Improved Survival after Pulmonary Metastasectomy for Soft Tissue Sarcoma

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Introduction: Survival after pulmonary metastasectomy for soft tissue sarcoma (STS) has been lower than in osteosarcoma (14–40% versus 40–50%). With improved patient selection criteria and advanced chemotherapy agents, we hypothesized that survival after metastasectomy for STS has improved in recent years.

Methods: Retrospective study of 48 patients undergoing pulmonary metastasectomy for STS between 1995 and 2007. Potential predictors of overall survival and disease-free survival (DFS) were examined using the log-rank test or Cox regression. Multivariate analysis was conducted using Cox regression.

Results: Overall survival after initial metastasectomy was 67% and 52% at 3 and 5 years, respectively; DFS was 17% and 10% at 3 and 5 years. Univariate analysis indicated that ≤2 pulmonary metastases ($p = 0.03$), diameter of largest metastasis ≤2 cm ($p = 0.09$), and the absence of extrapulmonary metastases ($p = 0.10$) were associated with longer overall survival. Absence of extrapulmonary metastases ($p = 0.07$) and smaller size of the largest pulmonary metastasis ($p = 0.06$) were associated with longer DFS. Before 2001, 46.7% of patients received adjuvant chemotherapy versus 72.7% after ($p = 0.10$). Neither use of chemotherapy nor chemotherapy type was related to overall survival or DFS.

Conclusion: Five-year overall survival is substantially higher after pulmonary metastasectomy for STS in our study relative to previously published results (52% versus 14–40%). This improvement does not seem to be the result of greater use of, or newer, chemotherapeutic regimens. Among potential explanations, improved patient selection is the most likely factor.

Key Words: Soft tissue sarcoma, Pulmonary metastases, Chemotherapy, Surgery.

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Soft tissue sarcomas (STSs) are a diverse group of malignancies which are diagnosed in approximately 8000 patients each year in the United States.[1,2] Distant metastases occur in approximately 20 to 50% of patients, with the lung being the primary metastatic site.[1,3,4] Pulmonary metastasectomy is a well-accepted intervention that seems to provide the only opportunity for patients with lung metastases to obtain long-term survival.[5–7]

Nonrandomized studies evaluating the use of pulmonary metastasectomy for patients with STS report overall 5-year survival rates ranging from 15 to 40%.[5,8–14] Similar studies evaluating pulmonary metastasectomy for patients with osteosarcoma (OS) report 5-year survival rates ranging from 40 to 50%.[15–17] The lower success for patients with STS has been attributed to various causes, including less effective adjuvant chemotherapy for STS when compared with OS and the greater difficulty palpating small STS versus OS nodules. Over the last decade, doxorubicin-ifosfamide (D/I)-based regimens have emerged as the adjuvants of choice for metastatic STS.[18,19] Data supporting the use of adjuvant therapy, however, have been conflicting with some reports documenting positive effects[20] but others describing little to no influence.[12,21,22]

Given the lower survival after pulmonary metastasectomy for patients with STS, considerable effort has been placed in identifying candidates who would be most likely to benefit from resection. Several prognostic indicators have been associated with longer survival including fewer pulmonary metastases, smaller size of pulmonary metastases, tumor histology, complete resection of pulmonary disease, prolonged disease-free interval (DFI), absence of extrapulmonary metastases, younger age, and use of perioperative chemotherapy.[2,4–7,10–14,23]

We retrospectively reviewed our experience with metastasectomy for STS to evaluate the role of pulmonary metastasectomy in this era of improved patient selection and putatively more effective chemotherapy protocols. With the advent of these advancements, we hypothesized that survival time after metastasectomy for STS will have improved in recent years.

PATIENTS AND METHODS

Subject Selection

Patients were identified using the Thoracic Surgery Database within the University of Pennsylvania Health System (UPHS). Fifty-six patients who had undergone one or more pulmonary resections for histologically confirmed pul-

monary metastases of STS between 1995 and 2007 were initially identified. The few patients who underwent pulmonary resection with active extrapulmonary disease ($n = 2$) were excluded from analysis. Six additional patients were excluded as follow-up data could not be obtained.

Prognostic Variables and Data Acquisition

Prognostic variables were abstracted from the medical records. Variables included age at diagnosis, year of surgery, sarcoma histological variant, size of largest pulmonary metastasis, number of lung metastases (as proven by pathology), lymph node involvement, history of resected extrapulmonary metastases, and history of successfully treated recurrence at the primary site. Chemotherapy regimen was noted if used at any point after the diagnosis of pulmonary disease. Procedural details and postoperative course were also documented. All bilateral procedures, including staged bilateral thoracotomies occurring within 6 weeks of one another, were considered as a single intervention in the analysis.

Survival and disease status information were obtained from the most recent UPHS medical record. If the most recent record available was greater than 6 months before the time of data collection or the patient maintained follow-up outside UPHS, the patient/family was contacted and requisite information was obtained by a standardized phone interview. If follow-up data could not be obtained within 6 months of data collection, patient data were obtained from the last documented follow-up, and the patient was appropriately censored during survival analysis. Dates of death were determined using the Social Security Death Index or by contacting relatives. The study was approved by the University of Pennsylvania Institutional Review Board.

Statistical Analysis

Kaplan-Meier analysis was used to determine both overall survival and disease-free survival (DFS). Overall survival was defined as the date of initial pulmonary metastasectomy to the date of death or last follow-up. DFS was calculated from the date of initial pulmonary metastasectomy to the date of recurrence, last follow-up, or death.

The log-rank test was used to assess survival differences between groups identified by the following categorical variables: age at diagnosis of primary site ($\leq$50 versus $>$50 years), size of largest pulmonary metastasis ($\leq$2 cm versus $>$2 cm), number of pulmonary metastases ($\leq$2 versus $>$2 metastases), histological variant (malignant fibrous histiocytoma [MFH] versus other), recurrence at primary site (no versus yes), extrapulmonary disease before pulmonary involvement (no versus yes), hilar or mediastinal lymph node involvement (no versus yes), margin status at pulmonary resection (negative versus positive), use of adjuvant chemotherapy for pulmonary disease (no versus yes), type of chemotherapy regimen (D/I based versus other), date of pulmonary metastasectomy (before 2001 versus 2001 or after), and surgical approach (thoracoscopic versus open resection).

Univariate Cox regression analysis was used to examine the relationship of overall survival and DFS with the following continuous variables: size of largest pulmonary metastasis, age at diagnosis of primary site, and DFI (only as a predictor of overall survival and defined as the period from resection of the primary tumor until initial documentation of metastases).

Multivariate Cox regression analysis was used to evaluate the independent predictive value of variables for overall survival and DFS. Variables with a p value less than 0.20 found in log-rank or univariate analyses were included in the final multivariate models. Statistical analyses were performed using SPSS version 16.0 (SPSS, Inc. Chicago, IL).

Results are expressed as mean (standard deviation) unless otherwise noted. Because of the modest sample size and the exploratory nature of our analysis, p less than 0.10 was considered to be statistically significant.

RESULTS

Patient Information

Between 1995 and 2007, 56 patients underwent pulmonary metastasectomy for STS within UPHS, 48 of whom were included for analysis. Twenty-two (45.8%) were men and 26 (54.2%) were women. Mean age at diagnosis at the primary site was 47.9 (15.4) years (range: 12–72 years).

Population characteristics and distribution of tumor variants are listed in Tables 1 and 2, respectively.

Procedures and Findings

A total of 89 metastasectomies were performed in the 48 patients. Eighteen patients underwent a single pulmonary resection, 23 underwent a total of two resections, four underwent three resections, two underwent four resections, and a single patient underwent five resections. Of the 48 patients, five patients underwent an initial bilateral procedure by median sternotomy, four patients underwent initial staged bilateral thoracotomies several weeks apart, and 13 patients (all with less than three nodules on preoperative imaging) underwent video-assisted thoracoscopic surgery (VATS) resection. There were no perioperative deaths.

The mean number of nodules on computed tomography (CT) before initial resection was 1.6 (1.2); the mean number of pathologically proven nodules was 2.3 (2.2) ($p = 0.08$). The range for both nodules on CT and pathologically proven nodules was 1 to 12.

Overall Survival

Median overall survival after pulmonary metastasectomy was 5.3 years. Three-year and 5-year overall survival was 67% and 52%, respectively (Figure 1). By univariate analysis, variables significantly associated with increased overall survival included $\leq$2 pulmonary metastases ($p = 0.03$), largest pulmonary metastasis $\leq$2 cm ($p = 0.09$), and the absence of extrapulmonary metastases ($p = 0.10$). Other categorical and continuous variables did not significantly influence overall survival and are further described in Tables 3 and 4. No variables were found to be significantly associated with overall survival in multivariate Cox regression models (Table 5).