Impact of surgery in patients with metastatic soft tissue sarcoma: A monocentric retrospective analysis

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Background and Objectives: The role of local surgical procedures in patients with metastatic soft tissue sarcoma is still undefined. Few retrospective studies have reported survival benefits for patients with pulmonary metastases after complete surgical resection. Treatment decisions are therefore mainly based on personal experiences rather than on reproducible knowledge.

Method: A total of 237 patients with metastatic sarcoma, treated between 1982 and 2015 at the University Hospital Tübingen, Germany, were eligible for inclusion. Out of the 237 screened patients, 102 patients underwent at least one metastasectomy. Overall survival was defined as the primary endpoint in this study. For association of non-linear relationship to the endpoint, significant prognostic factors were included into a recursive partitioning model. A subgroup analysis for long-term survivors was also performed.

Results: The median overall survival was 64 months. The 3-, 5-, 10-, and 20-years overall survival rates were 70.7%, 50.3%, 24.7%, and 14.8%, respectively. The number of resections and the progression-free intervals were independent prognostic factors in three statistical models.

Conclusion: Repeated resections of metastases from different localizations are a strong predictor for prolonged survival. We suggest that the progression-free interval after metastasectomy should be considered as a predictive factor for benefit from further surgery.

Keywords
local treatment, metastases, metastasectomy, pulmonary metastases, sarcoma

1 INTRODUCTION

Soft tissue sarcomas (STS) represent a heterogeneous group of malignant tumors. With an incidence of approximately 12,390 new cases every year in the USA, STS belongs to the group of rare...
neoplasms. Early hematogenic metastases is a typical feature of high-grade STS. The most common localization of synchronous and metachronous metastatic disease is the lung. This fact leads to high-grade STS. The most common localization of synchronous and reconfirm the diagnoses. Neuropathology at the University Hospital Tuebingen in order to classification. Tissue samples of all primary patients were sarcoma after reassessment of the reference pathology according to different metastatic sites. Metastatic STS is generally considered incurable. Due to limited systemic treatment options for the majority of patients, complete surgical resection may be the most efficient therapy for achieving long-term responses or even cure in selected cases. Some retrospective analyses have revealed that resection of lung metastases may be accompanied by a longer chemotherapy-free interval, a longer progression-free interval (PFI), or even an improved overall survival (OS). However, the benefit from local surgical procedures in individual cases remains unclear.

The aim of this study was to retrospectively analyze the database of the South-West German Cancer Center at the University of Tuebingen in order to establish prognostic and predictive factors associated with metastasectomies at different anatomic locations.

2 | PATIENTS AND METHODS

2.1 | Legal requirements

Ethics approval for the retrospective data analysis was obtained from the faculty of the Eberhard-Karls-University and the University Hospital Tuebingen Ethics Committee (Project Number: 582-2015-BO2).

2.2 | Patients

All patients diagnosed with STS, who underwent any surgical procedure from October 1982 to October 2015 at the University Hospital Tuebingen were screened. The patient selection method followed the "Gießener Tumordokumentationssystem" (GTDS)—an established documentation system for hospital cancer registries for scientific analysis of the treatment of cancer patients. The search criteria were as follows: (1) diagnosis of sarcoma; (2) age at diagnosis >18 years; (3) presence of metastases; and (4) surgical resection of metastases. Medical records, surgical reports, and histological as well as radiological findings of all patients were reviewed and transferred into an Excel database sheet.

Inclusion criteria were defined as: any surgical procedure due to local and/or distant metastases. Exclusion criteria included insufficient documentation and patients who did not suffer from sarcoma after reassessment of the reference pathology according to the, at the time point of evaluation, valid 7th edition of the TNM classification. Tissue samples of all primary patients were histologically reassessed at the Institute of Pathology and Neuropathology at the University Hospital Tuebingen in order to reconfirm the diagnoses.

2.3 | Prognostic variables

An analysis of potentially prognostic variables that may influence the OS of metastatic sarcoma patients was conducted, which included the following: (1) Patient demographics (gender and age at diagnosis); (2) factors related to primary tumor (histological subtype, anatomical site, resection of the primary tumor, location of primary histological diagnosis, histological grade, and tumor size); (3) metastatic pattern (time of occurrence of metastases, location and number of metastases at first occurrence); (4) treatment of metastases (resection at first occurrence of metastases, number of metastasectomies, surgeries according to number of metastases, number of pulmonary resections performed for metastases, applied technique for the resection of lung metastases, type of lung resection); (5) course of disease (existence of a local relapse before metastases, PFI until date of the first recurrence); (6) first-line therapy (surgery only, surgery and radiotherapy, surgery and radiochemotherapy, surgery and chemotherapy).

2.4 | Statistical analysis

OS was defined as the primary endpoint of the analysis. The 3-, 5-, 10-, and 20-year survival rate was calculated from the date of diagnosis of the primary tumor and was modeled by the Kaplan-Meier estimate. Patients who were alive at the time of analysis and those who got lost to follow-up were censored. Prognostic variables were reviewed for statistical significance (P < 0.05) using the log-rank test for univariate analysis. To avoid any bias due to confounders among the variables, a multivariate analysis was performed with the variables of P < 0.05 in the univariate analysis. Multivariate analysis was performed using the Cox proportional hazards model. Statistical analysis was conducted using the SPSS software (Version 22.0; IBM Co., Armonk, NY). For the enhancement of the prognostic value of the analysis and for the generation of the decision tree, a recursive partitioning model was applied using the variables with P < 0.05 in the multivariate analysis. Recursive partitioning was performed using free software (R version 3.3.3; rpart package version 4.1-10). A subgroup analysis of various prognostic factors of patients who survived for ≥10 years (long-term survivors) versus patients who survived for <10 years was performed. Due to the small sample sizes, especially in the group of long-term survivors, the analysis was performed with Fisher’s exact test for univariate analysis. Variables with P < 0.05 were considered to be significant and were applied in the multivariate analysis for the adjustment of confounders and avoidance of any bias. Multivariate analysis was performed using the binary logistic regression. Statistical analysis was conducted using the SPSS software (Version 22.0; IBM Co.).

3 | RESULTS

3.1 | Patients

According to the pre-defined searching criteria, 237 patients were included in the retrospective analysis. Five patients (2.1%) did not
develop sarcoma. Therefore, reference pathology was performed for 160 patients (67.5%). It revealed one misdiagnosis of sarcoma (0.4%). Overall, 25 patients (10.6%) did not undergo resection of metastases and 32 patients (13.5%) showed non-adult STS histology (osteosarcoma, n = 11, Ewing’s sarcoma, n = 9, GIST, n = 7, chondrosarcoma, n = 5) and were excluded from the analysis. Finally, a total of 102 patients (43.0%) with metastatic STS were included in the planned study (Figure 1).

3.2 | Reference pathology of the 102 patients

Unfortunately, no tumor material could be obtained for histological reference from 26 patients (25.5%) because the period of retention for their cases exceeded 10 years and tumor material was therefore disposed in these particular cases. Of the remaining 76 patients (74.5%), nine (8.9%) showed a change in the sarcoma entity and 14 (13.7%) showed a change in the histological grade after reference pathology; three of these patients (2.9%) showed a change in the tumor entity as well as in the histological grade.

3.3 | Distribution of patients according to the histological subtype of the primary tumor

STS patients were re-categorized as per the 7th edition of TNM classification. Almost all histological variants of STS were represented among the patients with metastatic diseases. The most common subtype was leiomyosarcoma with 32 patients (31.4%), followed by 15 patients (14.7%) with pleomorphic sarcoma, 12 patients (11.8%) with synovial sarcoma, and nine patients (8.8%) with liposarcoma. A total of 34 patients (33.3%) were pooled in the “others” group, which comprised of a small sample size of different individual subtypes (Table 1).

3.4 | Prognostic factors

3.4.1 | Demographic data

The median age of the 102 patients at primary diagnosis was 47 years (age range: 19-85). 42 were males (41.2%; median age: 49 years, range 19-78) and 60 were females (58.8%; median age: 47 years, range 23-85).

3.4.2 | Characterization of the primary tumor

The histological subtypes of the remaining 102 patients are listed in Table 1. The most common anatomical primary site was the trunk (46 of 102 patients, 45.1%), followed by the uterus (22/21.6%), lower extremities (21/20.6%), and other sites (13/12.7%), which included upper extremities (7/6.8%) and the head and neck region (6/5.9%).

Resection of the primary tumor was performed in 99 patients (97.1%), whereas three patients (2.9%) did not undergo resection of the primary tumor at initial diagnosis because of advanced disease.

The location of the primary histological diagnosis could be determined in 96 cases (94.1%), including 38 cases (37.2%) at the University Hospital Tuebingen, Center of Soft Tissue Sarcomas, GIST and Bone Tumors (UKT-ZWS) and 58 cases (56.9%) at other centers. The location remained unknown because of insufficient documentation in six cases (5.9%).

| TABLE 1 | Histological subtype of metastatic soft tissue sarcoma patients |
|----------------|-------------------------------------------------------------|
| **Histology**          | **No. of patients (%)**                            |
| Leiomyosarcoma          | 32 (31.4)                                         |
| Pleomorphic sarcoma     | 15 (14.7)                                         |
| Synovial sarcoma        | 12 (11.8)                                         |
| Liposarcoma             | 9 (8.8)                                           |
| Malignant peripheral nerve sheath tumor | 6 (5.9)                       |
| Angiosarcoma            | 6 (5.9)                                           |
| Rhabdomyosarcoma        | 5 (4.9)                                            |
| Uterine stromal sarcoma | 4 (3.9)                                            |
| Alveolar soft part sarcoma | 3 (2.9)                        |
| (Uterine) Carciinosarcoma | 3 (2.9)                               |
| Myxofibrosarcoma        | 2 (1.9)                                            |
| Solitary fibrous tumor  | 1 (1.0)                                            |
| Adenosarcoma of the uterus | 1 (1.0)                                        |
| Clear cell sarcoma      | 1 (1.0)                                            |
| Histiocytic sarcoma     | 1 (1.0)                                            |
| Granular cell tumor     | 1 (1.0)                                            |
The histological grade was documented for 89 of the 102 patients (87.3%), which included 37 metastatic sarcoma patients (36.3%) with initially low-grade (grade 1 or 2) disease and 52 patients (51.0%) with high-grade (grade 3) disease.

Tumor size at primary diagnosis was documented in 50 cases (49.0%). In four patients (3.9%), the primary lesion measured <5 cm, whereas it was ≥5 cm in 46 cases (45.1%).

### 3.4.3 Metastatic pattern

At the time of primary diagnosis, 24 patients (23.6%) displayed synchronous metastases and 69 patients (67.6%) developed metachronous metastatic disease. A total of 72 patients (70.6%) suffered from unilocular and 30 patients (29.4%) from multilocular metastatic disease.

The initial unilocular cases occurred in the lungs in 44 patients (43.1%) and in other organs in 28 cases (27.5%), which included the bones (n = 7; 6.9%), abdomen (n = 7; 6.9%), liver (n = 3; 2.9%), thorax (n = 2; 1.9%), lymph nodes (n = 1; 1.0%), CNS (n = 1; 1.0%), and other organs (n = 7; 6.9%).

The number of metastases at the time of first occurrence was documented in 73 cases (71.6%), of which 43 patients (42.2%) were presented with 1-4 metastases (oligometastasized), including single metastases (n = 29; 28.5%), two metastases (n = 10; 9.8%), three metastases (n = 3; 2.9%), and four metastases (n = 1; 1.0%). 30 patients (29.4%) presented with >4 metastases.

### 3.4.4 Treatment of metastases

A total of 80 of the 102 patients (78.4%) underwent resection of the metastases at the first time-point of documented metastatic disease. Twenty-two patients (21.6%) received a surgery at a later time point; 49 patients (48.0%) underwent a singular resection. Fifty-three patients (52.0%) underwent >1 resection, including those who underwent two surgeries (n = 28; 27.5%), three surgeries (n = 17; 16.7%), four surgeries (n = 3; 2.9%), five surgeries (n = 3; 2.9%), six surgeries (n = 1; 0.1%), and seven surgeries (n = 1; 0.1%).

Fifty-seven out of 102 patients (55.9%) who underwent metastasectomy, 37 (36.3%) had oligometastatic disease, and 20 (19.6%) polymetastatic disease.

Of the 102 patients, 58 (51.0%) underwent resections of lung metastases, 36 (35.3%) underwent a singular resection, and 22 (21.6%) underwent repeated resections because of recurrent lung metastases, which included two resections (n = 13; 12.7%), three resections (n = 6; 5.9%), four resection (n = 2; 2.0%), and five resections (n = 1; 1.0%). A total of 44 patients (43.1%) did not receive any surgery for the lung metastases because their case was advanced (16.7%) or revealed a multilocular infiltration pattern (26.4%).

In 15 cases (14.7%), an alternative approach was selected, including segmental resection (3.9%), lobectomy (9.8%), and pneumonectomy (1.0%).

### 3.4.5 Course of disease

Of the 102 patients, 12 (11.8%) suffered from a local relapse prior to distant metastases. 90 patients (88.2%) displayed solely metastatic relapses.

PFI was determinable in 96 of the 102 patients, from which 44 patients showed a PFI of <12 months (43.1%) and 52 patients a PFI of ≥12 months (51.0%).

### 3.4.6 First-line therapy

Surgery was exclusively performed in 44 of the 102 patients (43.1%). Overall, 23 patients with metastatic STS (22.6%) underwent surgery + radiotherapy, 19 patients (18.6%) underwent surgery + radiochemotherapy, and 14 patients (13.7%) underwent surgery + chemotherapy; one patient (1.0%) underwent exclusive radiotherapy, whereas another (1.0%) underwent exclusive radiochemotherapy.

### 3.4.7 Prognostic factors of metastatic patients with STS

All 102 patients were eligible for the OS analysis, 69 patients (67.7%) died during the follow-up because of their diseases, 30 (29.4%) were alive at the time of analysis, and three (2.9%) were lost to follow-up due to relocation, change of physician, or for unknown reasons. Of the 30 patients who were alive at the time of analysis, the disease was still present in 18 patients (17.6%). In 9 patients (9%), there was no clinical or radiological evidence of tumor. The status of disease was unclear in two patients (2.0%) because of a recently performed surgery.

OS was calculated over a maximum of 20 years. The median OS of the 102 patients was 64 months, and the 3-, 5-, 10-, and 20-years survival rates were found to be 70.7%, 50.3%, 24.7%, and 14.8%, respectively (Figure 2).

In the univariate analysis, age, resection of primary tumor, histological grade, time-point of metastasization, surgery at the first occurrence of distant metastases, the number of metastasectomies, and the PFS were associated with prolonged OS (Table 2). In the multivariate analysis, only the resection of primary tumor, time-point of metastasization, number of metastasectomies, and PFS remained significant (Table 3).

![FIGURE 2](image-url) The Kaplan-Meier curve of the overall survival. The median overall survival was 64 months for 102 patients. The 3-, 5-, 10-, and 20-years survival rates were 70.7%, 50.3%, 24.7%, and 14.8%, respectively.
### TABLE 2  Univariate analysis of prognostic factors

| Characteristics (n) | Number (%) | Median OS (months) | P-value |
|---------------------|------------|--------------------|---------|
| **Demographic data** |            |                    |         |
| Age at diagnosis (n = 102) |            |                    |         |
| <60 years | 76 (74.5) | 67 ± 8.7 | 0.011 |
| ≥60 years | 26 (25.5) | 41 ± 2.8 |         |
| Gender (n = 102) |            |                    | 0.220   |
| Male | 42 (41.2) | 64 ± 19.5 |         |
| Female | 60 (58.8) | 59 ± 10.2 |         |
| **Primary tumor** |            |                    |         |
| Histological subtype (n = 102) |            |                    | 0.843   |
| Leiomyosarcoma | 32 (31.4) | 70 ± 10.1 |         |
| Undiff. pleomorphic sarcoma | 15 (14.7) | 44 ± 3.9 |         |
| Synovial sarcoma | 12 (11.8) | 80 ± 19.4 |         |
| Liposarcoma | 9 (8.8) | 64 ± 38.8 |         |
| Others | 34 (33.3) | 41 ± 4.6 |         |
| Anatomical site (n = 102) |            |                    | 0.500   |
| Trunk | 46 (45.1) | 45 ± 5.9 |         |
| Uterus | 23 (22.5) | 66 ± 12.0 |         |
| Lower extremities | 21 (20.6) | 82 ± 31.2 |         |
| Others (upper extremities, head, and neck) | 12 (11.8) | 64 ± 9.3 |         |
| Resection of primary tumor (n = 102) |            |                    | <0.001  |
| Performed | 99 (97.1) | 65 ± 9.4 |         |
| Not performed | 3 (2.9) | 16 ± n. a. |         |
| Location of primary diagnosis (n = 96) |            |                    | 0.308   |
| UKT-ZWS | 38 (39.6) | 82 ± 23.6 |         |
| Others | 58 (60.4) | 45 ± 5.5 |         |
| Histological grade (FNCLCC) (n = 89) |            |                    | 0.032   |
| Low-grade (grade 1 or 2) | 37 (41.6) | 82 ± 18.6 |         |
| High-grade (grade 3) | 52 (58.4) | 44 ± 4.7 |         |
| Tumor size (n = 50) |            |                    | 0.601   |
| <5 cm | 4 (8.0) | 82 ± 26.5 |         |
| ≥5 cm | 46 (92.0) | 50 ± 11.4 |         |
| **Metastatic pattern** |            |                    |         |
| Time-point of metastasization (n = 93) |            |                    | 0.034   |
| Synchronous | 24 (25.8) | 39 ± 11.9 |         |
| Metachronous | 69 (74.2) | 67 ± 17.0 |         |
| Number of metastatic sites (n = 102) |            |                    | 0.730   |
| Monolocular | 72 (70.6) | 49 ± 13.9 |         |
| Multilocular | 30 (29.4) | 66 ± 9.9 |         |
| Synchronous singular metastatic site (n = 72) |            |                    | 0.610   |
| Lung | 44 (61.1) | 41 ± 6.7 |         |
| Others | 28 (38.9) | 50 ± 17.3 |         |
| Number of metastases at first occurrence (n = 73) |            |                    | 0.614   |
| 1-4 metastases (oligometastatic) | 43 (58.9) | 50 ± 16.2 |         |
| >4 metastases | 30 (41.1) | 59 ± 20.8 |         |

(Continues)
Recursive partitioning analysis was calculated using significant prognostic factors from multivariate analysis, for which a decision tree was subsequently created (Figure 3). The three terminal nodes were identified based on PFI and the number of metastasectomies. Three prognostic groups were formed based on the median survival time of the terminal nodes. Due to the small sample size of the variables, resection of primary tumor, and time-point of metastasization, it was not feasible to perform a split and, therefore, a grouping for both the variables was also not feasible. Therefore, Group A included metastatic sarcoma patients with a PFI of <12 months (1 or >1 metastasectomies) and included 44 observations with a median survival time of 34 months; Group B included patients...
TABLE 3  Multivariate analysis of prognostic factors

| Characteristics                        | HR (95%CI) | P-value |
|----------------------------------------|------------|---------|
| Age at diagnosis ≥60 years             | 1.283      | 0.422   |
| <60 years                              | 0.901      | 0.073   |
| Histological grade (FNCLCC)            |            |         |
| Low-grade (grade 1 and 2)              | 0.066      | 0.001   |
| High-grade (grade 3)                   |            |         |
| Resection of primary tumor             |            |         |
| Performed                              |            |         |
| Not performed                          |            |         |
| Time-point of metastasization          | 1.094      | 0.037   |
| Synchronous                            |            |         |
| Metachronous                           |            |         |
| Surgery at first occurrence of distant | 1.077      | 0.818   |
| metastases                             | (0.573-2.026)|       |
| Done                                   |            |         |
| Not performed                          |            |         |
| Number of metastasectomies             | 0.580      | 0.045   |
| 1 metastasectomy                       | (0.341-0.989)|       |
| >1 metastasectomies                    |            |         |
| Progression-free interval              | 0.278      | <0.001  |
| <12 months                             | (0.157-0.490)|       |
| ≥12 months                             |            |         |

HR, hazard ratio, CI, confidence interval.

...with a PFI of ≥12 months, (1 metastasectomy) and included 23 observations with a median survival time of 49 months; and Group C included patients with a PFI of ≥12 months, (>1 metastasectomies), and included 29 observations with a median survival time of 117 months. The 10-year survival rate was 13.4% for Group A, 28.3% for Group B, and 40.7% for Group C. The grouping allowed a significant separation of the Kaplan-Meier survival curves among the three groups (Figure 4).

3.4.9 | Detailed analysis of long-term survivors

In this analysis, a remarkable number of patients (n = 15) with metastatic diseases survived for ≥10 years (14.7%). A detailed analysis was performed according to similar prognostic factors applied to the entire population of metastatic patients with STS (Supplementary Table S1). The Fisher's exact test for univariate analysis revealed a significant correlation with a better OS for the number of metastasectomies (P = 0.004) and PFI (P = 0.009) in the group of long-term survivors versus patients who survived for <10 years (Supplementary Figures S1 and S2). In the binary logistic regression for multivariate analysis, the number of metastasectomies (P = 0.013, OR = 0.134) and PFI (P = 0.011, OR = 0.128) remained significant (Supplementary Table S2). The median OS of the long-term survivors who underwent >1 metastasectomy and had a PFI of >12 months could not be determined because of the large number of patients (n = 9; 60.0%) who remained alive. The median OS of patients who survived for <10 years and had only undergone one metastasectomy was 39 month and 32 month for those who survived <10 years and had a PFI of ≥12 month.

4 | DISCUSSION

The overall poor prognosis and still unfavorable course of disease under medical treatment require application of multimodal therapeutic strategies for patients with metastatic STS.

The aim of the present study was to retrospectively analyze the impact of local surgical procedures on the OS of patients with metastatic adult-type STS.

After a median observation time of 118 months, the median OS of the finally analyzed cohort of 102 STS patients was 64 months, with 3-, 5-, 10-, and 20-year survival rates of 70.7%, 50.3%, 24.7%, and 14.8%, respectively. This compares very favorably to other historical reports. The data suggest that the development of a highly specialized center aimed at the long-term survival for STS patients, including even those with metastatic disease, is achievable.

In contrast to previously published reports, we have herein also looked at surgical removal of metastases from non-pulmonary sites. Neither occurrence of metastases at non-pulmonary localizations, nor the number of pulmonary resections or the technical procedure of lung surgery showed any statistical significance with regard to the OS. However, repeated surgery of metastatic disease of any localization emerged as a significant prognostic factor for OS, which has been shown for repeated resection of pulmonary metastases.

Indeed, the median OS for patients who underwent only one metastasectomy was 40 months whereas patients with repeated surgery displayed an OS of 87 months (P = 0.009). While this difference may include significant selection bias, repeated metastasectomies should be considered in any eligible patient. Comorbidities of the patients were systemically recorded and repeated surgery of metastases was also performed in presence of concomitant diseases like lung embolism, coronary heart disease, or tachycardia. Unfortunately, the available data and number of patients in this study were not sufficient to further evaluate the contribution of individual tumor biology or individual patient characteristics like general health status or fitness. Therefore the diagnostic evaluation for a patients capacity for tolerating surgery should be assessed in the interdisciplinary tumor conference and should be finally decided by the surgeon and anesthesiologist. Another beneficial prognostic factor was a PFI of ≥12 months after first-line of therapy in multivariate analysis. This...
result is in line with other published reports.\textsuperscript{4,12–14,17} Although different studies reported conflicting conclusions,\textsuperscript{8,10–11} the result of the present analysis highlighted the high significance in univariate and multivariate analyses. Again, patients presenting with a PFI of ≥12 months after a prior treatment may suffer from biologically less aggressive disease, but this notion may help in the decision-making process for repeated surgeries in the future.

The time-point of metastatic spread was prognostic in both univariate and multivariate analysis with a median OS of 67 versus 39 months in patients with metachronous versus synchronous metastasis. The sample size of 24 patients with synchronous metastasis may be relatively small, but is still comparably higher than in previously published studies, where the time-point of metastatic spread was not found to be prognostic.\textsuperscript{12,15} The exceptionally unfavorable prognosis of the three patients, whose primary tumor had not been removed is very plausibly due to their initially advanced disease and not due to the fact that their primary tumor was not resected.

Other variables such as age, histological grade, or resection of metastases at the time-point of occurrence of the first distant metastases, which were identified as prognostic in other reports,\textsuperscript{4–17} were found to be significant in the univariate, but not in the multivariate analysis in this study. Owing to the rareness of the disease and lack of funds in its research, future prospective analyses are not expected. Nevertheless, a pooled analysis using data from international centers may deliver a basis for a valid statistical evaluation.

Analysis of other factors such as histological subtypes, tumor size, the number of metastases, or different forms of therapy applied was not statistically significant in the current analysis with regard to the OS for both univariate and multivariate analyses. Again, the sample size may be a limiting factor.
Because of the peculiar biology of oligometastatic disease, several authors have suggested that surgery may especially beneficial in this selected patient population.\(^4,5,10,11,13,15,17\) We found no significant survival effect, when probability of survival for patients with oligometastatic versus polymetastatic disease were compared, which is in line with most previously published reports.\(^4,10,13,15,17\) Only two studies demonstrated a survival benefit for patients with a limited number of metastases.\(^22,23\) However, in the third analysis performed by the same research group, a few years later, these results were relativized.\(^25\)

In order to create a clinically relevant decision tree, a recursive partitioning analysis was performed. This approach allowed linking of complex non-linear relationships to the endpoint. By the stepwise splitting of the independent prognostic variables, patients were appropriately grouped according to their characteristics.\(^26\) Kang et al.\(^17\) initially adopted this approach for a survival analysis of patients with metastatic STS.\(^17\) The results of the present analysis considered two factors for grouping patients: 1) PFI and 2) the number of metastasectomies.

For the resection of the primary tumor and the assessing time-point of metastasization, grouping was not feasible because of the small sample size. This favors the high projection quality of our model. For patients who underwent repeated resection of metastases and those with a PFI of ≥12 months, the recursive partitioning analysis showed the best prognosis for long-term survival with a 10-year survival rate of 40.7%. This finding can be considered for interdisciplinary advice in individual patients.

Notably, 15 patients (14.7%) survived for at least 10 years. To the best of our knowledge, there are currently no publications on long-term survival in metastatic STS of comparable durations. Billingsley et al.\(^6\) and Rehders et al.\(^11\) have performed a subgroup analysis on 13 and 20 patients, respectively, who survived for ≥5 years.

A subgroup analysis of long-term survivors versus patients who survived for <10 years revealed no differences in median age (48 and 47 years, respectively), histology or point of origin of the primary tumor, or metastatic distribution pattern. None of the applied treatment modalities in the group of long-term survivors (only surgery or surgery in combination with chemo- and/or radiotherapy) demonstrated any significance and therefore, there was no survival benefit for a specific therapeutic regimen.

Thirteen of the 15 long-term survivors (86.7%) underwent repeated resections (up to six times) of metastases. Notably, they all had a PFI of ≥12 months after the first-line therapy. The subgroup analysis in the exact Fisher’s test for univariate analysis and binary logistic regression model for multivariate analysis revealed a prognostic value for the PFI and repeated resections. The risk to live for <10 years was higher for patients who underwent only one resection of metastases (OR = 0.134) and had a PFI of <12 months (OR = 0.128).

Our argument that repeated resections of metastases results in a better prognosis for long-term survival is in line with those by Billingsley et al.\(^6\) and Rehders et al.\(^11\)

The present analysis has some limitations that should be considered while interpreting the results, which are as follows: 1) the retrospective character of the study demands attention on data quality, missing data, and information; 2) sarcoma is a very rare and heterogeneous disease. Therefore, only a small group of patients with metastatic STS was found to be suitable for analysis and they were studied over a very long period of time. The analyzed data should therefore be validated in a multicentric, national, or international setting. Alternatively, a pooled analysis can be considered; 3) due to the small sample sizes, the current analysis included all histological subtypes. Therefore, a stratification regarding treatment strategy for specific histological subtypes was not feasible; 4) during the long time period of data collection, repeated changes occurred in the therapeutic strategies as well as with the releases of new drugs, which altogether significantly influenced the patient prognosis.\(^27\)

5 | CONCLUSION

This study aimed at evaluating the role of surgical procedures in patients with metastatic STS. Different statistical models and subgroup analyses of long-term survivors confirmed that the PFI and repeated surgery of metastases are significant prognostic variables that are statistically relevant for the survival benefit of these patients. Importantly, this finding applies not only for patients with pulmonary metastases but also for those with metastases of any other localization. As long as the technical requirements are met, an adequate health status is maintained and informed consent is obtained, resection of metastases demonstrates an effective therapeutic option for a significant survival benefit at the time of primary diagnosis, as well as for recurrent occurrence. Notably, long-term survival of ≥10 years was achieved in a significant proportion of patients. The PFI after prior treatments should be considered as a decision support for repeated resection of metastases.

Fortunately, for some of the long-term survivors in the current analysis, disease activity was not evident for several years after treatment, which confirms that curing metastatic disease by repeated resections of metastases may be feasible in selected cases.

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CONFLICTS OF INTEREST

None.

AUTHORS’ CONTRIBUTIONS

H-GK and FM studied by were responsible for the conception and design and helped in correction of the manuscript. RL, VS, and FT performed the surgery. BS and HB contributed to reference pathology. SW was responsible for acquisition of data and data analysis. SW and KH drafted the manuscript. All authors have read and approved this manuscript.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.