

## CLINICAL SCIENCE

# Pulmonary metastasectomy from soft tissue sarcomas

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**INTRODUCTION:** Isolated pulmonary metastases from soft tissue sarcomas occur in 20-50% of these (the issue is about metastases, not lung cancer) patients, and 70% of these patients will present disease limited only to the lungs. Surgical resection is well accepted as a standard approach to treat metastases from soft tissue sarcomas isolated in the lungs, and many studies investigating this technique have reported an overall 5-year survival ranging from 30-40%. The most consistent predictor of survival in these patients is complete resection. The aim of the present study was to determine the demographics and clinical treatment-related variables associated with long-term (90-month) overall survival in patients with lung metastases undergoing pulmonary metastasectomy from soft tissue sarcomas.

**METHODS:** We performed a retrospective review of patients admitted in the Thoracic Surgery Department with lung metastases who underwent thoracotomy for resection following treatment of the primary tumor. Data regarding primary tumor features, demographics, treatment, and outcome were collected.

**RESULTS:** One hundred twenty-two thoracotomies and 273 nodules were resected from 77 patients with previously treated soft tissue sarcomas. The median follow-up time of all patients was 36.7 months (range: 10-138 months). The postoperative complication rate was 9.1%, and the 30-day mortality rate was 0%. The 90-month overall survival rate for all patients was 34.7%. Multivariate analysis identified the following independent prognostic factors for overall survival: the number of metastases resected, the disease-free interval, and the number of complete resections.

**CONCLUSION:** These results confirm that lung metastasectomy is a safe and potentially curative procedure for patients with treated primary tumors. A select group of patients can achieve long-term survival after lung resection.

**KEYWORDS:** Lung; Metastases; Soft tissue sarcomas; Metastasectomy; Prognostic factors.

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## INTRODUCTION

Sarcomas are a group of very uncommon malignant tumors that compromise 1% of all adult malignancies.<sup>1</sup> Approximately 11,590 new diagnoses and 3,560 deaths from soft tissue sarcomas (STS) and bone sarcomas occur annually in the United States.<sup>1</sup> Isolated pulmonary metastases from STS occur in 20-50% of these patients, and 70% of these patients will have disease limited only to the lungs.<sup>2</sup> Once systemic metastatic disease develops, the prognosis is typically poor.<sup>3</sup> Patients with extremity sarcomas are more likely to develop distant metastatic disease as the initial site of recurrence, whereas those with retroperitoneal and visceral sarcomas tend to present local recurrence.<sup>4</sup>

Although considerable progress has been achieved in both chemotherapy and surgical treatment of STS, pulmonary metastases remain a major cause of mortality. Given that a diagnosis of pulmonary metastases significantly affects outcome, treatment and prognosis, the detection of such pulmonary metastases is of vital importance.<sup>5</sup>

Surgical resection is well accepted as a standard approach for the treatment of metastases from STS isolated to the lungs, and many studies investigating this technique have reported an overall 5-year survival ranging from 30-40%.<sup>6,7</sup> Chemotherapy has not been shown to increase survival following the complete resection of pulmonary metastases.<sup>6</sup>

Pulmonary metastasectomy is currently indicated for patients with the following criteria: primary tumor controlled, possibility of complete resection verified by computed tomography (CT) of the chest, pulmonary function and performance status compatible with the proposed lung resection, and lack of another available treatment that would be more effective than the surgical procedure.<sup>8</sup>

Although the results obtained for pulmonary metastasectomy are encouraging, there is a need to better select and

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identify the patients who would benefit most from surgical removal of pulmonary metastases to avoid unnecessary surgical procedures. Many authors have reviewed their experience in an attempt to clearly identify the variables associated with better survival. Important predictors of survival include disease-free interval, histology of the tumor, the number of metastases and complete resection.<sup>5-7</sup> Among these, the most consistent predictor of survival is complete resection.<sup>6,7,9</sup> The number of metastatic nodules and their impact on survival was initially considered to be an independent predictor of survival.<sup>10</sup> However, if complete resection can be achieved, the number of pulmonary metastatic nodules does not seem to influence survival.<sup>6,7,11</sup>

Since the early 1990s, our institution has employed a prospective protocol-oriented approach for the treatment of patients with resectable lung metastases to define factors related to outcome following lung metastasectomy.

The aim of this study was to report the outcomes of patients with pulmonary metastases from STS who were submitted to surgical resection and to identify prognostic factors that affect overall survival in a group of patients from a single institution.

## MATERIAL AND METHODS

We retrospectively analyzed 77 patients with previously treated STS who had developed pulmonary metastases. The patients were referred to the Thoracic Surgery Department of AC Camargo Hospital between 1990 and 2006. All patients were included and followed according to a prospective protocol. This study was approved by the ethics review board at our institution.

Data were collected following a medical record review of each patient. The following characteristics of the primary tumors were recorded: primary tumor site (extremity vs. others), completeness of surgical resection, histological type and grade, and neoadjuvant and adjuvant treatment.

All patients were evaluated for the presence of lung nodules before treatment of the primary STS, followed by evaluations at routine follow-up appointments. The disease-free interval was defined as the time period between treatment of the primary tumor and the diagnosis of pulmonary metastases.

Patients with the following characteristics were considered eligible for pulmonary resection: 1) primary tumor controlled, 2) nodules confined to the lung parenchyma, 3) nodules that were amenable to complete surgical resection, 4) pulmonary function and clinical condition compatible with the scheduled operation, and 5) the unavailability of more effective treatment options for the patient at that time. In addition to the evaluations, we collected variables related to the pulmonary metastases, including the number of pulmonary nodules on the CT scan, the number of malignant pulmonary nodules resected, the size of the largest nodule resected and the laterality of the pulmonary nodules.

All patients underwent a chest CT scan prior to surgery to evaluate the possibility of complete resection. Radiological characteristics were analyzed in each patient as follows: the number of pulmonary nodules, the size of the largest nodule and the laterality of the nodules. The number of nodules reported in this study was the final number confirmed by the surgeon after complete resection.

A staged lateral thoracotomy was employed when bilateral nodules were discovered at admission. This procedure was typically initiated on the side where complete resection was deemed more difficult and included the number and size of the nodules identified by chest CT scan, the anatomical position of one or more nodules relative to the pulmonary hilum, and the potential need for a more complex and extensive lung resection.

Patients underwent surgery with general anesthesia and single lung ventilation. In all cases, we attempted a complete resection while preserving the lung parenchyma with a margin of 10 mm. A one-sided lateral thoracotomy was performed. Even in cases of bilateral disease, we routinely performed a staged thoracotomy. At our institution, mediastinal lymph node dissection is not routinely performed in patients with lung metastases. In cases of a single pulmonary nodule at surgery, frozen sections were collected. If the histological evidence suggested the possibility of primary lung cancer, the patient was submitted to lobectomy with radical mediastinal lymph node dissection whenever possible.

The date of surgery, type of resection (complete or incomplete), number of malignant or benign nodules resected, size of the largest nodule, and type of lung resection (wedge, segmentectomy, lobectomy or pneumonectomy) were documented.

Some patients received chemotherapy based on the discretion of the medical oncologist, before or after surgical resection of the lung metastases. The type of radiological response (partial, stable, complete, or progression) as defined by RECIST<sup>12</sup> criteria was documented.

After surgery, the patients were discharged from the hospital following chest tube removal and in good clinical condition. After hospital discharge, the patients were followed-up with clinical and radiological examinations (chest X-ray and CT scan) every three months during the first two years and every six months subsequently until the fifth year. An annual radiological (chest X-ray) follow-up was performed after five years. The observed postoperative complications were fever > 38°C, bleeding, air leakage for more than seven days, intensive care unit stay for more than two days, cardiac complications (arrhythmia, ischemia, and infarction), pulmonary atelectasis, embolism or respiratory failure, stroke and infection. Recurrence was recorded when new lesions were identified in the lung or elsewhere. Whenever necessary, a histological confirmation of the new tumor was performed. If the recurrence was confined to the lungs and if the nodules were considered resectable by the thoracic surgeon, the patient was offered another attempt at complete disease resection.

## Statistical Analyses

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 death or until the last follow-up. Overall survival was estimated using Kaplan-Meier<sup>13</sup> analysis. The log-rank and Breslow tests were used to compare survival differences for each variable.

Multivariate analyses to determine the independent prognostic factors for overall survival were performed using the Cox proportional hazard model<sup>14</sup> as identified by the univariate analyses. Survival time was determined

whenever more than one pulmonary metastasectomy was performed, with time zero denoting the first thoracotomy.

Statistical analyses were performed using SPSS 11.5 for Windows. Significant differences were defined as  $p < 0.05$ .

## RESULTS

The patients included in this retrospective study ( $n = 77$ ) underwent a total of 122 thoracotomies (mean of 1.6 thoracotomies / patient); 273 nodules were resected, with a mean of 3.5 nodules per thoracotomy. Five of the nodules were carcinomas and were treated as primary lung tumors, and more than four nodules were resected in each of 18 (18.1%) patients.

According to the primary STS, 66 (85.7%) patients had extremity tumors, and 11 patients (14.3%) had visceral or retroperitoneal tumors. In 64 patients (83.1%), the primary STS histology (Table 1) and grade (Table 2) were registered as well. In the 13 remaining patients, we could not find sufficient detailed information regarding the histological type and grade of the primary tumors in the medical records because the primary tumors of these patients had been resected at other institutions. Based on the final confirmation of sarcomas from the pathology of the pulmonary metastases, these tumors were classified as undetermined and excluded from statistical analyses in which histology was considered.

The median follow-up time was 36.7 months (range: 10-138 months). Twenty-nine patients were alive at the time of the final analyses, and 13 (16.9%) showed no evidence of disease. Thirty patients (39%) died due to metastatic STS, and 18 (23.4%) patients were considered lost to follow-up after missing two medical evaluations.

The postoperative complication rate was 9.1% ( $n = 7$ ). More than one complication occurred in some patients, including fever, atelectasis, prolonged air leakage ( $> 7$  days), infection and a prolonged hospital stay ( $> 30$  days). There was no 30-day mortality associated with the surgery used in this series.

The median overall survival for all patients was 36.7 months, with an estimated 5-year survival rate of 34.7% (Figure 1). The median survival for patients with one, two, three or more pulmonary metastasis resections was 15.1, 44.8 and 48.1 months, respectively. No significant difference in survival was detected between the groups with respect to the number of thoracotomies ( $p = 0.07$ ).

All other factors evaluated in the univariate analyses, including the response to adjuvant chemotherapy, type of

**Table 2 - Grade of STS in 64 patients submitted to pulmonary metastasectomy.**

GRADE	n	%
G3	50	78.1
G2	8	12.5
G1	6	9.3
Undetermined	13	18.1
Total	77	100

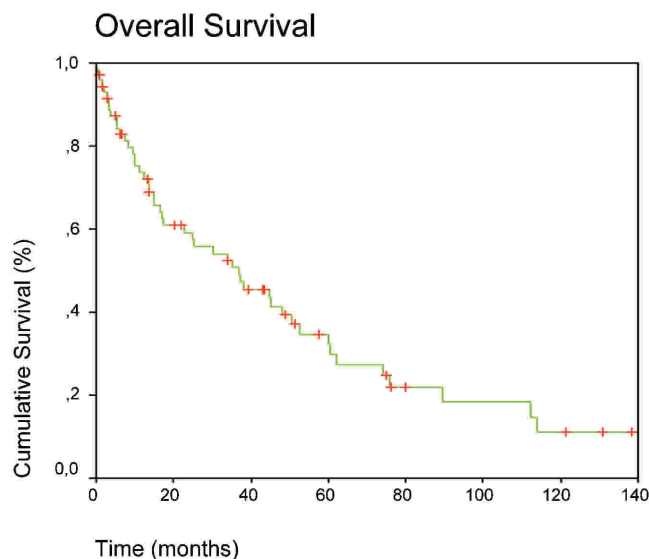
resection, number of resected nodules, laterality of the nodules on the CT scan, number of thoracotomies and size of the largest nodule resected, were not statistically significant ( $p > 0.05$ ). The patient characteristics and univariate analyses are shown in Table 3. Multivariate analyses identified the number of pulmonary nodules resected ( $p = 0.003$ ), the disease-free interval ( $p < 0.001$ ) and complete resection ( $p < 0.001$ ) as independent prognostic factors for overall survival (Table 4).

## DISCUSSION

The resection of pulmonary sarcomatous metastasis remains the cornerstone for treatment of isolated pulmonary metastases in patients with STS.<sup>14</sup> In the absence of other effective treatments and of contraindications, patients with lung metastases from STS benefit from surgical therapy.<sup>16,17</sup> Approximately 20-30% of patients undergoing pulmonary resection can experience long-term survival.<sup>5,6,18</sup> Improved survival following the resection of lung metastases has increased the surgical indications for such lesions, thus confirming that surgery itself affects the outcomes of patients who are candidates for a complete resection of nodules confined to the lungs. Therefore, resectability should be evaluated preoperatively according to specific criteria. The recent introduction of positron emission tomography using 18-fluorodeoxyglucose (FDG PET-CT) has proven to be of clinical value for the proper staging of cancer patients to better select the best candidates for resection. According to Pastorino et al., this method can eliminate 21% of patients who are otherwise considered as

**Table 1 - Histologic type in 64 patients submitted to pulmonary metastasectomy.**

Histology of the primary tumor	n	%
Malignant fibrous histiocyoma	15	23.4
Liposarcoma	11	17.1
Fibrosarcoma	10	15.6
Synovial sarcoma	9	14.0
Leiomyosarcoma	8	12.5
Spindle cell sarcoma	5	7.8
Epithelioid sarcoma	2	3.1
Rhabdomyosarcoma	2	3.1
Angiosarcoma	1	1.5
Hemangiopericytoma	1	1.5
Undetermined	13	18.1
Total	77	100



**Figure 1 - Overall survival rates for all patients  $n = 77$ .**

**Table 3 - Univariate analyses and characteristics of the 77 patients submitted to pulmonary metastasectomy.**

Variables	n	Median survival (months)	p (Log-rank)
Age (years)			
<45	37 (48.1%)	30.3	0.326
≥45	40 (51.9%)	52.5	
Gender			
Male	37 (48.1%)	36.7	0.152
Female	40 (51.9%)	33.9	
Primary tumor site			
Extremities	66 (85.7%)	38.2	0.389
Others	11 (14.3%)	17.0	
Neoadjuvant chemotherapy			
Yes	26 (33.8%)	12.5	0.018
No	51 (66.2%)	45.2	
Adjuvant chemotherapy			
Yes	n = 18 (23.4%)	25.4	0.077
No	59 (76.6%)	38.2	
Disease-free interval (months)			
≤16	31 (40.3%)	8.3	<0.001
>16	46 (59.7%)	60.0	
Number of thoracotomies			
1	35 (48.6%)	15.1	0.077
2	24 (33.3%)	44.8	
≥3	13 (18.1%)	48.1	
Laterality of the nodules			
Right	24 (31.2%)	35.0	0.076
Left	15 (19.5%)	36.7	
Bilateral	38 (49.4%)	36.0	
Complete resection at last thoracotomy			
Yes	61 (79.2%)	44.8	<0.001
No	16 (19.0%)	9.5	
Number of malignant nodules resected			
1	43 (55.9%)	38.2	0.930
2-4	20 (26.0%)	24.8	
>4	14 (18.1%)	36.7	
Type of resection			
Segmentectomy/wedge	63 (81.8%)	36.7	0.944
Lobectomy	12 (15.6%)	35.0	
Biopsy	2 (2.6%)	9.5	
Diameter of the largest nodule resected			
≤2 cm	21 (27.4%)	62.2	0.231
>2-4 cm	38 (49.8%)	44.8	
>4 cm	18 (22.8%)	33.9	

surgery candidates.<sup>19</sup> Unfortunately, PET-CT was not available at our institution for most of the patients in this study.

Several studies have been conducted to identify prognostic factors for pulmonary metastasectomy in STS.<sup>5-7,17</sup> The factors evaluated included the disease-free interval number of metastatic lesions resected, tumor doubling time, laterality, number of thoracotomies and resectability of the lesions.<sup>20-23</sup> STSs are an extremely heterogeneous group of

tumors with a variable biological behavior. Therefore, the histological type and grade of malignancy are the most important prognostic factors in the treatment of primary tumors.<sup>24</sup> Moreover, other studies have found histology to be predictive of pulmonary metastasis, resectability, and overall survival in extremity STS.<sup>6,25</sup>

The 77 patients included in this study underwent 122 thoracotomies for the treatment of lung metastases. The estimated 5-year overall survival of our patients was 34.7% at an average follow-up of 36.7 months. This outcome is similar to previous reports.<sup>5,7,9</sup> In a review of the National Cancer Institute, the overall 5-year survival rate was 28%, with a 35% 3-year survival rate for patients who underwent complete resection. In that series, patients who experienced incomplete resection demonstrated a median survival of 9 months.<sup>26</sup> With a median follow-up period of 27 months, the International Registry of Pulmonary Metastases repor-

**Table 4 - Multivariate analyses of the overall survival.**

Variables	p
Disease-free interval (>16 months)	<0.001
Number of malignant resected nodules (<4)	0.003
Complete resection	<0.001

ted a 5- and 10-year survival rate in 936 patients with STS lung metastases of 30% and 22%, respectively.<sup>7</sup> However, this result does not compare to the 14-21% overall survival reported by some studies with longer follow-up periods.<sup>6</sup>

Several reports have demonstrated the prognostic importance of the number of nodules detected in the preoperative workup. The sensitivity of detecting pulmonary nodules varies depending on the technique used.<sup>23</sup> In a prospective study including 182 patients with cancer and pulmonary metastases by Younes et al., CT scan detected the exact number of nodules resected in 47% of the patients. However, CT scan underestimated the actual number of lung nodules found during surgery in 28% of the cases and overestimated that number in 24%.<sup>27</sup> In the present study, we discovered a poorer outcome in patients in which  $\geq 4$  nodules had been resected, as shown in the multivariate analysis.

For some authors, the number of pulmonary metastases does not preclude resection because the ability to achieve complete resection is of greater prognostic value than the number of lesions removed.<sup>28</sup> In a review of the European Organization for Research and Treatment of Cancer (EORTC) database, the majority of patients undergoing resection (53%) had only one lesion, although 15% of the patients had more than four lesions at the time of pulmonary metastasectomy.<sup>29</sup>

Previous studies have examined the number of nodules resected and the presence of unilateral and bilateral metastatic disease as prognostic factors. Casson et al. demonstrated that patients with three or fewer nodules survived significantly longer than did patients with four or more nodules resected.<sup>9</sup> Similar findings have been noted by Putnam et al.<sup>5</sup> who found that patients with four or fewer nodules survived longer than did patients with more than four nodules resected. The same group demonstrated that unilateral versus bilateral disease is not a significant indicator for prognosis. In most studies published to date, no differences have been observed in the survival of patients with metastases confined to one lung compared to bilateral lesions, despite the histology of the primary tumor.<sup>7</sup> The current study did not identify laterality as an independent indicator of prognosis.

In the present study, the number of nodules resected had a significant effect on long-term survival in both univariate and multivariate analyses ( $p=0.003$ ). Although the maximum number of pulmonary metastases often predicts survival,<sup>5,10</sup> subgroup analyses have found that complete resection is a stronger predictor of survival, regardless of the number or size of the nodules.<sup>31</sup>

Based on multivariate analysis, patients with synchronous metastases (DFI $<16$  months) presented with a significantly lower survival rate ( $p<0.001$ ) than did patients with metachronous disease, as reported in other studies.<sup>6,7,21,22,32</sup> The correlation between DFI and survival is not consistent in the published data. Depending on the study, DFI ranging from 8 months to as long as 5 years have been a significant prognostic factor; however, the results are vague and inconclusive according to some authors.<sup>29,31</sup>

Previous reports have been unable to consistently demonstrate a correlation between the primary site of STS and survival.<sup>29,33</sup> In the current series, univariate analyses demonstrated better survival for patients with non-extremity primary tumors. In the multivariate analyses, however, the site of the resected primary tumor did not affect the

long-term survival of patients submitted to pulmonary metastasectomy.<sup>6</sup> Similarly, no significant effect on outcome was observed between extremity tumors and those present in other primary sites.

Preoperative and postoperative systemic therapy had no significant effect on the long-term survival rate in this patient population, which is consistent with previously published data.<sup>34,35</sup> Although the patients ( $n=26$ ) submitted to neoadjuvant treatment with chemotherapy prior to primary tumor resection demonstrated a numeric difference in the univariate analyses ( $p=0.018$ ), this variable did not have a significant effect in the multivariate analyses.

Complete resection was achieved in 62 patients (80.5%). This variable was a strong prognostic indicator in the multivariate analyses ( $p<0.001$ ), which is consistent with previous reports.<sup>5-7,10,11,21,22</sup> The median survival for patients who underwent complete resection was 44.8 months, as compared to 9.5 months in the group who underwent incomplete resection ( $n=15$ ). In the present study, 15 (19.5%) patients were resubmitted to surgery for recurrent metastases, which ranged from one to four thoracotomies for complete resection. Curiously, these patients demonstrated better survival (median survival: 48.1 months) than did those who underwent one thoracotomy for metastasectomy (median survival: 15.1 months), which is consistent with previously published data.<sup>21,22,31,36</sup> Weiser et al. investigated a series of 86 patients who had undergone repeat resections. A poorer survival after repeat resection was associated with the following factors: more than three nodules, lesions larger than 2 cm, and high-grade histopathology. The presence of 0-1 adverse factors was associated with a disease-specific survival of 65 months. In comparison, the presence of 2-3 factors was associated with a disease-specific survival of 10 months.<sup>37</sup>

The type of surgical resection and the total number of thoracotomies failed to significantly influence patient outcome. The majority of our patient population (81.8%) underwent a sublobar resection, and ten (15.6%) patients required a lobectomy for complete resection. As reported previously, limited resection with lung parenchyma preservation is considered adequate to achieve clear margins and thus to provide local control of the disease. Recently, Cerfolio et al. showed that among 37% of patients who were candidates for video-assisted thoracic surgery (VATS), intraoperative palpation during a thoracotomy detected more nodules than had been identified using preoperative imaging by CT scan.<sup>38</sup> There may be a role for minimally invasive surgery in the pulmonary metastasectomy setting; however, additional prospective studies are required.

Although randomized controlled studies comparing observations to surgery are impossible, the current data suggest that the patients most likely to benefit from metastasectomy have a longer disease-free interval, single metastases, and complete resection of the metastases. The administration of neoadjuvant or adjuvant therapy may allow for further prolonged survival in some instances, despite the finding that surgery alone fails to treat lung metastases in the majority of patients. It should be emphasized that surgery does not change the biology of the tumor or the metastatic process, and a definitive cure for most patients represents the combination of host histology, tumor spread, response to systemic therapy, and surgical resection, which together render the patient free of disease.

## CONCLUSION

This retrospective study identified a group of patients who may benefit from pulmonary metastasectomy. All patients with resectable nodules evaluated by CT scan and selected by the inclusion criteria should be considered as candidates for surgical resection because they might reveal an interesting overall survival, as shown by the present study.

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