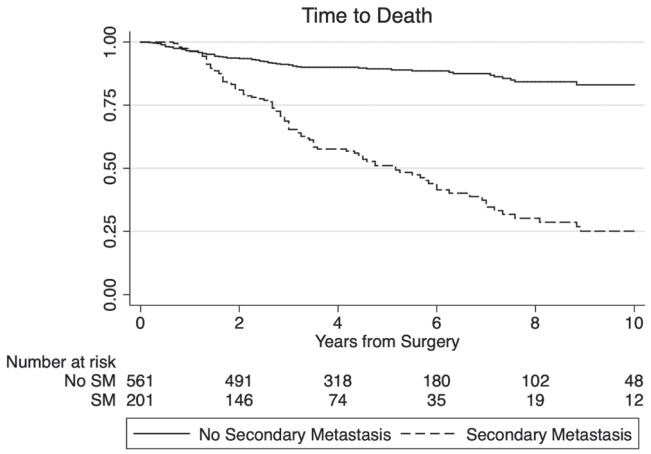

FIGURE 3 Survival curves for patients developing secondary metastasis (SM; dashed line) and those patients who did not (no SM; solid line; $P < .0001$)

negative prognostic parameter regarding the development of AM as the first metastatic manifestation, irrespective of grading (Table 3).

3.4 | Outcome

At last follow-up, 523 patients were alive without (68.0%) and 67 alive with disease (8.7%). One-hundred-nineteen patients had died of STS (15.5%), and 57 due to other causes (7.4%), whereas in four patients the cause of death remained unknown (0.4%). Depending on their metastasis status, nine patients with AM (37.5%), 86 patients with SM (51.1%) and 497 patients without metastases were still alive (87.8%).

Patients without SM had a significantly better OS than patients with SM (log-rank $P < .0001$; Figure 3). There were no differences in PMS between patients with AM at any time point and patients with SM other than AM ($P = .585$; Figure 4). Patients undergoing surgery for their metastasis had a significantly better PMS than patients

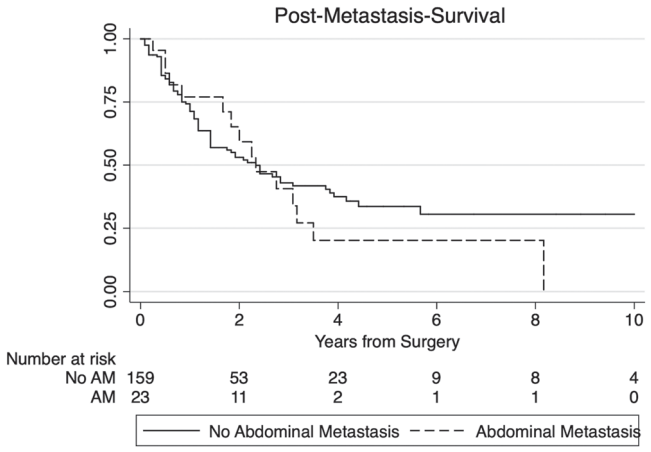

FIGURE 4 Difference in post-metastasis survival between patients with SM other than abdominal metastasis (no AM; solid line) and those with AM (FAM+LAM, dashed line; $P = .585$), calculated from the date of onset of SM or AM. AM, abdominal metastases

treated by CTX, radiotherapy (RTX) or best supportive care (HR, 0.544; 95%CI, 0.328-0.902; $P = .018$).

Interestingly, there was also no difference in PAMS between patients with FAM and those with LAM (log-rank $P = .884$), suggesting that occurrence of AM at any time point similarly reduces survival probability. Additionally, PAMS did not significantly differ between patients with liver metastases vs AM to other sites (HR, 1.610; 95%CI, 0.537-8.833; $P = .395$).

4 | DISCUSSION

STS metastasise most commonly via the bloodstream to the lungs.[17] AM, on the other hand, are extremely uncommon.[8] Few case reports and studies have been published, describing the course of patients with abdominal or retroperitoneal metastases from STS.[7,13,14,18-20] These studies either included relatively low numbers of patients with AM or did not describe factors associated with a higher risk of developing AM in a time-dependent manner.

Thompson et al[21] described 140 STS-patients who were screened with CT-scans of the abdomen, and found that a total of four patients (2.9%) developed AM.[21] In another single-centre study, 19 AMs developing during the course of disease were observed in a group of 2127 STS (<1%).[7] In our cohort, 24 out of 769 patients with localised extremity and trunk STS developed AMs-most commonly to the liver-resulting in a total frequency of 3.1%. This discrepancy may be explained by the fact that in our collective, most patients with AM were diagnosed by CT-scans (followed by ultrasonography), whilst in the study by Behranwala et al,[7] the use of abdominal CT-scans was not clearly described. Therefore, some AM may have remained undiagnosed in that study, explaining the lower rate.

Raising the question why AM from STS are extremely rare, one has to look at to basic research; according to two experimental studies by Skubitz et al,[22,23] STS have different metastatic propensities based on their gene expression patterns. This suggests that not only the histological subtype, tumour size and grading have an influence on the propensity of STS-metastasis to occur, but also the individual genetic profile of STS most probably results in a different affinity to specific tissues.

Assuming that the affinity of STS to viscera is low, the time interval until development of AM should also be rather long. Indeed, in our cohort it took a mean of 2.4 years for FAM to occur, while the mean interval until development of LAM following first metastases to other sites was also long (2.0 years). This is comparable to the 2.3 years interval observed by Behranwala et al[7] for patients with any AM. On the other hand, initial metastases to, for example, lungs and bones developed after a median of 15 months in our cohort.

In our study, patients with liposarcomas as the underlying histological subtype had a significantly higher risk of developing AM, irrespective of grading. This is corresponding to observations made by Behranwala et al[7] and Lev-Chelouche et al,[6] in whose studies six out of 19 patients (myxoid subtype) and four out of 10 patients with AM, respectively, had liposarcomas as the underlying histotype.[6,7] In our collective, patients with liposarcoma NOS, a myxoid or pleomorphic subtype had an equally high risk of developing AM. Of note, myxoid liposarcomas tend to metastasise at higher rates to sites other than the lung (including bone and abdomen/retroperitoneum) in comparison to most STS subtypes.[7,24] This observation could be confirmed in the present study, with myxoid liposarcoma-patients having significantly higher risks of developing AM as compared with all other histologies pooled together. However, we did not find a higher risk of AM for myxoid liposarcoma-patients when compared to other liposarcoma subtypes, indicating that at least in the frequency of abdominal surveillance (ie, CT-scans, sonography), no difference between the liposarcoma subtypes should be made.

The development of AMs at any time point was associated with a similar reduction in survival probability in our collective. This suggests that once STS gain affinity to the viscera, they have already converted into more aggressive tumours.

A recent study has shown that surgical resection of STS-metastases, in general, may be associated with an improved survival outcome, irrespective of confounding factors.[25] In that study, however, most metastases were located in the lungs and soft tissues rather than the abdomen. In our cohort, most patients with AM were administered CTX, whilst two patients underwent additional surgery. Consequently, we only analysed the effect of metastasectomy on PMS for all patients rather than patients with AM only, revealing that surgery for metastases was associated with an improved outcome.

Due to the retrospective design of the study, not all questions can be answered, though, including the issue whether an earlier detection of AM would result in a survival benefit and at which frequency to perform abdominal ultrasound or CT-scans. These issues may be addressed in the frame of a prospective study, similar to the study by Puri et al,[26] with patients assigned to various standardised protocols differing in intervals and methodology. Recently, two apps (Sarculator,[27] PERSARC[28]) have been developed based on a thorough analysis of the risk of local recurrence and distant metastasis as well as OS in patients with eSTS, aiming at individualising patient treatment and aftercare. Based on these advancements, follow-up may in the future slightly differ from the proposed ESMO guidelines,[12] taking into account individual risk factors altering rates of LR and DM, as well as overall prognosis.

There are some major limitations to the present study. As three different centres participated and patients over a long time period where included, the surveillance-schemes may have changed over the years, thus not guaranteeing that AM were detected as often and early at every period. Moreover, due to the retrospective design of this study, confounding factors as patient symptoms, leading to the conduction of an abdominal CT-scan outside routine follow-up, cannot be eliminated. Additionally, no data on diagnostic delay of AM or SM was uniformly available, wherefore no conclusion on whether earlier detection of AM would alter patient prognosis could be drawn. Furthermore, due to the low rate of AM in the present collective, the number of variables being analysed in the multivariate setting was limited.

On the other hand, we were able to include a very large number of patients with eSTS, treated according to at the time current guidelines at experienced tertiary referral sarcoma centres, factors which we believe largely offset the impact of the above limitations.

5 | CONCLUSIONS

AM from soft tissue sarcoma constitutes a very rare event. Survival is likewise reduced in patients with first AM and those with late AM, signifying that tumours developing abdominal metastasis are equally aggressive, and that outcome is generally poor. Patients with liposarcomas appear to be at a significantly higher risk of developing AM, wherefore at least in this these patients, surveillance with abdominal CT-scans or sonography in follow-up should be considered. Nevertheless, prospective, randomised studies are warranted to investigate the frequency and methodology of future follow-up protocols.

CONFLICT OF INTERESTS

Author MvdS reports grants from Daiichi Sankyo, outside the submitted work. Author AL reports grants from Johnson & Johnson and Alphamed, outside of the submitted work. The remaining authors have no conflicts of interest relating to the present manuscript to declare.

ETHICS STATEMENT

The current study has been carried out in accordance with the ethical standards of the Declaration of Helsinki and has been approved by the local ethics committee (EK-Nr. 24-573 ex 11/12).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Surgery for metachronous metastasis of soft tissue sarcoma – A magnitude of benefit analysis using propensity score methods

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ABSTRACT

Introduction: Metastasectomy is hypothesised to improve OS in metastatic STS, but evidence in favour of this approach derives from non-controlled single-arm cohorts affected by selection bias. The objective was to quantify the effect of metastasectomy vs. non-surgical management on overall survival (OS) in patients with metachronous metastases from extremity- and trunk soft tissue sarcoma (STS).
Materials and methods: From a population of 1578 STS patients, 135 patients who underwent surgery for localised STS at two European centres between 1998 and 2015 and developed metachronous STS metastases were included. Propensity score analyses with inverse-probability-of-treatment-weights (IPTW) and landmark analyses were performed to control for selection and immortal time bias, respectively.
Results: OS was significantly longer in the 68 patients undergoing metastasectomy than in the 67 patients who were treated non-invasively for their metastasis (10-year OS: 23% vs. 4%; hazard ratio (HR) = 0.34, 95% CI: 0.22–0.53, $p < 0.0001$). This association prevailed after IPTW-weighting of the data to control for the higher prevalence of favourable prognostic factors in the surgery group (adjusted 10-year OS: 17% vs. 3%, log-rank $p < 0.0001$; HR = 0.33, 95% CI: 0.20–0.52, $p < 0.0001$). Five-year OS estimates were 27.8% in patients who had and 14.5% in patients who had not undergone metastasectomy within the first 3 months after diagnosis of a metastasis ($p < 0.0001$).
Conclusion: In this observational bi-centre study, metastasectomy was associated with prolonged survival in patients with metachronous STS metastases. In the absence of randomized studies, our results indicate that metastasectomy should be considered as an important treatment option for metachronous STS metastases.

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Introduction

Soft tissue sarcomas (STS) constitute a group of rare mesenchymal tumours with diverse molecular, histologic, and clinical features [1]. While a significant number of patients with localised STS can be cured with wide surgical resection, up to a third of patients will develop metachronous distant metastases [2]. Patients with metastatic STS have limited systemic treatment options and in general a poor prognosis, with median survival averaging one year [3,4].

Although chemotherapy is considered the standard treatment for advanced STS [5], metastasectomy represents an emerging practise in this patient population [5]. Evidence in favour of a surgical approach in the metastatic setting comes from several large retrospective case series investigating overall survival (OS) outcomes of patients who had undergone (mostly pulmonary) metastasectomy [6–23]. These studies have shown very encouraging survival outcomes, far beyond the expected average median survival of around 1 year for metastatic STS. Furthermore, cases with long-term remissions or even potential cure after complete surgical excision of STS metastases have been reported in this context [24]. However, as current studies on metastasectomy in STS are not only retrospective in their nature but also uncontrolled for biases, the question whether metastasectomy improves outcomes as compared to a purely "non-invasive" approach with chemotherapy and supportive measures is currently unknown [25]. Indeed, most evidence on metastasectomy comes from single-centre cohorts within highly specialised tertiary centres involving patients that were likely selected for potentially favourable prognostic factors such as a good performance status, a long metachronous interval, resectable lesions, and/or low metastatic tumour load. Thus, whether favourable outcomes in these cohorts were due to metastasectomy or rather due to the selection of patients with a favourable prognosis for metastasectomy is unclear [25].

While a randomized controlled trial of metastasectomy versus non-invasive treatment would be optimal for quantifying the benefit of surgery in this setting, data from such a trial are unavailable at present, and unlikely to become available in the future due to ethical and logistical reasons [26,27]. In the absence of randomized data, comparative effectiveness studies of observational data may provide guidance for surgeons, medical oncologists and patients [28]. In this study, we perform a comparative effectiveness analysis of surgery versus "non-surgery in patients with metachronous metastases of STS using propensity-score analysis and Inverse Probability of Treatment Weight (IPTW)-modelling. However, even this controlled study is subject to potential selection bias, because treatment assignment to surgery is non-random. A naïve analysis of such data may lead to an overestimation of the potential benefit of metastasectomy. To overcome this limitation, we use advanced comparative effectiveness methods involving propensity scores [29,30].

Patients and methods

Patients

In this bi-centre historical cohort study, we retrospectively included 135 patients who were diagnosed with metachronous metastases from histologically-confirmed extremity and trunk STS at two European tertiary centres (Medical University of Graz: n = 87, Leiden University Medical Centre: n = 48). All 135 patients had previously undergone surgery with curative intent for localised STS at these centres, and were drawn from the greater population of 517 patients who had undergone surgery for localised STS between 1998 and 2017 at the Medical University of Graz and 1030 corresponding patients treated between 2000 and 2015 at the Leiden University Medical Centre. Patients with a short follow-up or missing essential information were excluded (Supplementary Figure 1). Two patients initially diagnosed with grade 1 STS were likewise included, as they were subsequently upgraded (Table 1).

Demographic variables and tumour- and treatment-related factors – with special focus on management of metastatic disease – were documented retrospectively as previously described [31,32]. *Eastern Cooperative Oncology Group* (ECOG) status, as well as haemoglobin and albumin levels, were determined for each patient, as documented at the latest Tumour Board Meeting (TBM) prior to treatment of the metastases.

Date of diagnosis of disseminated disease was defined as the first clinical appointment where imaging studies (i.e. computed tomography, magnetic resonance imaging, chest X-ray, positron-emission tomography) provided an indication for metastatic spread that was consecutively confirmed by further metastatic spread, progressive disease or histological examination of resected metastatic nodules. Two study groups were defined retrospectively based on their treatment post diagnosis of metastases: (1) Patients who had undergone any surgical intervention, and (2) patients who had not undergone any surgical intervention. Both groups included patients that received non-invasive treatment approaches, such as chemotherapy or palliative radiotherapy. Treatments were indicated by the multi-disciplinary TBM. Follow-up was calculated from the date of diagnosis of disseminated disease ("baseline date") until death or end of records. Primary endpoint of this study was OS.

Statistical methods

All statistical analyses were performed using Stata (Windows version 14.0, Stata Corp., Houston, TX, USA). Standardized mean differences (SMDs) were used to quantify differences in means and proportions of variables between the two study groups (surgical intervention vs. no surgical intervention), with SMDs $\geq$ 0.3 being considered indicative of a relevant between-group imbalance. Median follow-up was computed according to the method of Schemper and Smith [29], and OS with a Kaplan-Meier estimator. For comparison of survivor functions between the two study groups, we used log-rank tests. To investigate the association of risk factors with survival, uni- and multivariable Cox models were estimated. The proportionality of hazard assumption was evaluated by fitting an interaction between a variable of interest and linear follow-up time. The propensity score was defined as the probability of undergoing surgical intervention conditional on baseline covariates [30]. This propensity score was predicted from a multivariable logistic regression model (all included covariates are reported in Supplementary Table 1 and are based on clinical experience as well as literature [4,33,34]). For this propensity score model, missing baseline covariates were imputed with a chained equations algorithm with 10 imputation datasets (list with conditional imputation models available from FP upon request). The inverse-probability-of-treatment-weight (IPTW) was then defined as the inverse of the probability of receiving the treatment that the patient received (also known as the "average treatment effect on the treated"). Following best practise recommendations, SMDs were recalculated after weighing of the data with the IPTWs as a method of balance diagnostics [30]. Here, we pre-specified that the IPTW achieved sufficient balance if an unadjusted SMD $\geq$ 0.3 was lowered below this threshold. The primary endpoint of the analysis, i.e. the association between treatment assignment and OS, was then studied with a univariable Cox model which was weighted for the IPTW, as well as IPTW-weighted Kaplan-Meier estimators and log-rank

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Table 1
Baseline characteristics of the study population. Distribution overall and by treatment group.

	n (% missing)	Overall (n = 135)	No surgical intervention (n = 67)	Surgical intervention (n = 68)	p-value	SMD	SMD-IPTW
Gender							
Male	135 (0%)	80 (59%)	43 (64%)	37 (54%)	0.248	0.20	0.09
Female		55 (41%)	24 (36%)	31 (46)			
Location of Primary Tumour							
Upper limb	135 (0%)	37 (27%)	21 (31%)	16 (24%)	0.510	0.17	0.01
Lower limb		90 (67%)	43 (64%)	47 (69%)		0.10	0.03
Trunk		8 (6%)	3 (4%)	5 (7%)		n/a	n/a
Histology of Primary Tumour							
Angiosarcoma	135 (0%)	6 (4%)	4 (6%)	2 (3%)	0.557	n/a	n/a
MPNST		13 (10%)	8 (12%)	5 (7%)		n/a	n/a
Myxofibrosarcoma		38 (28%)	18 (27%)	20 (29%)		0.06	0.05
Synovial Sarcoma		18 (13%)	9 (13%)	9 (13%)		0.01	0.08
UPS		10 (7%)	3 (4%)	7 (10%)		n/a	n/a
Spindle cell sarcoma		5 (4%)	1 (1%)	4 (6%)		n/a	n/a
Liposarcoma		6 (4%)	2 (3%)	4 (6%)		n/a	n/a
Other		39 (29%)	22 (33%)	17 (25%)		0.17	0.06
Size of Primary Tumour	133 (2%)	10.0 [6.0–13.3]	10.0 [6.0–13.2]	9.5 [5.5–14.0]	0.480	0.19	0.13
Grade of Primary Tumour							
G1	132 (2.2%)	2 (2%)	0 (0%)	2 (3%)	0.407	n/a	n/a
G2		23 (17%)	13 (19%)	10 (15%)		0.11	0.04
G3		107 (81%)	54 (81%)	53 (82%)		0.02	0.00
Surgery Primary Tumour							
Limb Salvage	105 (22%)	90 (86%)	41 (79%)	49 (92%)	0.055	0.39	0.04
Amputation		15 (14%)	11 (21%)	4 (8%)			
Adjuvant Therapy							
No Adjuvant Therapy	96 (29%)	25 (26%)	16 (33%)	9 (19%)	0.356	0.31	0.06
(Neo-)Adjuvant RTX		61 (64%)	27 (55%)	34 (72%)		0.36	0.08
(Neo-)Adjuvant CTX		3 (3%)	2 (4%)	1 (2%)		n/a	n/a
Both		7 (7%)	4 (8%)	3 (6%)		n/a	n/a
Count of Metastases							
Singular	135 (0%)	51 (38%)	15 (22%)	36 (53%)	**<0.0001**	0.66	0.15
Multiple		84 (62%)	52 (48%)	32 (47%)			
Number of Metastases*	135 (0%)	2 [1–9]	6 [2–9]	1 [1–3]	**<0.0001**	0.96	0.20
Age at Metastasis (Years)	135 (0%)	65 [50–75]	67 [52–78]	63 [47–74]	0.158	0.25	0.07
Time to 1st Metastasis (Months)	134 (0.7%)	11 [4–20]	7 [3–20]	14 [6–25]	**0.020**	0.11	0.02
Location of Metastasis**							
Lungs	134 (0.7%)	99 (74%)	56 (85%)	43 (63%)	**0.039**	0.50	0.15
Soft tissues + LN		21 (16%)	4 (6%)	17 (25%)		0.54	0.17
Bone		7 (5%)	3 (5%)	4 (6%)		n/a	n/a
Organs		2 (1%)	1 (1.5%)	1 (1%)		n/a	n/a
Skip lesion		5 (4%)	2 (3%)	3 (4%)		n/a	n/a
Haemoglobin (g/dL)	98 (27%)	12.9 [11.0–14.3]	12.6 [10.6–13.3]	13.5 [11.5–14.8]	**0.006**	0.57	0.22
Albumin (g/dL)	61 (55%)	4.2 [3.5–4.6]	4.0 [3.2–4.2]	4.5 [4.0–4.8]	**0.002**	0.81	0.35
ECOG PS	103 (24%)	1 [0–1]	1 [0–2]	0.5 [0–1]	**0.019**	0.54	0.27

Summary estimates represent medians [25th–75th percentile] for continuous variables, and absolute frequencies (%) for count data; *P*-values are from χ^2-tests, Fisher's exact tests, and rank-sum tests; SMDs $\geq$ 0.3 were considered indicative of a potential covariate imbalance between the two treatment groups; p-values in bold are statistically significant; *Number of metastases was truncated at 9 metastases in case of "innumerable" metastases according to radiology report; **In case of multiple metastastic sites, this variables refers to the location of the clinically predominant metastatic site; Abbreviations: n (% missing) – Number of patients with available data for the respective variable (% of patients with missing data), SMD – Standardized mean difference, SMD-IPTW – SMD after weighting of the data with the Inverse-Probability-of-Treatment-Weight (IPTW), n/a – not applicable (SMDs were only calculated for rows that included at least 15 patients), MPNST – Malignant Peripheral Nerve Sheath Tumour, UPS – Undifferentiated Pleomorphic Sarcoma, RTX – Radiotherapy, CTX – Chemotherapy, LN – Lymph nodes, ECOG PS – Eastern Cooperative Oncology Group Performance Status.

tests [35]. Importantly, metastasectomy was treated as a time-dependent variable in this main analysis to account for potential immortal time bias due to the time between metastasis diagnosis and metastasectomy [36–38]. Key prognostic variables and variables which did not achieve an SMD < 0.3 after IPTW-weighting were subsequently included in this Cox model to account for potential residual confounding. In a sensitivity analysis, we used a "truncated" IPTW excluding patients with an IPTW <5% or >95% of the IPTW's distribution [30]. To study potential predictive biomarkers for benefit from surgical intervention, we fitted interactions between treatment assignment and several clinical and laboratory markers. Due to the low power of interaction tests and the moderately large sample size, a $p \leq 0.1$ was considered to indicate statistical significance for this interaction analysis. To further control for potential immortal time bias due to the time between metastasis diagnosis and metastasectomy, we finally performed landmark analyses with the landmark set at 3 and 6 months after diagnosis of metastases [36–39]. The full analysis code is available on request from FP.

Results

Baseline characteristics

The median age of the cohort at diagnosis of metachronous metastases was 65 years [25th–75th percentile: 50–75], and 55 patients (41%) were female. Further patient characteristics are found in Table 1.

On average, patients developed metastatic disease after a median follow-up of 11 months (IQR: 4–20 months). Ninety-nine patients first presented with lung metastases (73%), 21 with metastases to soft tissues and lymph nodes (16%) and 7 patients with metastases to bone (5%). Furthermore, 5 patients had skip lesions (4%) and 2 patients presented with intestinal metastases (1%).

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Information on location of metastases was missing in one patient (1%). Fifty-one patients had one metastatic lesion only (38%) while 84 patients presented with multiple metastases (62%). Fifty-nine patients developed further metastases after diagnosis of the first metastasis (44%).

Of the 99 patients with primary metastases to the lungs, 28 presented with a singular pulmonary nodule (28%) and 71 with multiple lesions (72%). Forty-seven patients had pulmonary nodules restricted to one side (48%) and 51 patients had metastatic lesions in both lungs (52%). In one patient, the involvement of the other side was uncertain.

Altogether, 67 patients (50%) were not treated surgically, of whom 32 received best supportive care (BSC) and 35 were administered CTX ± RTX. The remaining 68 patients underwent surgery (50%, Supplementary Table 2). Surgical interventions in the metastatic setting included wedge-resections (n = 16, 23%) and lobectomies (n = 28, 41%) of lung metastases, as well as (lymph node) extirpations (n = 10, 15%) and resections (n = 14, 21%) for peripheral metastases.

As expected, patients in the surgical group had a significantly higher baseline prevalence of favourable prognostic factors as compared to patients in the non-surgery group. For example, patients who underwent surgery had less metastatic lesions (median: 1 vs. 6 [SMD = 0.96]), a better ECOG performance status (median: 0.5 vs. 1 [SMD = 0.54]), and higher haemoglobin levels (median: 13.5 vs. 12.6 g/dL [SMD = 0.57], Table 1).

After the diagnosis of metachronous metastases, patients were followed up for a median interval of 4.9 years (range: 1 day–16.6 years). Seventy-five percent and 25% of the cohort were followed up for at least 1.9 years and 9.3 years, respectively. During follow-up we observed 89 deaths (66%), corresponding to 1-, 5-, and 10-year OS estimates of 63%, 24%, and 15% (Supplementary Figure 2). Seventy-three (82%) of these 89 deaths were due to disease progression, five deaths (6%) were due to other causes, while cause of death was unknown in 11 cases (12%). Prognostic factors for OS in the univariate setting are reported in Table 2. The strongest univariable predictors of worse OS were higher ECOG performance status, upper limb tumour location, a higher number of metastases, the presence of brain metastases, anaemia, and hypoalbuminaemia, respectively.

Surgery and OS in metachronous metastases of STS

In the unadjusted analysis, OS was significantly longer in those 68 patients who had undergone surgical interventions compared to the 67 patients who had not (Fig. 1). One-, 5-, and 10-year OS-estimates were 83%, 34% and 23% in the surgery group, and 38%, 11% and 4% in the non-surgery group, respectively (log-rank-p<0.0001). Median OS was 2.7 years since diagnosis of first metastasis (95% CI: 1.6–3.9) in the surgery group, and 0.8 years (95% CI: 0.4–1.2) in the non-surgery group, respectively.

To account for the significantly higher prevalence of favourable prognostic factors in the surgery group (consistent with a non-random assignment to the two treatment groups), we predicted a propensity score and an inverse-probability-of-treatment-weight (IPTW, see Supplementary Table 1 and Supplementary Fig. 3A, B). Re-weighting of the data removed nearly all imbalances in key prognostic variables between the two groups, except for albumin (Table 1). For example, the SMD for the number of metastatic lesions was reduced from 0.96 to 0.20, for ECOG performance status from 0.54 to 0.27, and for haemoglobin from 0.57 to 0.22, respectively.

The favourable association between any surgical intervention and lower risk of death prevailed after re-weighting the data for the IPTW. In detail, the IPTW-weighted 1-, 5-, and 10-year OS-estimates were 86%, 31% and 17% in the surgery group, and 39%, 10% and 3% in the non-surgery group, respectively (log-rank-p<0.0001, Fig. 2). The corresponding IPTW-adjusted median OS estimates were 3.3 years and 0.9 years in the surgery and non-surgery group, respectively. Further multivariable adjustment for other relevant predictors of worse OS, such as poor ECOG performance status, higher number of metastases, low haemoglobin and low albumin did not alter this association (adjusted HR for metastasectomy treated as a time-dependent variable = 0.55, 0.30–0.98, Table 3).

Exploration of potential predictive factors for benefit from metastasectomy

We fitted interactions between treatment assignment and selected clinical covariates within IPTW-adjusted Cox-models to

Table 2
Univariable Analysis of Prognostic Factors for Overall Survival (OS).

Variable	HR	95% CI	p-value
Female gender	0.99	0.65–1.52	0.971
Age at metastasis (per 5 years increase)	1.03	0.97–1.09	0.414
ECOG performance status (per 1 point increase)	1.81	1.29–2.56	**0.001**
Primary tumour location			
Upper limb	Ref.	Ref.	**0.016**
Lower limb	0.55	0.35–0.87	
Trunk	1.25	0.52–3.01	
Tumour grade G3	1.49	0.86–2.57	0.155
Multiple metastases	1.47	0.95–2.27	0.081
Number of metastases* (per 1 metastasis increase)	1.07	1.00–1.13	**0.039**
Time to 1st metastasis (per 5 months increase**)	0.98	0.93–1.04	0.546
Metastasis location			
Any lung metastasis	2.05	1.19–3.55	**0.010**
Any soft tissue and/or lymph node metastasis	0.62	0.36–1.06	0.079
Any bone metastasis	1.35	0.72–2.55	0.354
Any solid organ metastasis (excluding lung and brain)	1.32	0.70–2.49	0.388
Any brain metastasis	1.97	1.07–3.63	**0.030**
Limb amputation upon primary surgery	1.68	0.88–3.24	0.118
Haemoglobin (per 1 g/dL increase)	0.87	0.78–0.98	**0.019**
Albumin (per 1 g/dL increase)	0.56	0.35–0.89	**0.016**

Estimates were obtained with univariable Cox proportional hazards models in multiply-imputed data. p-values in bold are statistically significant; *Number of metastases was truncated at 9 metastases in case of "innumerable" metastases according to radiology report; ** The date of primary surgery was used as the baseline date for calculation of the "time to 1st metastasis" variable. Abbreviations: HR – Hazard ratio, 95% CI – 95% confidence interval, p – Wald-test p-value, ECOG – Eastern Cooperative Oncology Group.

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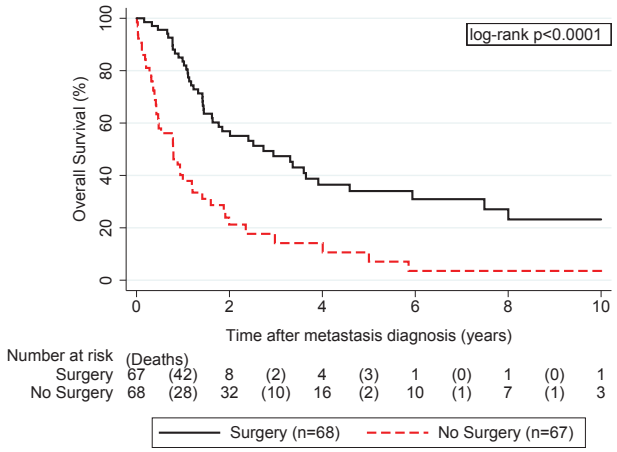

Fig. 1. Crude Kaplan-Meier Overall Survival (OS) functions by treatment group for metastasis. Numbers in round brackets in the risk table report the number of deaths in the respective time interval.

identify potential subgroups with a very high or low benefit from surgical intervention (Table 4). In this analysis of predictive markers, the potential benefit of surgical intervention was consistent across important clinical subgroups such as patients (1) with and without poor ECOG performance status, (2) a metachronous interval of ≥ or < 12 months or (3) an age ≥ or <70 years at metastasis diagnosis. Importantly, with the modified threshold of statistical significance of $p < 0.1$ for this interaction analysis, the benefit of metastasectomy was stronger in patients with a single metastasis (HR = 0.21) than in patients with multiple metastases (HR = 0.44, p for interaction = 0.096). Although not statistically significant, the regression coefficients at least pointed in the direction of metastasectomy being slightly more efficacious in patients with a metachronous interval of at least 12 months.

Landmark analysis

The median time between metastasis diagnosis and metastasectomy was 1.7 months [IQR: 0.7–3.6]. In previous analyses, this potential immortal time bias was controlled for by treating metastasectomy as a time-dependent covariable. In a sensitivity

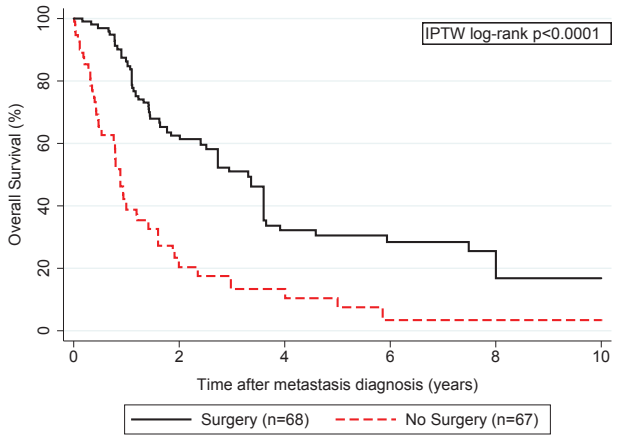

Fig. 2. Inverse-probability-of-treatment-weighted (IPTW) Kaplan-Meier Overall Survival (OS) functions by treatment group. No risk table is displayed because the numbers of patients at specific time points are non-integers in an IPTW-weighted sample.

Table 3
Multivariable IPTW-weighted analysis of Overall Survival (OS).

Variable	HR	95% CI	p-value
Multivariable Cox regression Model			
Metastasectomy as a time-dependent covariate	0.55	0.30–0.98	**0.043**
ECOG performance status (per 1 point increase)	1.72	1.22–2.42	**0.002**
Number of metastases* (per 1 metastasis increase)	0.99	0.91–1.07	0.730
Haemoglobin (per 1 g/dL increase)	1.00	0.83–1.20	0.984
Albumin (per 1 g/dL increase)	0.81	0.39–1.65	0.541

Multivariable Model#1 is a multivariable Cox model, which was weighted with the Inverse-Probability-of-Treatment-Weight (IPTW). Multivariable Model #2 is also an IPTW-weighted multivariable Cox Model. with, metastasectomy was treated as a time-dependent covariate Both models were estimated from multiply-imputed data. p-values in bold are statistically significant; *Number of metastases was truncated at 9 metastases in case of "innumerable" metastases according to radiology report. Abbreviations: HR – Hazard ratio, 95% CI – 95% confidence interval, p – Wald-test p-value, ECOG – Eastern Cooperative Oncology Group.

analysis of immortal time bias, we performed IPTW-–weighted landmark analyses with landmarks at 3 and 6 months after metastasis diagnosis, respectively. With a landmark at 3 months, the 5-year OS estimates were 27.8% and 14.5% in the surgery and non-surgery group, respectively (Fig. 3A), and similar results were observed for a landmark at 6 months (Fig. 3B).

Discussion

Previous non-controlled observational studies have reported very favourable survival outcomes in patients with metastatic STS who underwent metastasectomy [6–23]. However, whether these encouraging results are attributable to metastasectomy or simply due to selection bias has so far not been adequately proven [25–27]. Aiming to fill this gap of evidence, we performed a comparative effectiveness analysis of surgery versus non-surgery for patients with metachronous metastasis of STS. Using propensity score methods, landmark analysis, and time-dependent Cox modelling to control for selection and immortal time bias, we observed that metastasectomy was associated with prolonged overall survival. In the absence of randomisation, these data support the hypothesis that surgery may improve survival of patients with metachronous metastases of STS.

An important aspect of STS-management is the therapeutic approach in the metastatic setting. Depending on the patients' general condition, site of metastases and overall tumour load, non-surgical interventions (i.e. BSC, CTX, RTX) or a surgical approach may be chosen [40,41]. In our cohort, half of the patients underwent a surgical intervention for their metastases, about one quarter received RTX ± CTX and another quarter received BSC. Consistent with the literature, the most common location of primary metastasis in our cohort was the lung, followed by soft tissues and lymph nodes [6,34,42,43].

In the univariate setting, patients undergoing surgical interventions had significantly better 5- and 10-year survival of 34% and 23% vs. 11% and 4% for the non-surgery group (BSC ± RTX ± CTX), respectively. These data are in line with the observations made by *Billingsley* et al. in a large retrospective cohort of STS-patients with pulmonary metastases [6].

Given the retrospective design of this study and the non-controlled design of many studies performed in the past [6–23,33,34,44,45], one may argue that the benefit of surgical intervention can be explained by favourable clinical parameters prevailing in the surgical-group. Indeed, patients undergoing surgical resection in our cohort presented with fewer metastases and a longer interval between initial surgery and occurrence of metastasis, and also had a better ECOG performance status and higher haemoglobin level at the time of treatment decision. These features

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Table 4
Predictive factors for overall survival (OS) benefit from metastasectomy – Interaction analysis.

	Hazard ratio	95% CI	Interaction p-value
ECOG performance status: 0 points	0.43	0.18–1.02	0.373
ECOG performance status: 1–2 points	0.27	0.13–0.42	
Time between primary surgery and metastasis onset <12 months	0.49	0.21–0.78	0.154
Time between primary surgery and metastasis onset ≥12 months	0.27	0.14–0.50	
Age < 70 years	0.36	0.21–0.62	0.678
Age ≥ 70 years	0.30	0.15–0.59	
Number of metastases: Single	0.21	0.10–0.43	0.096
Number of metastases: Multiple	0.44	0.26–0.77	

All estimates were obtained from IPTW-weighted Cox models after multiple imputations of missing data. Hazard ratios are for metastasectomy versus non-invasive management. Because interaction analyses generally have low power, a p-value of <0.1 was considered to indicate statistical significance. Abbreviations: ECOG – Eastern Cooperative Oncology Group.

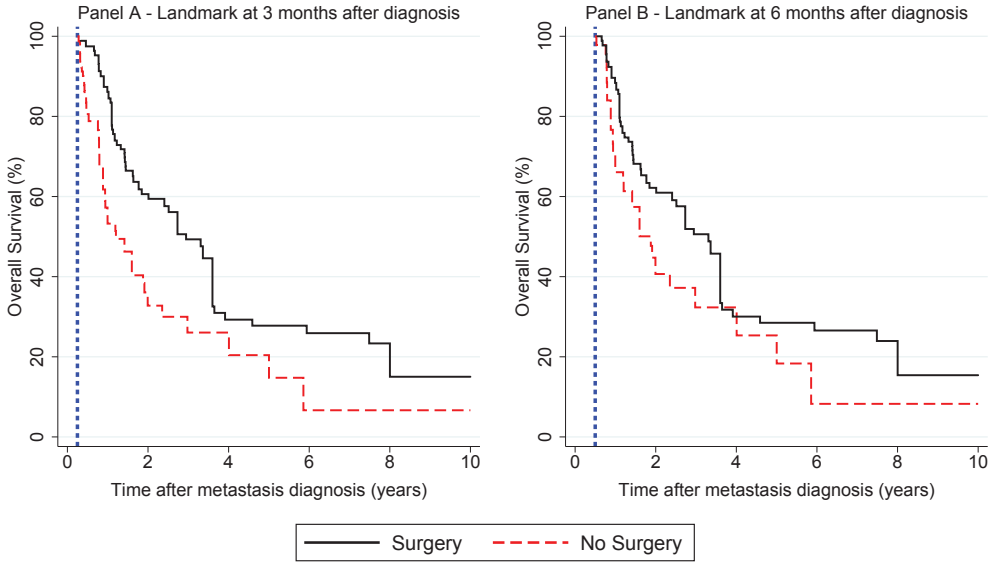

Fig. 3. Landmark analysis of estimated Overall Survival (OS) by treatment group. Survivor functions were predicted from univariable Cox models. Panel A: Landmark point (short-dashed blue vertical line) set at 3 months after metastasis diagnosis. Panel B: Landmark point set at 6 months after metastasis diagnosis.

have already been identified as prognostic factors for prolonged survival of STS-patients with metastatic disease [4,33,34].

Therefore, we used a propensity score approach with IPTW-weighting to compensate for differences at treatment decision between patients undergoing surgical interventions and those who did not. After weighting all patients for the IPTW-score and re-calculating the uni- and multivariable time-to-death analyses, any surgical intervention remained a significant positive prognostic factor for post-metastasis-survival independent of ECOG performance status, number of metastases, haemoglobin- and albumin-levels. The magnitude of association of surgery with OS was large, suggesting that patients with metachronous metastases from STS may gain more than two years in median OS from metastasectomy. The potential benefit of surgery even prevailed in the landmark and time-dependent Cox regression analyses in which immortal time bias due to time between metastasis diagnosis and surgery was accounted for.

By fitting interactions between clinically relevant baseline covariates and treatment assignment, we aimed to identify predictive markers of benefit from surgery. This analysis suggested that the benefit of surgery was greater for patients with singular metastasis at the time of surgery, but was otherwise consistent across several clinically-meaningful subgroups.

Our study is not without limitations. Due to its retrospective design, the study depends on the quality and availability of medical records, pathology reports and medical images. Moreover, the validity of the IPTW analysis depends on the difficult-to-test assumption that the propensity score model is correctly specified [35]. Furthermore, other hidden confounding factors, such as comorbidities not covered by the ECOG performance status, could not be considered in the calculations. Otherwise, a major strength of our analysis is that all study patients were drawn from established cohorts at Graz and Leiden that included all consecutive patients who had previously undergone resection with curative intent for localised STS. With this approach, we could reduce selection bias in both surgery and non-surgery groups.

Conclusion

This comparative effectiveness analysis of observational data using propensity score methods supports the hypothesis that surgery may be an efficacious treatment option for metachronous metastases of STS with a potentially sizeable benefit in terms of improving overall survival. Moreover, the potential benefit of surgical intervention appears to be consistent across clinically important subgroups, although surgery may be less efficacious in patients with multiple metastases. These data should be taken into account by clinicians treating sarcomas and their patients when planning treatment for metachronous metastases of STS.

Conflicts of interest statement

Florian Posch has received support in kind for any aspect by MSD Oncology, GWT TUD GmbH, PharmaMar, Novartis, Ipsen,

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejso.2018.06.019.

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Individualizing Follow-Up Strategies in High-Grade Soft Tissue Sarcoma with Flexible Parametric Competing Risk Regression Models

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Abstract: Currently, patients with extremity soft tissue sarcoma (eSTS) who have undergone curative resection are followed up by a heuristic approach, not covering individual patient risks. The aim of this study was to develop two flexible parametric competing risk regression models (FPCRRMs) for local recurrence (LR) and distant metastasis (DM), aiming at providing guidance on how to individually follow-up patients. Three thousand sixteen patients (1931 test, 1085 validation cohort) with high-grade eSTS were included in this retrospective, multicenter study. Histology (9 categories), grading (time-varying covariate), gender, age, tumor size, margins, (neo)adjuvant radiotherapy (RTX), and neoadjuvant chemotherapy (CTX) were used in the FPCRRMs and performance tested with Harrell-C-index. Median follow-up was 50 months (interquartile range: 23.3–95 months). Two hundred forty-two (12.5%) and 603 (31.2%) of test cohort patients developed LR and DM. Factors

significantly associated with LR were gender, size, histology, neo- and adjuvant RTX, and margins. Parameters associated with DM were margins, grading, gender, size, histology, and neoadjuvant RTX. C-statistics was computed for internal (C-index for LR: 0.705, for DM: 0.723) and external cohort (C-index for LR: 0.683, for DM: 0.772). Depending on clinical, pathological, and patient-related parameters, LR- and DM-risks vary. With the present model, implemented in the updated Personalised Sarcoma Care (PERSARC)-app, more individualized prediction of LR/DM-risks is made possible.

Keywords: soft tissue sarcoma; follow-up; flexible parametric competing risk regression model; local recurrence; distant metastasis

1. Introduction

Patients with high-grade extremity soft tissue sarcoma (eSTS) are at risk of developing local recurrences (LR) and even more so of developing distant metastases (DM) after having undergone surgical resection of the primary tumor [1–5]. These rates differ substantially per size, grade, and subtype [6]. Close follow-up regimens are currently used in order to detect LR and DM at stages where they are still potentially treatable by re-resection or metastasectomy, respectively [7]. There is no clear consensus when, by what means, and how often to perform follow-up in eSTS patients, with many centers and guidelines having introduced a heuristic approach: for the first 3 years after surgery, patients would be checked three or four times a year, then biannually for the following two years and annually thereafter [8,9].

Imposing all eSTS patients on these strict follow-up regimens has raised public, scientific, and health economic concerns over the last years. Numerous factors interact with the risk of developing LR or DM, such as histological STS-subtypes, surgical margins, tumor size, grade, administration of neo(adjuvant) radiotherapy (RTX) or chemotherapy (CTX), and patient-derived factors [1–4,10–12]. Consequently, the current approach of "one-size-fits-all" may not account for the unequal risk of recurrence in the heterogeneous eSTS population, involving an excessive number of surveillance imaging, possibly leading to unnecessary delivery of imaging-induced radiation exposure, and the inherent burden for radiology departments, as well as inappropriately refraining from it, a high number of outpatient visits and financial costs and emotional stress for each individual patient [13]. However, an evaluation of prognostic factors for LR and DM taking into consideration the time-varying rate for the occurrence of events in a multicenter cohort, including important patient-(i.e., age, gender), tumor-(e.g., size, grade, histological subtype), and treatment-related features (e.g., margins, (neo)adjuvant CTX/RTX), is currently missing.

Therefore, the aim of the present study was to estimate and validate two models predicting risks of LR and DM over the first 5 years of follow-up by applying flexible parametric competing risk regression modeling in a large, multicenter cohort of patients with primary localized high-grade eSTS. The results have been implemented into the Personalised Sarcoma Care (PERSARC)-app [14] for Individualized Sarcoma Care and follow-up.

2. Results

Patients had undergone surgery with curative intent between January 1994 and October 2014 for the test cohort and between January 2000 and December 2013 for the validation cohort, respectively. There was a slight male predominance (n = 1038; 53.8%) and the median patient age was 59 years (interquartile range (IQR): 44.7–70 years). With 55.8%, 17.9%, and 13.9%, most tumors in the test cohort were located in the thigh (n = 1078), upper arm (n = 346), and lower leg (n = 268), while the lower arm (n = 142), the foot or toes (n = 65), and the hand or fingers (n = 32) were affected in 7.3%, 3.4%, and 1.7%, respectively. Further clinicopathological features for both the test and validation cohort are listed in Table 1.

Table 1. Patient characteristics and clinical, pathological, and treatment-related parameters.

Variables		Test Cohort (n = 1931)		Validation Cohort (n = 1085)		
		N (%)	Missing (%)	N (%)	Missing (%)	p-Value *
Age (continuous; years; median + IQR)		59 (44.7–70)	45 (2.3)	61 (47–74)	0 (0.0)	**<0.0001**
Gender	Male	1038 (53.8)	0 (0.0)	615 (56.7)	0 (0.0)	0.121
	Female	893 (46.2)		470 (43.3)		
Tumor Location	Upper Extremity	520 (26.9)	1 (0.05)	312 (28.8)	0 (0.0)	0.285
	Lower Extremity	1410 (73.1)		773 (71.2)		
Depth	Epifascial	518 (26.9)	2 (0.1)	291 (26.8)	0 (0.0)	0.984
	Subfascial	1411 (73.1)		794 (73.2)		
Tumor Size (continuous; cm; median + IQR)		7 (4–11)	30 (1.6)	7.5 (5–12)	5 (0.5)	**0.026**
Histology	Myxoid liposarcoma	222 (11.6)	16 (0.8)	111 (10.2)	0 (0.0)	**<0.0001**
	MPNST	83 (4.3)		43 (4.0)		
	Myxofibrosarcoma	451(23.6)		104 (9.6)		
	Synovial Sarcoma	174 (9.1)		79 (7.3)		
	UPS	325 (17.0)		375 (34.6)		
	Angiosarcoma/Vascular Sarcoma	22 (1.1)		20 (1.8)		
	Dedifferentiated/Pleomorphic Liposarcoma	141 (7.4)		85 (7.8)		
	Leiomyosarcoma	221 (11.5)		118 (10.9)		
	Others	276 (14.4)		150 (13.8)		
Grading	G2	719 (37.8)	30 (1.6)	382 (35.8)	19 (1.8)	0.282
	G3	1182 (62.2)		684 (64.2)		
Margins	R0	1494 (77.4)	0 (0.0)	768 (70.8)	0 (0.0)	**<0.0001**
	R1/2	437 (22.6)		317 (29.2)		
CTX	No	1408 (73.0)	1 (0. 05)	1039 (95.8)	0 (0.0)	**<0.0001**
	Neoadjuvant	262 (13.6)		40 (3.7)		
	Adjuvant	209 (10.8)		6 (0.6)		
	Neoadjuvant + Adjuvant	51 (2.6)		0 (0.0)		
RTX	No	619 (32.9)	50 (2.6)	335 (30.9)	0 (0.0)	**<0.0001**
	Neoadjuvant	303 (16.1)		460 (42.4)		
	Adjuvant	956 (50.8)		275 (25.4)		
	Neoadjuvant + Adjuvant	3 (0.2)		15 (1.4)		
Follow-up (continuous; months; median + IQR)		50 (23.3–95)	11 (0.6)	56 (21–91)	0 (0.0)	0.254

* p-values calculated with Wilcoxon rank sum test for continuous variables, with chi2-test for binary and categorical variables. p-values in bold are considered statistically significant. Abbreviations: CTX = chemotherapy. IQR = interquartile range. MPNST = Malignant Peripheral Nerve Sheat Tumor. RTX = radiotherapy. UPS = Undifferentiated pleiomorphic sarcoma.

Five- and 10-year overall survival (OS) was 73.6% (95%CI: 71.3–75.7) and 62.7% (95%CI: 59.8–65.5) in the test cohort. In the validation cohort, 5- and 10-year OS were 64.9% (95%CI: 61.8–67.8) and 52.9% (95%CI: 48.9–56.8), respectively. Gender, tumor size, histological subtype (except for angiosarcoma/vascular sarcoma (p = 0.127) and dedifferentiated/pleomorphic liposarcoma (p = 0.254), margins, neoadjuvant and adjuvant RTX, as well as adjuvant CTX (all $p < 0.05$) had a significant influence on risk of LR in the stepwise backward selection of the Fine and Gray model. Grading as a time-dependent effect was kept in the model (p = 0.108), while age (p = 0.082) and neoadjuvant CTX (p = 0.214) were excluded. Consequently, gender, grading, tumor size, neoadjuvant and adjuvant RTX, histological subtype, and adjuvant CTX were included in the flexible parametric competing risk regression model (Table 2).

The subdistribution hazard and cumulative incidence functions for LR using ten clinical examples are shown in Figure 1A,B (definition of these examples found in Table S1, together with estimated conditional risks of LR). As an example, a male patient with a G2 myxofibrosarcoma sized 10 cm, with contaminated resection margins (R1/2), no neoadjuvant or adjuvant RTX, and no adjuvant CTX, has a significantly increased risk of developing LR, especially within the first 15 months of follow-up (=clinical example IX). On the other hand, a male patient with a 6 cm large, G3 synovial sarcoma, resected with clear margins (R0), without adjuvant CTX or (neo-)adjuvant RTX, has a moderate LR risk during the first 15 months, and an estimated low risk thereafter (=clinical example VIII).

Table 2. Estimated coefficients along with their 95% confidence intervals for local recurrence.

Variables		Coefficient	95%-CI		*p*-Value
			Lower	*Upper*	
Local Recurrence					
Gender	Male	1			**0.011**
	Female	0.698	0.529	0.921	
Grading	G2	1			0.199
	G3	0.816	0.598	1.113	
Tumor size		1.026	1.004	1.049	**0.019**
Margins	R0	1			**<0.001**
	R1/R2	2.761	2.021	3.774	
Histology	Myxoid Liposarcoma	1			
	MPNST	4.227	1.837	9.729	**0.001**
	Myxofibrosarcoma	4.156	2.056	8.400	**<0.001**
	Synovial Sarcoma	3.116	1.429	7.014	**0.005**
	UPS	3.373	1.620	7.025	**0.001**
	Angiosarcoma/Vascular Sarcoma	3.316	0.981	12.341	0.074
	Dedifferentiated/Pleomorphic Liposarcoma	1.727	0.719	4.143	0.221
	Leiomyosarcoma	2.779	1.294	5.966	**0.009**
	Others	2.385	1.123	5.065	**0.024**
Neoadjuvant RTX	No	1			**<0.001**
	Yes	0.298	0.178	0.494	
Adjuvant RTX	No	1			**0.001**
	Yes	0.603	0.447	0.814	
Adjuvant CTX	No	1			**0.008**
	Yes	*1.711*	*1.154*	*2.538*	
Restricted cubic spline 1		2.104	1.851	2.392	**<0.001**
Restricted cubic spline 2		1.332	1.230	1.442	**<0.001**
Restricted cubic spline 3		0.980	0.937	1.026	0.391
Restricted cubic spline for time-dependent effect of grading		0.944	0.813	1.096	0.449
Constant		0.048	0.024	0.097	**<0.001**
Death					
Gender	Male	1			**0.005**
	Female	0.736	0.595	0.910	
Grading	G2	1			**<0.001**
	G3	2.215	1.655	2.964	
Tumor size		1.065	1.048	1.081	**<0.001**
Margins	R0	1			0.296
	R1/R2	1.153	0.883	1.057	
Histology	Myxoid Liposarcoma	1			
	MPNST	1.205	0.664	2.187	0.540
	Myxofibrosarcoma	1.208	0.795	1.836	0.375
	Synovial Sarcoma	1.461	0.888	2.404	0.136
	UPS	1.150	0.753	1.758	0.517
	Angiosarcoma/Vascular Sarcoma	4.729	2.335	9.580	**<0.001**
	Dedifferentiated/Pleomorphic Liposarcoma	1.420	0.863	2.338	0.167
	Leiomyosarcoma	2.154	1.402	3.309	**<0.001**
	Others	1.516	0.975	2.356	0.065
Neoadjuvant RTX	No	1			**0.007**
	Yes	1.543	1.127	2.111	
Adjuvant RTX	No	1			0.296
	Yes	1.145	0.888	1.476	
Adjuvant CTX	No	1			**0.022**
	Yes	0.679	0.488	0.946	
Restricted cubic spline 1		4.220	3.393	5.250	**<0.001**
Restricted cubic spline 2		1.487	1.329	1.663	**<0.001**
Restricted cubic spline 3		0.965	0.921	1.011	0.139
Restricted cubic spline for time-dependent effect of grading		0.714	0.580	0.889	**0.002**
Constant		0.050	0.032	0.078	**<0.001**

p-values in bold are considered statistically significant. CI = Confidence interval. RTX = radiotherapy. CTX = chemotherapy. UPS = undifferentiated pleomorphic sarcoma. MPNST = Malignant Peripheral Nerve Sheat Tumour.

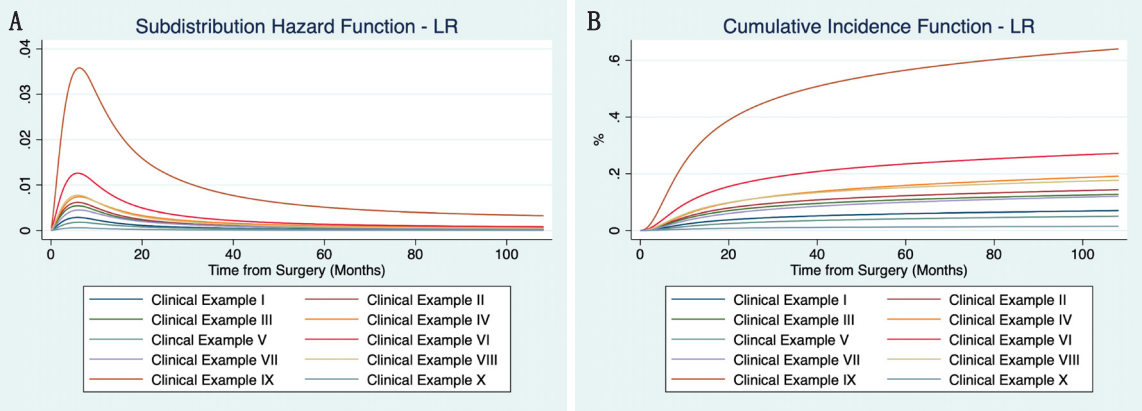

Figure 1. Subdistribution hazard function (**A**) and cumulative incidence function (**B**) of the flexible parametric competing risk regression model for local recurrence using ten clinical examples (constellation of parameters shown in Tables S1 and S2).

In the stepwise backward selection of the Fine and Gray model for distant metastasis (DM) histological subtype (except for myxofibrosarcoma ($p = 0.641$), angiosarcoma/vascular sarcoma ($p = 0.067$) and dedifferentiated/pleomorphic liposarcoma ($p = 0.592$), grading, tumor size, gender, margins, and neoadjuvant RTX (all $p < 0.05$) were significantly associated with development of metastases. Age ($p = 0.852$), adjuvant RTX ($p = 0.116$), neoadjuvant CTX ($p = 0.095$), and adjuvant CTX ($p = 0.536$) were excluded via stepwise backward selection. Thus, histological subtype, grading, tumor size, margins, gender, and neoadjuvant RTX were included in the flexible parametric competing risk regression model (Table 3).

In Figure 2A,B, subdistribution hazard and cumulative incidence functions for DM (using the same ten clinical examples as in Figure 1A,B) are shown. Once again referring to clinical examples IX (male, myxofibrosarcoma, G2, 10 cm, R1/2-margins, no neoadjuvant RTX) and VIII (male, synovial sarcoma, G3, 6cm, R0-margins, no neoadjuvant RTX), risk of DM is lower in clinical example IX in comparison to clinical example VI, while LR-risks are just the opposite, highlighting the importance of an individualized follow-up strategy.

The conditional risks of these ten clinical examples changing over time estimated based on the models presented above are provided in Table S1 for LR and Table S2 for DM. Conditional risks for all possible combinations of prognostic factors may be estimated and have been implemented in the updated version of the PERSARC app.

The Harrell C index for LR was equal to 0.705 and 0.683 for the internal and external cohort, respectively. For DM, Harrell C statistics was equal to 0.723 for the internal cohort and 0.772 for the external cohort. Calibration plots for LR (Figure 3A) using test and validation cohort showed that the LR model tended to underestimate the actual patient risk, especially in the validation cohort. On the other hand, calibration plots for DM with test and validation cohort (Figure 3B) showed very good model calibration.

Table 3. Estimated coefficients along with their 95% confidence intervals for distant metastasis.

		Coefficient	95%-CI		*p*-Value
			Lower	Upper	
Distant Metastasis					
Gender	**Male**	1			**<0.001**
	Female	0.720	0.605	0.857	
Grading	G2	1			**<0.001**
	G3	1.737	1.412	2.136	
Tumor size		1.069	1.056	1.083	**<0.001**
Margins	R0	1			**0.006**
	R1/R2	1.347	1.087	1.669	
Histology	Myxoid Liposarcoma	1			
	MPNST	1.825	1.158	2.875	**0.009**
	Myxofibrosarcoma	1.064	0.750	1.508	0.729
	Synovial Sarcoma	1.986	1.343	3.976	**0.001**
	UPS	1.445	1.033	2.022	**0.032**
	Angiosarcoma/Vascular Sarcoma	2.016	1.022	3.797	**0.043**
	Dedifferentiated/Pleomorphic Liposarcoma	1.209	0.786	1.861	0.387
	Leiomyosarcoma	2.689	1.900	3.797	**<0.001**
	Other	1.835	1.293	2.604	**0.001**
Neoadjuvant RTX	No	1			**0.005**
	Yes	1.351	1.097	1.663	
Restricted cubic spline 1		2.928	2.591	3.308	**<0.001**
Restricted cubic spline 2		1.458	1.374	1.547	**<0.001**
Restricted cubic spline 3		0.965	0.926	1.006	0.096
Restricted cubic spline 4		1.040	1.020	1.062	**<0.001**
Restricted cubic spline 5		0.995	0.982	1.008	**0.427**
Restricted cubic spline for time-dependent effect of grading		0.723	0.640	0.817	**<0.001**
Constant		0.108	0.078	0.149	**<0.001**
Death					
Gender	Male	1			0.864
	Female	0.968	0.666	1.407	
Grading	G2	1			**0.018**
	G3	1.873	1.116	3.145	
Tumor size		1.023	0.997	1.050	0.087
Margins	R0	1			0.198
	R1/R2	1.378	0.846	2.244	
Histology	Myxoid Liposarcoma	1			
	MPNST	2.506	0.844	7.442	0.098
	Myxofibrosarcoma	3.136	1.325	7.418	**0.009**
	Synovial Sarcoma	0.600	0.150	2.416	0.472
	UPS	1.781	0.714	4.443	0.216
	Angiosarcoma/Vascular Sarcoma	11.165 *	3.507 *	35.542 *	**<0.001** *
	Dedifferentiated/Pleomorphic Liposarcoma	3.331	1.259	8.812	**0.015**
	Leiomyosarcoma	1.798	0.675	4.782	0.241
	Other	2.408	0.963	4.782	0.060
Neoadjuvant RTX	No	1			**0.048**
	Yes	0.541	0.295	0.993	
Restricted cubic spline 1		3.604	2.494	5.211	**<0.001**
Restricted cubic spline 2		1.270	1.060	1.523	**0.010**
Restricted cubic spline 3		0.952	0.863	1.049	0.316
Restricted cubic spline 4		0.953	0.908	1.001	0.057
Restricted cubic spline 5		0.974	0.569	1.199	0.097
Restricted cubic spline for time-dependent effect of grading		0.826	0.569	1.199	0.314
Constant		0.010	0.004	0.025	**<0.001**

p-values in bold are considered statistically significant; CI = Confidence interval. RTX = radiotherapy. CTX = chemotherapy. UPS = undifferentiated pleomorphic sarcoma. * too few events.

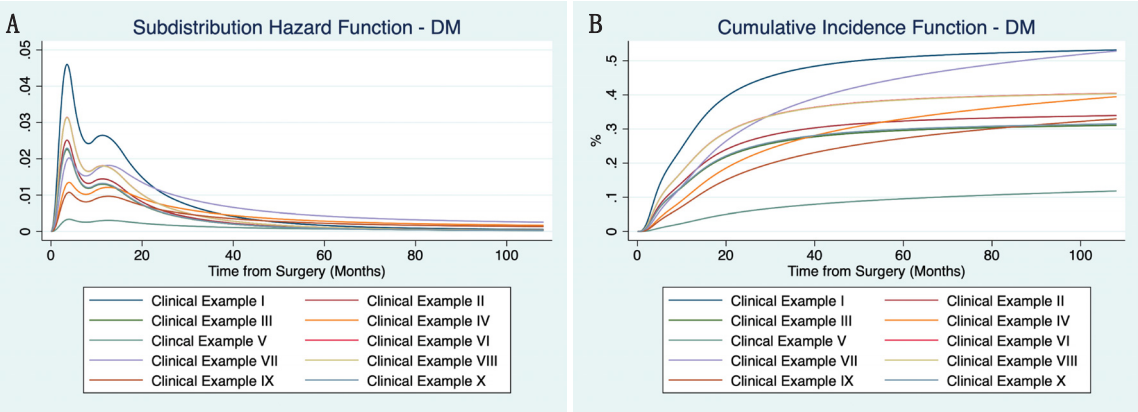

Figure 2. Subdistribution hazard function (**A**) and cumulative incidence function (**B**) of the flexible parametric competing risk regression model for distant metastasis using the same ten clinical examples as in Figure 1A,B (constellation of parameters shown in Tables S1 and S2).

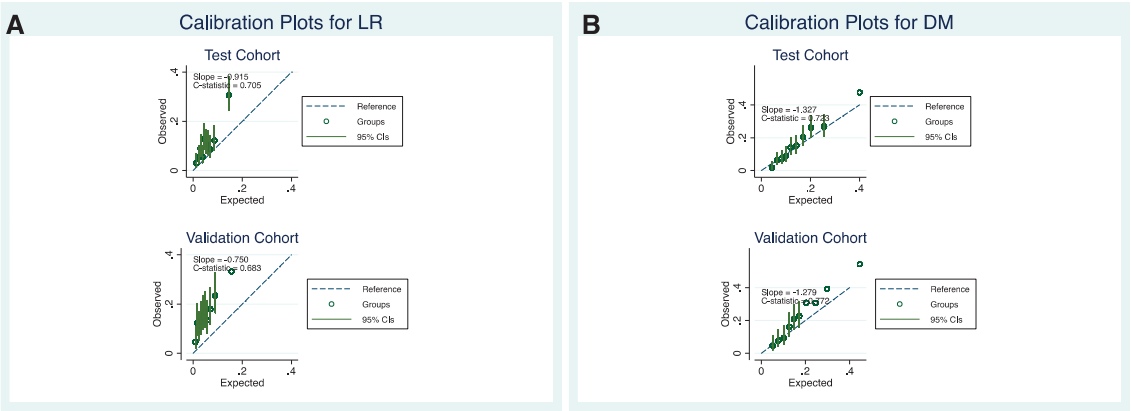

Figure 3. Calibration plots for the flexible parametric competing risk regression model regarding local recurrence (**A**) and distant metastasis (**B**) for the test (top) and validation cohort (bottom).

3. Discussion

In the present retrospective multicenter cohort study, flexible parametric competing risk regression modeling was applied in order to estimate individual three-to-six-month risks for local recurrence and distant metastasis during the first 5 years of follow-up in patients undergoing curative resection for high-grade extremity soft tissue sarcoma. It offers an evidence-based opportunity to individually schedule follow-up visits instead of adhering to calendar-based guidelines [8,9]. The number of radiological investigations for assessing disease status, especially after R0 resections and taking histological subtype into account, could be significantly restricted, reducing patient- and healthcare burden. The advantage of using flexible parametric competing risk regression models to estimate LR- and DM-risks in eSTS-patients is based on the fact that these rates strongly vary upon time (i.e., they do not constantly increase or decrease). To overcome this issue, flexible parametric competing risk regression models represent the baseline distribution function as a restricted cubic spline function of log time instead of a linear function of log time [15]. Moreover, it allows smooth estimation of both the cause-specific hazard rates and cumulative incidence functions. Both models performed well at internal and external calibration, with c-indexes comparable to previously published studies [14,16].

One of the limitations of the present study is its retrospective design, resulting in possible selection biases regarding diagnosis, treatment, and follow-up of patients included, due to slightly differing policies at the respective centers. By incorporating these factors in the statistical models, we aimed at reducing this bias. Moreover, during the study period, several histological STS-subtypes were

reclassified (i.e., malignant fibrous histiocytoma to undifferentiated pleomorphic sarcoma). At some, but not all, participating centers, all histological diagnoses had been reevaluated by pathologists and, if applicable, reclassified according to the current classification systems. In order to limit the impact of this limitation, we only included patients treated in tertiary reference sarcoma centers with experienced and dedicated sarcoma pathologists.

Another limitation of the present study is that the models were developed based on patient cohorts from experienced, tertiary tumor centers. This implies that generalizability of the predicted risks to patients not treated at such centers has to be questioned. Moreover, considering that we did only include patients with high-grade (G2/3), primary eSTS who had undergone surgery with curative intent, the risks estimated are not applicable to patients with low-grade disease or metastases at initial presentation. Furthermore, estimated risks of the current models should be applied with caution after patients have already developed an event (i.e., LR or DM) during follow-up. Due to the retrospective design of the study, not all variables could be ascertained in every patient, thus potentially reducing the statistical power. However, it can be assumed that in this large patient collective, missing data may have little to no bias to the conclusions made, wherefore cases with missing information on clinical and/or pathological variables were not excluded [17].

As outlined in the introduction, current follow-up strategies follow a heuristic approach, with 3- to 4-months intervals for the first three years, followed by biannual check-ups until the end of the 5th year and annual appointments thereafter [8,9].

In clinical practice, it is not only of interest to estimate a patient's cumulative risk after a specific period of time but also to know about the conditional risks from one follow-up appointment to the next, in case no event had occurred. We addressed this question by calculating conditional risks for LR and DM depending on different, clinically relevant, examples. Notably, the present model allows risk prediction at any constellation of variables, which are at the moment included in the updated PERSARC app. This app allows the patient's individualized risk of LR and DM to be estimated by entering relevant prognostic parameters, such as histological subtype, tumor size, and resection margins. With the estimated event-risk in time, physicians and patients may decide together when the next follow-up examination should be scheduled. In light of the heterogeneity of eSTS with part significantly differing outcomes, estimated event risks would facilitate planning of an individualized follow-up protocol for each patient.

Arbitrary thresholds of 4% for LR and 2% for DM were chosen in the present study to be of clinical "relevance", considering that LR is usually detected during clinical examination or even noticed by patients themselves, while DM (most commonly to the lungs) require visualization by chest x-ray or thoraci computed tomography (CT) scan [18,19]. However, thresholds should be changed on patients' preference and clinical significance.

Previously published studies have well-investigated risks of LR, DM, and overall survival (OS) in large, retrospective cohorts of patients with eSTS [14,16,20,21]. The nomogram for OS by Kattan et al. [21] in 2002 and the two more recent nomograms for DM and OS by Callegaro et al. [16] published in 2016 added significant value to predict individual patient risks. Both studies used Cox-regression models as the basis for their nomograms. In comparison to Cox-regression models, flexible parametric competing risk regression models have a major advantage; while the Cox-regression models only estimate the relative effects (i.e., hazard rates), flexible parametric competing risk regression models estimate the baseline hazard using restricted cubic splines [22]. The cumulative incidence functions of LR and DM predicted from flexible parametric competing risk regression models demonstrate the clear variance in event rates. By applying a flexible parametric competing risk regression model, we aimed at incorporating non-constant hazards, time-varying covariates, and death as the competing event in order to obtain a robust, comprehensible, and accurate prediction of individual patient risks. Moreover, with the clinical examples provided, the risk peaks during the first year of follow-up is clearly visible. Although appointments may be safely skipped in some patients due to very low risks of LR and/or DM, others would benefit from closer follow-up intervals.

Potentially due to the application of the present statistical model, interesting results emerged: Female gender was independently associated with a significantly lower risk of LR and DM. An association between gender and overall survival (OS) has been observed by Maretty-Nielsen et al. and Wu et al. [2,23]. However, an association between gender and LR-free as well as DM-free survival has not been described thus far [24]. Moreover, tumor grading, which is a well-known prognostic factor of LR, was not significantly associated with an altered risk in the current flexible parametric competing risk regression model. This may be explained by the fact that patients with usually fast-growing, highly-aggressive G3 tumors will present with LR at early time points, while in those with relatively slower-growing G2 tumors, LR is most probably detected at a later date. This hypothesis is corroborated by the fact that grading did not meet the proportional hazards assumption, wherefore it was treated as a time-varying covariate. On the other hand, another recently published multicenter study for grade III eSTS did not incorporate grade II in the multivariate model for OS [14]. The current model has broader applicability as it also incorporates patients with grade II eSTS. Additionally, margins as classified in the current study only divide "clear" from "contaminated" margins, not taking into consideration that histological subtypes with infiltrative growth pattern as undifferentiated pleiomorphic sarcoma (UPS) and myxofibrosarcoma potentially require broader margins to markedly reduce LR-risk [25]. Thus, unsurprisingly, also in the current flexible parametric competing risk regression model for LR, these histological subtypes showed significantly higher LR-risks in comparison to other histologies.

4. Materials and Methods

In this retrospective multicenter study, 1931 consecutive patients with primary nonmetastatic high-grade (G2/3) eSTS managed with surgery at a curative intent were included in the test cohort, with patient information deriving from prospectively maintained STS databases at 5 participating tertiary sarcoma referral centers. Patients with missing information on oncological follow-up (i.e., development of LR/DM) had to be excluded (n = 42). Extremity STS were defined as tumors from the shoulder to the fingers (=upper limb) and from the pelvic girdle, excluding intrapelvic STS, to the foot (=lower limb). The validation cohort consisted of 1085 patients with identical inclusion criteria as for the test cohort from two independent tertiary sarcoma referral centers. As described above, patient monitoring after surgery usually followed a standardized approach with clinical examination, radiography using chest X-ray (CXR) or chest CT-scan (chest-CT) for control of DM and sonography or magnetic resonance imaging (MRI) for control of LR.

Demographic variables (patient age at diagnosis, gender), tumor-related parameters (tumor size, depth, location, grading, histological subtype), treatment (histological margins, (neo)adjuvant CTX/RTX), and outcome variables (date of LR or DM, date of death/last follow-up) were reported. Histological resection margins were divided into "clear" margins (=R0) and "contaminated" margins (=R1/2), as classification and definition of margin status have changed over time [26–28]. Histological subtypes were classified into 9 categories, with myxoid liposarcoma as the reference, compliant with previous studies and the current World Health Organisation (WHO) classification (Table 1) [6,16]. The FNCLCC grading system (Fédération Française des Centres de Lutte Contre le Cancer/French Federation of Centres for the Fight against Cancer) was used to categorize tumors into either intermediate (=G2) or high-grade (G3) [29]. (Neo-)adjuvant RTX and CTX had been administered in case a high risk of LR or DM had been anticipated by the multidisciplinary tumor board, according to locally preferred guidelines, LR was defined as a radiologically and/or histologically confirmed tumor recurrence. DM must have been confirmed by radiography (sonography, MRI, CXR, chest-CT) and/or histologically. In the case of pulmonary nodules without subsequent surgical exploration, an increase in size of the suspected metastasis must have been present. Patient, tumor, and treatment-related factors were ascertained using medical records, histological reports, and prospectively maintained databases at the respective centers.

Ethics approval was obtained in each participating center. The study was performed according to the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz, Austria (IRB-approval-number: 31-046 ex 18/19; date of approval: 24 May 2019).

Statistical Analysis

We focused on the first five years of follow-up to predict the conditional risk at the usually scheduled follow-up times (every 3 months from 1st to 3rd year; every 6 months in 4th and 5th year), i.e., the risk of experiencing an event at X + Y, given that the patient has not developed an event before X months. The variables age and tumor size were centered at their mean value in order to allow prediction at the average in case variables were not specified upon calculation. We used the Royston and Parmar approach to fit a flexible parametric competing risk regression model in order to estimate the risk of LR and DM, with death as the competing event [30]. In this model, the baseline distribution is modeled as a restricted cubic spline function of log time [15,22]. Splines constitute flexible mathematical functions defined by piecewise polynomials together with distinct constraints, ensuring that the overall curve is smooth [22]. A feature of restricted cubic splines as used in the present model is that the fitted function is forced to be linear before the first and after the last knot [31]. As automatic stepwise backward selection of variables is currently not available for the flexible parametric competing risk regression model, variable selection for the LR and DM models was based on a stepwise backward procedure using a multivariable Fine and Gray model [32]. Variables with a p-value < 0.05 were excluded from the model, except for histology, where all subtypes were kept in the analyses. The LR and DM models were fit on the log cumulative subdistribution hazard scale, directly modeling the cause-specific cumulative incidence function. Grading was incorporated in the model as a time-dependent effect for LR and DM, as it did not meet the proportional hazards assumption. The number of knots of the flexible parametric competing risk regression model for LR and DM was chosen based on the lowest AIC (=Akaike Information Criterion) after fitting several models with knots from 0 to 5. For the flexible parametric competing risk regression model estimating the risk of LR, two knots turned out as most accurate, while for the model predicting the risk of DM, four knots were used (with no internal knots for grading as a time-dependent covariate). Cumulative incidence functions were estimated based on the defined models. Conditional risks at the 3–6-months intervals were calculated based on the cumulative incidence functions of the flexible parametric competing risk regression model. Threshold was set to 4% for LR, considering that they are often palpable and diagnosed during the clinical examination or by patients themselves [18]. On the other hand, a 2% threshold for DM was chosen, as DM (and most commonly lung metastases) can only safely be diagnosed by chest X-ray or CT-scans of the thorax [19]. Model discrimination was tested using the Harrell C index, estimating the probability of concordance between observed and predicted outcomes. A value of 0.5 indicates no predictive discrimination, while a value of 1.0 indicates a perfect separation of patients with different outcomes [33]. Furthermore, calibration plots were compiled to assess model calibration in the test and validation cohort.

5. Conclusions

In conclusion, the present study provides a model to individually predict patient's LR and DM risks during follow-up, applying a flexible parametric competing risk regression approach. These models are at the moment being included in the updated version of the PERSARC app for Individualized Sarcoma Care and follow-up. Although a risk-threshold of 4% for LR and 2% for DM was chosen in the present study, the "optimal" threshold upon which an individual patient should undergo imaging with MRI, chest-CT, or CXR, is still subjected to experts' opinion and should be further discussed with patients concerned.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6694/12/1/47/s1, Table S1: Conditional Risks for Local Recurrence–Threshold 4%; Table S2: Conditional Risks for Distant Metastasis–Threshold 2%.

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