Risk stratification of patients undergoing pulmonary metastasectomy for soft tissue and bone sarcomas

Anthony Y. Lin, MD,[a] Svetlana Kotova, MD,[a,j] Jane Yanagawa, MD,[a] Osama Elbuluk, BS,[a] Gerald Wang, BS,[b] Nivedita Kar, BS,[c] David Elashoff, PhD,[d] Tristan Grogan, MS,[d] Robert B. Cameron, MD,[a,j] Arun Singh, MD,[e] Bartosz Chmielowski, MD,[e] Noah Federman, MD,[f] Scott D. Nelson, MD,[g] Percy Lee, MD,[h] Fritz C. Eilber, MD,[i] and Jay M. Lee, MD[a]

Objectives: Our objective was to identify risk factors associated with survival in patients who underwent pulmonary metastasectomy for soft tissue or bone sarcoma and to create a risk stratification model.

Methods: A retrospective review of the prospectively maintained University of California Los Angeles Sarcoma Database was performed. Clinical, pathologic, and treatment variables were analyzed for overall survival and disease-free survival. Univariate and multivariate analyses were performed, and variables that were identified as significant were included to create a risk model. A total of 155 patients who underwent pulmonary metastasectomy for soft tissue sarcoma (n = 108 patients) or bone sarcoma (n = 47 patients) from 1994 to 2010 were identified.

Results: Multivariate analysis identified 7 factors associated with poor overall survival: age more than 45 years, disease-free interval less than 1 year, thoracotomy, synchronous disease, location and type of sarcoma (soft tissue vs bone sarcoma), and performance of a lobectomy. The number of factors present was associated with poor overall survival, which varied widely from 64% in patients with 2 factors to 3% in those with 5 factors.

Conclusions: We have identified prognostic variables associated with overall survival after lung metastasectomy. Our model may be used as a risk stratification model to guide treatment decisions on the basis of the number of risk factors present. Although prospective studies are warranted to determine the benefit of surgical intervention in all cohorts compared with other local therapies or medical therapy, given the attendant dismal prognosis in patients with 5 or more risk factors, the benefit of surgical resection in this group is questioned. (J Thorac Cardiovasc Surg 2015;149:85-92)

From the Division of Thoracic Surgery,[a] Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, Calif; Division of Pulmonary and Critical Care Medicine,[b] Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, Calif; Departments of Biostatistics and Medicine,[c] David Geffen School of Medicine at UCLA, Los Angeles, Calif; Division of General Internal Medicine and Health Services Research,[d] David Geffen School of Medicine at UCLA, Los Angeles, Calif; Division of Hematology and Medical Oncology,[e] Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, Calif; Division of Pediatric Hematology and Medical Oncology,[f] Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, Calif; Department of Pathology and Laboratory Medicine,[g] David Geffen School of Medicine at UCLA, Los Angeles, Calif; Department of Radiation Oncology,[h] David Geffen School of Medicine at UCLA, Los Angeles, Calif; Division of Surgical Oncology,[i] Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, Calif; and Division of Thoracic Surgery,[j] Department of Surgery, Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, Calif.

Funded by the Jonsson Comprehensive Cancer Center Sarcoma Program.

Disclosures: Arun Singh reports lecture fees from Biomarin. Percy Lee reports consulting and lecture fees from Viewray, Inc. Bartosz Chmielowski reports consulting fees from CytRx; consulting and lecture fees from Merck, BMS, and Genentech; and lecture fees from Prometheus and Amgen. The other authors have nothing to disclose with regard to commercial support.

Read at the 40th Annual Meeting of The Western Thoracic Surgical Association, Dana Point, California, June 25-28, 2014.

A.Y.L. and S.K. contributed equally to this article.

Received for publication June 25, 2014; revisions received Sept 8, 2014; accepted for publication Sept 12, 2014; available ahead of print Oct 12, 2014.

Address for reprints: Jay M. Lee, MD, Ronald Reagan UCLA Medical Center, Division of Thoracic Surgery, Box 957313, Room 64-128 CHS, 10833 Le Conte Ave, Los Angeles, CA 90095-7313 (E-mail: jaymoonlee@mednet.ucla.edu).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2014.09.039

See related commentary on pages 93-4.

Pulmonary metastases occur in up to 50% of patients with sarcoma during the course of their disease,[1-3] and the lung is the sole site of metastasis in 19% of patients.[4] No randomized controlled trials have directly compared surgical resection with chemotherapy alone or the effects of chemotherapy given for metastatic disease on survival. Pulmonary metastasectomy has become an accepted treatment option in select patients with metastatic sarcoma isolated to the lung.[1-3,5-9] The prognosis for unresected disease is poor with a median survival of 11 months, whereas that for completely resected disease is up to 33 months.[2] Retrospective studies have shown a survival advantage in patients who underwent complete resection of pulmonary metastases with 5-year survival ranging from 13% to 49%.[1,10-12]

Although multiple risk factors associated with poor survival have been reported, stratification of these variables into patient cohorts to guide surgical treatment is not well defined.[2] The objective of this study is to identify prognostic variables of overall survival (OS) and create a risk stratification model to guide surgical treatment of sarcoma metastasis to the lung.

Abbreviations and Acronyms
BS = bone sarcoma
DFI = disease-free interval
DFS = disease-free survival
OS = overall survival
STS = soft tissue sarcoma
VATS = video-assisted thoracoscopic surgery

GTS

We report the identification of 7 factors associated with poor OS after lung metastasectomy: age greater than 45 years, disease-free interval (DFI) less than 1 year, thoracotomy, synchronous disease, location and type of sarcoma (soft tissue sarcoma [STS] vs bone sarcoma [BS]), and performance of lobectomy. The combination of these factors was associated with OS, which varied widely from 64% in patients with 2 factors to 3% in those with 5 factors.

MATERIALS AND METHODS

Patient Population

A retrospective review of a prospectively maintained sarcoma database at our institution was queried to identify all patients who underwent pulmonary metastasectomy for sarcoma at the University of California, Los Angeles Medical Center between February 1994 and June 2010. Patients' records were reviewed to abstract the following data: demographics, type of primary sarcoma, initial therapy, time to pulmonary metastases, type of resection and additional therapy, disease-free survival (DFS), and OS. Follow-up was censored in May 2013. Three patients without any follow-up were excluded from the final analysis. Institutional review board approval was obtained.

Preoperative Evaluation

A multidisciplinary sarcoma tumor board evaluated patients with sarcomas metastatic to the lung preoperatively and postoperatively to determine the appropriateness of neoadjuvant and adjuvant treatments. All patients were considered for neoadjuvant chemotherapy followed by a single-stage or a 2-stage pulmonary metastasectomy for patients with bilateral diseases. Neoadjuvant chemotherapy was considered in those with (1) short DFI; (2) multiple lesions involving both lungs; (3) high-grade STS and high-risk BS (ie, osteosarcomas, Ewing's, and mesenchymal or dedifferentiated chondrosarcomas); and (4) synchronous pulmonary metastasis when neoadjuvant treatment was recommended for the primary lesion. Neoadjuvant therapy was defined as chemotherapy or chemoradiation given within 1 year before the pulmonary metastasectomy.

Pathologic Evaluation

All resected specimens were examined by a dedicated musculoskeletal pathologist. If the primary site resection was performed at an outside hospital, an attempt was made to obtain the original slides for our pathologist to confirm the diagnoses. The completeness of resection for the primary sites was determined from the available operative and pathology reports. The completeness of pulmonary metastasectomies was described using the residual tumor classification (R stage) system. R0 was defined as a complete resection. R1 was defined as residual microscopic tumor. R2 was defined as gross residual tumor left at the time of lung resection, multiple nodules that were not all resected, and unresected primary tumors treated with nonsurgical modalities.

Survival

Patients' survival data were obtained from the hospital records and the Social Security Death Index. DFI was defined as the time from primary tumor resection to pulmonary metastasectomy performed at our institution. OS was defined as the time between the first pulmonary metastasectomy performed at our institution to the date of death or May 2013 (the date when data collection was censored). DFS was defined as the time from pulmonary metastasectomy to the date of recurrence at all sites. The date of pulmonary metastasectomy was used as the date of recurrence if R2 resection was performed at the time of the pulmonary metastasectomy.

The Kaplan–Meier method was used to calculate OS and DFS probabilities. All survival and recurrence dates were calculated from the date of the first pulmonary metastasectomy. In cases when a 2-stage or sequential resection was planned, the date of the second pulmonary metastasectomy was used if no other intervention was performed in between the 2 operations and if the interval between the 2 operations was less than 3 months.

Statistical Analysis

OS and DFS were graphically displayed using Kaplan–Meier curves. Survival estimates for 1, 3, and 5 years were extracted and plotted. Differences between groups were assessed by the log-rank test. Age, gender, sarcoma type, primary location, grade, size, margin, histology, DFI, metastasectomy approach, type of resection, pulmonary metastasis size, grade, margin status, neoadjuvant therapy, adjuvant treatments, and number of further metastasectomies (including other sites) were included as potential predictors of survival. Variables that were statistically significant from the log-rank test were included in a multivariable Cox proportional hazards model. Hazard ratio estimates and 95% confidence intervals were estimated from the final models. To more easily interpret the results, a scoring system was developed by categorically dichotomizing patients' characteristics to whether they displayed the significant prognostic variable or not. The patients were then grouped according to the number of negative prognosis variables. A Kaplan–Meier curve was constructed summarizing the relationship between the scoring system variable and survival. Statistical analyses were conducted in R (version 3.0.2, www.r-project.org).

Patient and Clinical Presentation

A total of 158 patients underwent pulmonary resection for metastatic sarcoma during the study period. Three patients without available long-term data were excluded from this analysis; therefore, the final analysis was based on the remaining 155 patients. Patient and primary tumor characteristics are shown in Table 1. Neoadjuvant and adjuvant therapies surrounding resection of the primary sarcoma are shown in Table 1. Twenty-one patients (13.5%) underwent further resections for local recurrence before diagnosis of pulmonary metastases. Sixteen patients (10.3%) had prior pulmonary metastasectomies at another institution, and 8 patients (5.2%) had prior nonpulmonary metastasectomies.

RESULTS

Characteristics of Pulmonary Metastases

The characteristics of the resected pulmonary metastases are shown in Table 2. A total of 115 patients underwent open surgeries (74.2%), and 40 patients (25.8%) underwent video-assisted thoracoscopic surgery (VATS). Seven patients (4.5%) underwent staged bilateral exploration. A total of 102 patients (65.8%) underwent wedge resections, 27 patients (17.4%) underwent lobectomy, and 6 patients (3.9%) required pneumonectomy. The survival curves for the different types of resections