Value of Repeat Resection for Survival in Pulmonary Metastases from Soft Tissue Sarcoma

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Abstract. *Background: Pulmonary metastasectomy in soft tissue sarcoma (STS) can lead to long-term survival. The aim of our study was to report on prognostic factors and the value of repeat resection in recurrent disease. Patients and Methods: Seventy-eight pulmonary metastasectomies were performed on 42 STS patients from 1990 to 2005. Overall survival time and 3-year survival rate were evaluated. Subgroup analysis was performed on age, primary tumor stage, histological type and grade, occurrence and recurrence pattern, systemic treatment and number of resections. Results: The 3-year actuarial survival rate was 31%. Primary tumor grade and repeat resections were shown to be independent prognostic factors for survival. Conclusion: Patients with repeat resections due to recurrent metastasis show a significantly better prognosis than those with only one resection. Thus, lacking randomised controlled data of the natural course of patients with unresected lung metastases to compare these results, metastasectomy in STS patients is also recommended in recurrent disease.*

Soft tissue sarcoma (STS) is a rare neoplasm representing only 0.7% of adult malignancies (1). It comprises a heterogeneous group of neoplasms whose only common denominator is their derivation from mesenchymal tissue (2, 3). It may arise virtually anywhere, but the extremity is the most common primary site. The lungs are the most common sites of metastatic disease. Of patients with extremity sarcoma, approximately 20% will have isolated pulmonary metastases at some point in the course of their disease and this remains the primary cause of death in bone sarcoma and STS (2, 4, 5). Although pulmonary metastases most commonly arise from primary tumors in the extremities, they may arise from almost any histological variant or primary site (6).

There are some data that suggest that surgical resection is the treatment of choice for pulmonary metastases from soft tissue sarcoma (7-10), even for recurrent disease (11, 12), although the effect of a relatively long survival of patients after metastasectomy and repeat metastasectomy might be due to a positive selection of patients with favourable tumour biology and therefore resectable disease (13). Adjuvant chemotherapy does not seem to decrease the incidence of pulmonary metastases (14). Three-year survival rates after complete resection range from 30% to 42% (7). Several prognostic variables have been identified that are associated with favourable survival after pulmonary metastasectomy. Favourable factors include an extended disease-free interval, three or fewer pulmonary nodules and a longer tumor doubling time. The most consistent favourable prognostic factor is resectability of metastatic disease (12, 15). Since a prospective randomized study in which metastasectomy was compared to no surgery has not been undertaken, the true value of surgery for STS metastases in terms of survival benefit is still undefined. The aim of this study is to report post-metastasis survival for patients with pulmonary metastases from soft tissue sarcoma in a group of patients treated at a single institution.

Patients and Methods

From 1990 to 2005, 475 adult patients with soft tissue sarcoma were admitted and treated at the University Medical Centre, Hamburg-Eppendorf, Hamburg, Germany. All data were prospectively entered into the sarcoma database and patients were followed up per management protocol. During this interval, 42 of these patients underwent 78 pulmonary resections for pulmonary metastases. These patients comprise the study group for this report.

The histopathological diagnosis and grade for all patients was reviewed and confirmed by an attending pathologist at the University Medical Centre, Hamburg-Eppendorf. Tumor grade,

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Table I. *Histological type and grading of tumors from soft tissue sarcoma patients.*

Histology	No.	%
Alveolary sarcoma	2	5
Extraskeletal chondrosarcoma	4	9
Fibrosarcoma	2	5
Leiomyosarcoma	13	31
Malignant peripheral nerve tumor	3	7
Malignant fibrous histiocytoma	7	17
Synovial sarcoma	4	9
Spindle cell sarcoma	2	5
Other	5	12
Grade:		
G1	3	7
G2	8	19
G3	27	64
Not specified	4	10

size and anatomic location were recorded in the prospective database. After therapy for the primary tumor, patients were evaluated at regular intervals with chest CT-scans, either at our centre or by associated oncologists. For patients with extremity sarcoma, this evaluation involved an imaging study of the extremity (either a CT scan or magnetic resonance imaging). Patients with visceral or retroperitoneal primaries were followed up with regular abdominal imaging studies (primarily CT scan). When diagnosed with pulmonary metastases, patients were treated with surgical resection of the detected lesions unless a contraindication existed. Operative approaches included lateral thoracotomy, median sternotomy and clamshell operation. If, during follow up, recurrent resectable lung metastases developed, they were treated with repeat lung resection. Many patients with pulmonary metastases were treated with chemotherapy at some point in their clinical course. Patients prospectively randomized in chemotherapy trials as well as those who were given standard-of-care treatment based on prognosis were included. Because inclusion of nonrandomized treatment-related variables in any of the analyses would be likely to confound the effects of other factors, we have elected to include only the effect of surgical resection in the analyses.

Disease-specific survival was used as the endpoint of the study. Survival was calculated from the date of surgery of pulmonary metastases. Five-year and 3-year survival was also calculated from the date of diagnosis of the primary tumor. The time to death was modelled using the method of Kaplan and Meier. Deaths that resulted from the disease were treated as an endpoint for disease-specific survival; survival was treated as censored observations. Subgroup analysis was performed on age, time of occurrence, primary tumor stage, disease-free interval, preoperative systemic treatment, primary tumor grade, repeat resections, number of metastases, occurrence pattern, histology and size of metastasis. The association of these factors to time-to-event endpoints was analyzed using the log-rank test and the Cox proportional hazards model for multivariate analysis. In all statistical analyses, $p \leq 0.05$ was considered significant.

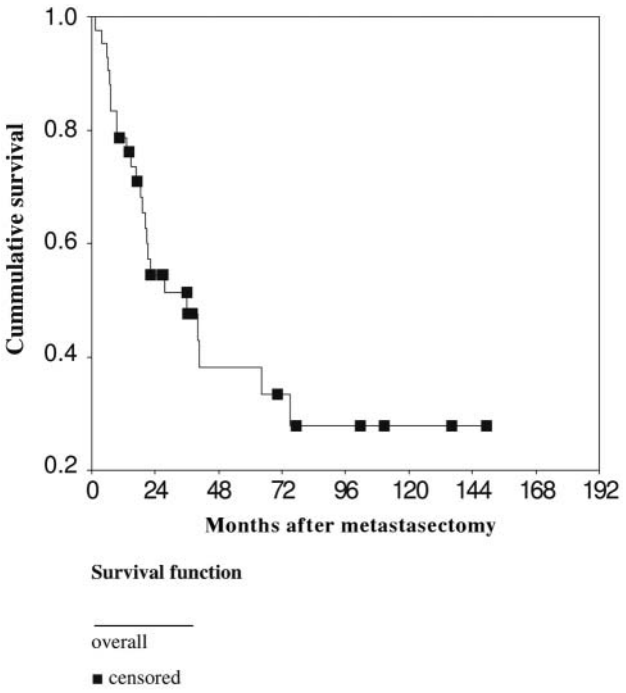

Figure 1. *Survival after metastasectomy.*

Results

During the time period under study, 42 patients underwent 78 pulmonary resections. Of these patients, 10 (24%) presented with primary disease and synchronous metastases, 32 (76%) presented metachronous metastases. There were 17 (40%) female and 25 male (60%) patients with a mean age of 50 years (range 17-73 years). The follow-up in this series was calculated from the date of operation for patients who underwent resection; the median follow-up after metastasectomy was 27 months.

Almost all the histological variants of soft tissue sarcoma were represented among the patients with pulmonary metastases. Analysis of the distribution of primary histology demonstrated that among patients who developed lung metastases, leiomyosarcoma was the most common histology (31%), followed by malignant fibrous histiocytoma (17%) and extraskeletal chondrosarcoma (9%). Twenty seven (64%) of the patients had high-grade sarcomas, eight (19%) were histologically classifed as medium grade and three (7%) as low grade lesions. Four patients had primary lesions of unknown or indeterminate grade. The data are shown in Table I.

The overall median survival after resection of the primary tumor was 66 months. The overall 3-year actuarial survival rate was 62%, with a five-year actuarial survival rate of 40. 5%. Median survival after complete resection

Table II. *Univariate analysis of post-metastasis survival*

Variable	n	%	Median survival (months)	*p*-value
Overall	37	100	36	
Age				
<50 yrs	17	40	75	
≥50 yrs	25	60	21	0.16
Time of occurence				
Synchronous	10	24	21	
Metachronous	32	76	40	0.55
Stage of primary tumor				
I-II b	29	69	40	
III a-IV	13	31	21	0.49
Disease-free interval				
>18 months	16	38	41	
≤18 months	26	62	21	0.24
Chemotherapy				
Preoperative	12	29	18	
None	30	71	36	0.98
Primary tumor grade				
G1-2	11	26	40	
G3	27	74	19	0.03
Number of resections				
Single	22	52	19	
Multiple	19	48	64	0.007
Number of metastases				
Solitary	16	38	22	
Multiple	26	62	40	0.79
Pattern of occurence				
Bilateral	20	48	40	
Unilateral	22	52	27	0.86
Histology				
Non-leiomyosarkoma	29	69	64	
Leiomyosarkoma	13	31	27	0.31
Size of metastases				
≤2 cm	22	52	27	
>2 cm	20	48	40	0.94

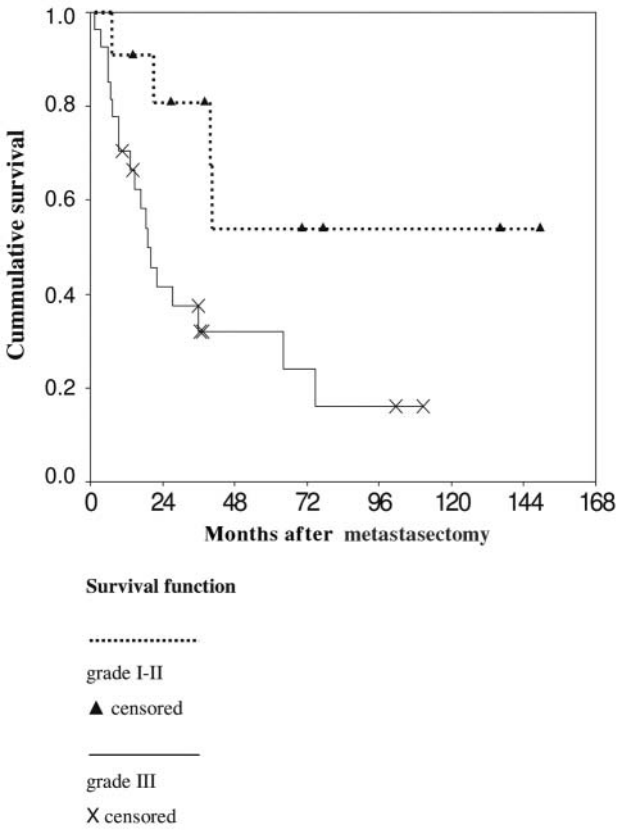

Figure 2. *Survival according to primary tumor grade.*

of metastases was 36 months (Figure 1). The actuarial 3-year survival rate after resection was 31%. For the 18 patients who were alive at the time of last follow-up, the median post-metastasis follow-up was 22 months. Of 13 patients who survived 3 years or longer after metastasectomy, three are alive without evidence of disease. Six patients are currently alive with disease and ten patients developed recurrent pulmonary disease and were treated with repeated lung resection. The number of lung resections in these patients ranged from one to four. Clinical and tumor-related variables were analyzed as potential determinants of survival (Table II).

On univariate analysis, patients with synchronous metastases showed significantly lower median survival of 21 months compared to 40 months in patients with metachronous metastases ($p=0.55$). After the development of pulmonary metastasis, the stage of the primary lesions was not a significant determinant of survival. Patients with primary tumor stage I to II b (UICC) had a medium survival of 40 months *versus* 21 months in the group of stage III a to IV. These data did not reach significance. The disease-free interval was defined as the time between the treatment of the primary lesion and the diagnosis of metastatic disease. The median disease-free interval for all patients with pulmonary metastases was 12 months. A disease-free interval of 18 months or less showed a shorter survival time, but was no significant indicator of poor prognosis in the univariate analysis ($p=0.24$). Eight patients with high grade primary tumor, two patients with medium grade primary tumor and two patients with unspecified tumor grade underwent preoperative chemotherapy. Median survival of these patients was still only 18 months compared to 36 months in the non-treated group (n.s., $p=0.98$) (data not shown). Primary tumor grade was a significant prognostic factor in univariate analysis. Median survival of patients with high grade tumors was 19 months after metastasectomy compared to 40 months in patients with low or medium grade tumors ($p=0.03$) (Figure 2).

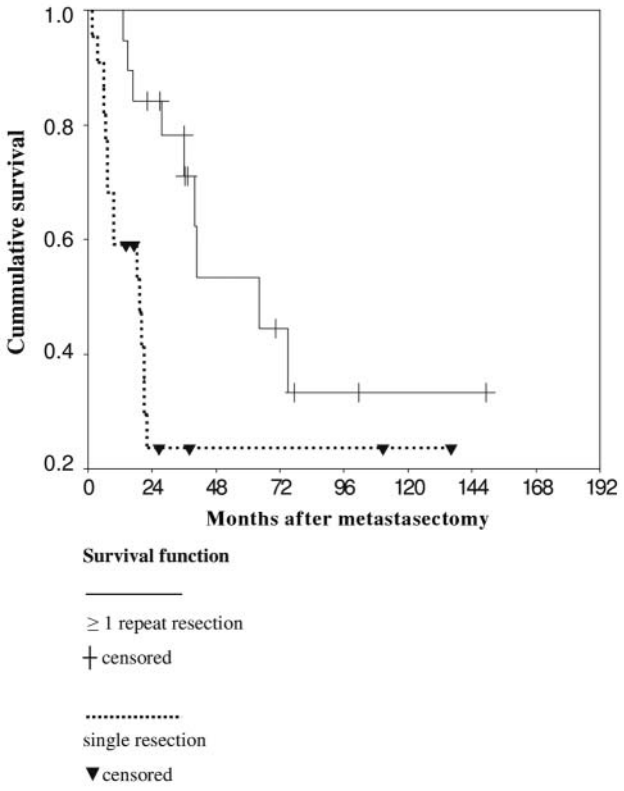

Figure 3. *Survival according to number of resections.*

Out of the 29 patients who suffered from recurrent metastases, 19 underwent at least one repeat resection. In univariate analysis, patients with repeat resections (50% of the patients) showed a median survival of 64 months compared to 19 months in all patients with a single resection ($p=0.0074$), which is significantly longer (Figure 3). Median survival from the second resection was 22 months. Patients with solitary metastases had a survival of 22 months, which was even lower than in patients with multiple lesions (40 months), but this did not reach significance. Twenty patients suffered from bilateral metastatic disease and showed a slightly longer median survival than patients with unilateral disease (40 *vs.* 27 months), but without any significance (data not shown). Five of these patients underwent sequential metastasectomy and had a median survival of 25 months, compared to 40 months in the 15 patients who underwent simultaneously metastasectomy through sternotomy or clamshell operation. Small metastases of 2 cm or less were not associated with an advantage in survival, but, in contrast, showed a slightly, though not significantly so, worse survival (data not shown). Patients with leiomyosarcoma had a shorter median survival than patients in the non-leiomyosarcoma group, although the difference did not reach significance (data not shown).

Table III. *Multivariate analysis of post-metastasis survival.*

Variable	Significance	(95% CI)	
Age	0.436	0.979	1.051
Primary tumor grade	0.036	0.979	0.924
Primary tumor stage	0.784	0.408	3.276
Disease-free interval	0.852	0.293	2.758
Repeat resection	0.021	0.092	0.824

CI: confidence interval.

Primary tumor grade and repeat resections for recurrent disease were shown to be independent prognostic factors in multivariate analysis (Table III).

Discussion

This series represents a single-institution experience with pulmonary metastases from soft tissue sarcoma. All 42 patients selected for analysis suffered from pulmonary metastases and underwent resection. Since there is an about 10-fold higher likelihood that a lung lesion appearing in the follow-up of a STS is a metastatic deposit rather than a benign or primary lung tumor (16), we did not perform needle biopsies preoperatively. Since early detection and excision have not been shown to improve survival, and multiple re-excisions are an acceptable option (17), we did not perform bilateral exploration, although CT-scans might underestimate the extent of disease by 25-50% (16). The overall median survival was 66 months. Median survival after complete resection was 36 months, which was in the same range as described in other studies (18). The overall actuarial 3-year survival rate was 62%, with a 5-year actuarial survival rate of 40.5%, which seems to be higher than in the data of Billingsley *et al.*, who report a 3-year actuarial survival of only 46% in patients who underwent resection. Several other institutions have focused on survival patterns after resection of lung metastases. In a review of 68 patients treated at the National Cancer Institute, the overall 3-year survival rate was 28%, with a 35% 3-year survival rate for patients who underwent complete resection (9). More favourable survival was described in a multi-institutional European study (19). These authors reviewed the collective experience from 11 hospitals involving 255 patients who underwent resection of pulmonary metastases. They reported an overall survival rate of 54% at 3 years and 38% at 5 years. Of 13 patients who survived 3 years or longer after metastasectomy in our series, three were alive without evidence of disease. Six patients were alive with disease. In ten of the long-term survivors, recurrent pulmonary disease developed and they were treated with repeated lung resection. The number of lung resections in

these patients ranged from one to four. Long-term survivors appear to belong to a subset of patients with indolent, lung-only disease. It is possible to control disease in patients with recurrent disease for an extended period with repeated pulmonary resection. Other groups have also documented the safety and utility of repeated pulmonary resections (12). The current report profiles the spectrum of pulmonary metastases in sarcoma, encompassing most histological variants. Leiomyosarcoma represents the major histological type, followed by malignant fibrous histiocytoma, which corresponds to the findings of Billingsley *et al.* (20). The relatively high incidence of chondrosarcoma is quite unusual and might be associated with the small group of patients analysed here. In this series no report can be made regarding the survival benefit of metastasectomy, as has been done in large series of STS, such as the study of Billingsley *et al.* of MSKCC in 1999, who demonstrated a significant survival benefit associated with resection of pulmonary metastatic disease (18). The aim was to evaluate the role of repeat resection and to target prognostic factors in metastatic disease.

In the last two decades, a variety of prognostic factors have been reviewed in multiple studies. In most series the ability to resect metastatic disease completely is consistently the most significant factor in determining post-metastasis survival (9, 18, 19, 21). An extended disease-free interval has also been demonstrated by a number of groups as a positive predictor of survival (15, 18). Although in our series patients with synchronous metastases had a median survival of 21 months compared to 40 months in patients with metachronous metastases, there was no significant difference in survival between patients with a disease-free interval of 18 months or less compared to patients with a longer disease-free interval. Similar findings are reported from Robinson *et al.* (22). In our study, 19 patients who underwent at least one repeat resection showed a significantly longer median survival compared to patients with a single resection. This was also shown in multivariate analysis. Pogrebniak *et al.* analysed data from 42 patients who underwent 89 repeat resections and found a median survival of 25 months in those who were shown to be resectable compared to 10 months if the metastasis were irresectable (23). In our study all patients who underwent a second metastasectomy were shown to have resectable disease; the median survival after the second resection in our group was 22 months. Casson *et al.* found a disease-specific survival of 28 months after re-resection (24), Weiser *et al.* even 51 months (11), while Van Geel *et al.* reported five patients surviving 10 years and longer after initial treatment of the primary STS (12).

Primary tumor stage did not appear to be a significant prognostic factor in our series, although patients with primary tumor stage I-II tended to have a longer median survival than patients with higher stages. In the literature, most commonly, the tumor grade was analysed as a possible prognostic factor. The European multi-institutional review demonstrated a more favourable survival for patients with low grade lesions (19). This corresponds to our findings. In our study, primary tumor grade was identified as an independent prognostic factor. Only two studies have identified patient age >40 years and >50 years old as poor prognostic indicators (18, 19). In our series, there was no impact of age even in univariate analysis.

We also examined the maximum size of nodules resected as well the presence of solitary *versus* multiple metastases as possible prognostic factors. Small metastases of 2 cm or less were not associated with an advantage in survival, but, in contrast, were associated with a slightly worse survival, without a significant difference. Prognostic significance associated with the number of nodules resected was shown by Casson *et al.* (7) who demonstrated that patients with three or fewer nodules on preoperative lung tomograms had a significantly longer survival than patients with four or more nodules. They also found that patients with four or fewer nodules resected at operation had a longer post-thoracotomy survival than patients with more than four nodules. Similar results were found by Putnam *et al.* (8) In our study, however, corresponding to the findings of Billingsley *et al.* (18), the number of nodules was not a significant prognostic factor. Patients with solitary metastases had a survival of 22 months, which was even slightly lower than in patients with multiple lesions. In contrast to the findings of Billingsley *et al.*, who found a favourable prognosis of leiomyosarcoma (18), in our trial patients with leiomyosarcoma had a shorter median survival than patients in the non-leiomyosarcoma-group, although the difference did not reach significance. Surprisingly, patients who suffered from bilateral metastasis in our trial showed a slightly longer median survival than patients with unilateral disease but without any significance, which is in contrast to the MSKCC data. In bilateral disease, patients who under went sequential metastasectomy had a shorter median compared to the patients who underwent simultaneously metastasectomy through sternotomy or clamshell operation.

The value of adjuvant or pseudo-neoadjuvant systemic treatment has not been fully elucidated. The clinical benefit associated with adjuvant chemotherapy in patients with high-risk extremity STS has been studied in multiple trials but remains unclear (25). There is no data concerning pseudo-neoadjuvant treatment in advanced STS. In our trial, the patients who underwent preoperative chemotherapy survived only 18 months compared to 36 months in the non-treated group. Since the impact of primary tumor grade on survival is essential and chemotherapy was performed mostly in high grade sarcoma, this might be the reason for this finding.

Conclusion

Long-term survival is possible after resection of pulmonary metastases from soft tissue sarcoma. Unfortunately, recurrent disease develops in a significant number of patients, but repeat resection in resectable recurrent disease can lead to long-term survival. Multiple variables have been analysed to detect possible prognostic factors with inconsistent results. Our series showed the primary tumor grade and the performance of repeat resections in recurrent disease to be significant prognostic factors. Some institutions try to select for patients with a favourable tumor biology through repeated CT-scans (16). There is thus so far no evidence that this will be of advantage for the further course of the disease. Given the continued paucity of meaningful therapeutic alternatives, surgical excision, especially of pulmonary metastases, is currently the only curative option for patients with metastatic disease and should remain the treatment of choice, regardless of age, disease-free interval, the extent of the disease or the necessary extent of resection.

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