Benefit of Surgical Treatment of Lung Metastasis in Soft Tissue Sarcoma

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Hypothesis: Patients with pulmonary metastatic soft tissue sarcoma benefit from resection, with long-term cure possible.

Design: Retrospective medical records review.

Setting: Academic tertiary care center.

Patients: Between January 1, 1991, and December 31, 2002, 61 patients (33 men and 28 women; median age at initial diagnosis, 42 years [age range, 18-74 years]) were surgically treated for pulmonary metastases of soft tissue sarcoma at University Hospital, Hamburg-Eppendorf, Germany.

Interventions: Sternotomy or anterior lateral thoracotomy was performed for metastasectomy, including wedge resection or lobectomy.

Main Outcome Measure: The effects of clinical and pathologic factors on disease-specific survival were analyzed using the log rank test and a multivariate Cox proportional hazards model.

Results: Primary tumor size was pT1 in 13 patients and pT2 in 48 patients. The differentiation was high in 7 patients, intermediate in 19 patients, and low in 35 patients. The mean number of resected pulmonary metastatic lesions was 5 (range, 1-48). An anterolateral thoracotomy was performed in 39 patients, and sternotomy in 22 patients. There were no significant postoperative complications that required surgical revision. The perioperative mortality was 0%. At a mean follow-up of 60 months, the mean survival time after metastasectomy was 33 months (range, 2-125 months). The 5-year survival was 25%. The number of resected lung metastatic lesions had no prognostic relevance (P = .37).

Conclusions: Patients with lung metastasis from soft tissue sarcomas benefit from surgical excision. This treatment has low complication rates and has a favorable influence on the course of the disease. Long-term survival is possible even when recurrent pulmonary disease is resected.

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Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumors accounting for approximately 1% of all malignancies. They metastasize predominantly to the lungs. Though in this situation chemotherapy is not considered a curative option, pulmonary metastasis from STS is no longer considered to have a uniformly fatal outcome.

In the past decades, several reports have shown promising results and prolonged survival after surgical treatment of these metastases. Nevertheless, it is still debatable which patients will benefit from surgical intervention. Several groups select only those patients for surgery who meet the Bethesda criteria, as follows: tumor doubling time of 20 days or longer, 4 metastatic nodules or fewer, and a disease-free interval of 12 months. Others recommend a more aggressive approach to the management of pulmonary metastases from STS, including surgical intervention in all patients with technically resectable metastases.

See Invited Critique at end of article

At University Hospital, Hamburg-Eppendorf, Germany, all patients with operable lung metastasis underwent radical surgical therapy regardless of the site or number of metastatic nodules. Patients who had pulmonary metastatic relapse after previous metastasectomy underwent reoperation if no disseminated disease was present.
revealed at chest computed tomography. In this article, we analyze our 12 years of experience in treating these patients, with emphasis on prognostic factors.

The strategy was as follows: patients with fewer than 6 metastatic lesions underwent primary tumor resection and patients with more than 6 pulmonary metastatic lesions received chemotherapy, usually doxorubicin hydrochloride (Adriamycin; Pharmacia Inc, Columbus, Ohio) based. Surgery was performed if either complete or partial regression or stable disease was noted after 6 courses of chemotherapy and no contraindication by pulmonary function test was evident.

Unless contraindicated, all patients with pulmonary metastasis from STS underwent surgical therapy with curative intent. Potential contraindications included insufficient control of the primary tumor, unresectable lung disease, extensive involvement of the mediastinum or the chest wall, and unresectable metastatic disease outside the lung. Further contraindications were insufficient pulmonary function or other comorbidities indicating that resection of all pulmonary nodules would not be tolerated by the patient.

All metastases were detected by means of plain chest x-ray film and computed tomography of the chest. Lung function was measured in all patients. The approach for surgical exploration was either sternotomy or anterolateral thoracotomy. During surgery, the deflated lungs were routinely palpated by the surgeon. All palpable nodules were removed by wedge resection or lobectomy and were sent for histopathologic examination.

Data were prospectively entered into a sarcoma database, and patients were followed up regularly per management protocol. We recorded histopathologic parameters, including tumor stage, grade, and histologic type, as well as resection margin at the primary surgery. Moreover, clinical parameters with potential prognostic effect were analyzed. We focused on the following factors: presence of predisposing conditions for STS, site of the primary tumor, number of metastatic lesions, time until lung metastasis occurred, concomitant metastasis to other organs, incidence of local recurrence, preoperative or postoperative radiation or chemotherapy, number and type of surgical interventions, and intraoperative and postoperative morbidity.

Postoperative follow-up was performed at 3-month intervals for 2 years, then every 6 months for 5 years, and every year thereafter. It consisted of a baseline chest x-ray study and computed tomography of the chest and abdomen, as well as either computed tomography or magnetic resonance imaging of the involved extremity. When recurrent pulmonary metastasis was diagnosed at follow-up examination, patients underwent repeat lung resection unless diffuse or bulky and technically unresectable pulmonary relapse was present or patients had multiple metastatic lesions at other sites as well. In such cases, patients were transferred to the oncology department for further palliative therapy.

**STATISTICAL METHODS**

The main outcome evaluated was death associated with the tumor. Survival was calculated from the time of resection of the primary tumor and from the time of first metastasectomy to the date of the last follow-up. Probabilities of survival were calculated according to Kaplan and Meier and compared using the log-rank test. Eight candidate variables were evaluated, including age, sex, tumor grade, number of metastatic lesions, bilateral pulmonary involvement, histologic type, location of the primary tumor, and duration of disease-free survival after the primary operation. The t test was used for comparison of mean values.

**RESULTS**

**CHARACTERIZATION OF PATIENTS AND PRIMARY TUMORS**

Between January 1, 1991 and December 31, 2002, 678 patients with STS were treated at the Department of Surgery, University Hospital. During follow-up, pulmonary metastasis of STS occurred in 121 patients. Patients with fewer than 6 metastastic lesions underwent primary tumor resection if no contraindication was found, and patients with more than 6 pulmonary metastatic lesions received chemotherapy. Of the 121 patients, 61 were eligible for surgical resection. All 61 patients underwent surgical therapy with curative intent. Thirty-three patients (54%) were men and 28 (46%) were women; their mean age was 42 years (age range, 18-74 years). The corresponding primary tumors were localized in the extremities in 44 patients (72%) and in the retroperitoneum or other sites in 17 patients (28%). The primary tumor was located superficially (pTxa) in 14 patients (23%) and deep (subfascially, pTxb) in 44 patients (72%). The remaining 3 patients (5%) had a primary sarcoma in the parenchymal organs. Ten patients (16%) had a predisposition for STS, such as thorotostasis or von Recklinghausen disease (NF1).

In the remaining 60 of 121 patients, resection was not performed because of diffuse pulmonary or systemic dissemination and insufficient pulmonary function. These patients received palliative chemotherapy, if wanted.

Almost all histologic variants of STS were represented among the patients with pulmonary metastases. Analysis of the primary histologic findings and tumor grade demonstrated that, in patients who develop lung metastases, malignant fibrous histiocytoma and leiomyosarcoma are the most common (Tables 1, 2, and 3).

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant fibrous histiocytoma</td>
<td>13 (21)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Synovial cell sarcoma</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Alveolar cell sarcoma</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Unclassified sarcoma</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Dermatofibrosarcoma</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Stromal sarcoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hemangioendothelioma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>1 (2)</td>
</tr>
</tbody>
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PRIMARY TREATMENT

Twenty-nine patients with pulmonary metastasis underwent resection of the primary tumor at our institution, and 32 patients with distant metastases underwent resection of the primary tumor at other hospitals. At primary surgery, 39 patients (64%) underwent complete resection of the primary tumor, with microscopically tumor-free margins. The primary tumor resection in 22 patients (36%) was classified as R1, because the tumor was visible during primary surgery, microscopic tumor cells were present at the resection margin, or tumor growth was noted along large vessels or nerves. Five of these patients underwent treatment of the primary tumor at our institution and had either denied additional surgery to treat the primary tumor or refused amputation to achieve wide tumor-free margins. Two of these patients developed local recurrence, which was resected, achieving wide margins. The other 17 patients were initially treated elsewhere and when seen at our institution demonstrated no local tumor. Fifteen patients (25%) received adjuvant chemotherapy and 10 patients (16%) received adjuvant radiation therapy at some point during the clinical course of their disease. Three patients (5%) received both adjuvant radiation therapy and chemotherapy. In this group, no statistical association between radiation therapy of the primary tumor and local recurrence could be evaluated.

LOCAL RECURRENCE AND METASTASIS AT OTHER SITES

Local recurrence occurred in 28 patients (46%), diagnosed at a mean of 6 months after initial resection. In 20 (71%) of these 28 patients, local recurrence was diagnosed before development of lung metastasis. All recurrent tumors had been resected.

PULMONARY METASTASIS

The median time until lung metastasis was diagnosed was 21 months (range, 1-3 months) after resection of the primary tumor. Forty-two patients (69%) had pulmonary recurrence within 2 years after resection of the primary tumor. Sixteen of these patients had synchronous pulmonary metastasis. In 19 patients (31%), lung metastasis was discovered more than 2 years (maximum, 73 months) after resection of the primary tumor. The mean number of metastatic lesions in the lung was 5 (range, 1-48) (Table 4). In 29 patients (47%), bilateral metastatic lesions were detected on the imaging studies.

SURGICAL THERAPY

In patients with pulmonary metastasis, those with fewer than 6 metastatic lesions underwent primary resection and patients with more than 6 pulmonary metastatic lesions received chemotherapy. In 20 patients, surgery was performed if either complete or partial response or stable disease was diagnosed after 6 courses of chemotherapy and no contraindication according to cardiovascular or pulmonary function was found. In 10 patients, rapidly progressive disease was noted during chemotherapy and pulmonary metastases were not resected. Operative approaches included the following: anterolateral thoracotomy, bilateral anterolateral thoracotomy, and median sternotomy. Bilateral thoracotomy was performed in 2 subsequent sessions to reduce perioperative morbidity. Most of the metastatic nodules could be removed by wedge resection, while in 9 patients lobectomy was performed because of either the size or intrapulmonary localization of the metastatic tumor (Table 5).

RESULTS OF METASTASECTOMY

Except for transient alveolar leakage, resulting in prolonged stay of pleural drainage (9 patients), wound infections (3 patients), or hypoventilation (3 patients), there
were no major postoperative complications requiring surgical intervention. The perioperative mortality was 0%. Tumor-free margins after pulmonary metastasectomy were achieved in 57 patients (93%) and confirmed at histopathologic examination. Resection was incomplete in 4 patients because of extended or unresectable pleural or mediastinal involvement.

SURVIVAL DATA

Follow-up was calculated from the date of primary surgery, and the primary end point was death. The mean overall follow-up after primary surgery was 60 months (range, 7-274 months). Mean tumor-free survival after metastasectomy was 16 months. Mean survival after metastasectomy was 33 months (range, 2-125 months), and the 5-year survival was calculated at 25% (Figure 1). A substantial number of patients (13 [21%]) survived for more than 5 years (Table 6).

PROGNOSTIC FACTORS

That there were 13 long-term survivors (21%) in our series suggests the existence of 2 populations with different risk profiles for tumor recurrence. Therefore, we searched for criteria to differentiate long-term survivors from the other patients.

In several studies, prognostic factors such as age, tumor grade, number of metastatic lesions, bilateral pulmonary involvement, histologic type, site of the primary tumor, and duration of disease-free survival after surgery to treat the primary tumor were found to be relevant in patients with lung metastasis from STS. In our patients, none of these factors showed any significant correlation with overall and tumor-free survival (Table 7). We also found no effect of duration of disease-free interval between primary surgery and the diagnosis of pulmonary metastasis, which was found to be of prognostic relevance by other groups.

In our study, the only patients at increased risk of early tumor recurrence and worse prognosis were those with a predisposing disease for STS, such as von Recklinghausen disease or exposure to thorotrust. The prognosis in this subgroup was significantly worse (P=.03) than in patients without such a condition (Figure 2).

Furthermore, no prognostic effect of the operative approach was noted. There was no significant difference between patients who underwent anterolateral thoracotomy and those who underwent sternotomy for surgical exploration of the chest. The different techniques used to resect the metastatic nodules, that is, wedge resection or lobectomy, also had no statistical effect on prognosis. Regimens of adjuvant therapy such as radiation therapy or chemotherapy, used during the course of disease in some patients, also showed no prognostic influence.

REPEATED METASTASECTOMY

When metastatic relapse to the lung occurred, 13 patients with technically resectable disease underwent reoperation. The mean survival in this subgroup was 55 months, calculated from the date of the first lung resection. Compared with the remaining patients, reoperation of metastatic relapse was a significant indicator of a more favorable prognosis and prolonged survival (P=.002) (Figure 3).
In the absence of other effective treatments,\textsuperscript{16-18} and if there is no contraindication, patients with lung metastasis from STS benefit from surgical therapy. Common risk factors such as the number of metastatic lesions, bilateral involvement, tumor grade, or disease-free interval until the occurrence of lung metastasis did not show significant difference for survival data in our series of 61 patients. Thus, it seems worthwhile to operate on every patient with lung metastasis unless serious comorbidity or technically unresectable metastatic disease is present. This point of view is shared by an increasing number of centers.\textsuperscript{15,19,20}

This policy is underlined by the low complication rate of surgical treatment. In our study, there was no perioperative mortality and no major postoperative morbidity that required reoperation.

Despite a large percentage of patients with potential risk factors (20 patients (33%) had >5 metastatic nodules, 29 patients (48%) had bilateral involvement, and 35 patients (57%) had high-grade tumors), the mean survival rate in our series was 33 months. In addition to these encouraging results, 13 patients (21%) survived more than 5 years, including 6 patients (46%) who underwent repeat thoracotomy because of recurrent pulmonary metastasis.

This observation, which is shared by other centers,\textsuperscript{21,22} prompted us to analyze the subgroup of patients who underwent repeat operation because of recurrent lung metastasis. Comparing the survival data in these patients with the remaining patients, we found that the patients who underwent a repeat operation had a significantly better prognosis ($P=.002$). However, in this context, it must be considered that these patients represent a select subgroup with a different recurrence pattern and generally better health. We conclude from these results that repeat resection, if technically feasible, could be a means of achieving long-term survival and should be recommended in patients with recurrence of pulmonary lesions.

Analysis of subgroups with increased risk of tumor recurrence showed that patients with a preexisting condition predisposing to STS, such as von Recklinghausen disease, have a significantly worse prognosis and shorter survival after lung resection. The reason for this is probably different tumor biology based on genetic alterations.\textsuperscript{23} In contrast, patients who were long-term survivors despite pulmonary tumor relapse after metastasectomy and subsequent repeat resection have a less malignant tumor biology.

Little is known about tumor genetics of STS. Further genetic screening studies with chip array analysis may enable better understanding of genetic alterations resulting in tumor progress in STS\textsuperscript{24,25} and offer multimodal therapeutic concepts specifically tailored to the tumor biology in each patient.

**Figure 2.** Kaplan-Meier overall survival curves according to sarcoma predisposition. Overall survival in patients with sarcoma predisposition was significantly shorter than in patients without sarcoma predisposition ($P=.03$, log-rank test).

**Table 7.** Predictors of Tumor-Related Death

<table>
<thead>
<tr>
<th>Variable</th>
<th>$P$ Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>.43</td>
</tr>
<tr>
<td>Sex</td>
<td>.52</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>.31</td>
</tr>
<tr>
<td>No. of metastatic lesions</td>
<td>.42</td>
</tr>
<tr>
<td>Bilateral involvement</td>
<td>.48</td>
</tr>
<tr>
<td>Histologic type</td>
<td>.45</td>
</tr>
<tr>
<td>Site of primary tumor</td>
<td>.6</td>
</tr>
<tr>
<td>Disease-free survival after primary operation$\dagger$</td>
<td>.53</td>
</tr>
</tbody>
</table>

*Univariate analysis, log-rank test.†Younger than 60 years vs 60 years or older.‡Subfascial vs subcutaneous.§Twenty-four months or less vs more than 24 months.

**Figure 3.** Kaplan-Meier overall survival curves according to repeat surgery because of recurrent pulmonary metastasis. Survival was significantly longer in patients who underwent repeat surgery ($P=.002$, log-rank test).

**CONCLUSIONS**

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Stoecklein, Knoefel, and Peiper. Drafting of the manuscript: Rehders, Hosch, Scheunemann, Stoecklein, and Peiper. Critical revision of the manuscript for important intellectual content: Rehders, Hosch, Scheunemann, Stoecklein, Knoefel, and Peiper. Statistical analysis: Rehders, Hosch, Scheunemann, and Peiper. Administrative, technical, and material support: Scheunemann, Knoefel, and Peiper. Study supervision: Hosch, Scheunemann, Stoecklein, Knoefel, and Peiper. Financial Disclosure: None reported.

REFERENCES