

PAPER 56

What factors differentiate early vs. late pulmonary metastases in soft tissue sarcoma of the extremities? A comparative cohort analysis

Alexander L. Lazarides, MD,^{1,2} Manit Gundavda, MD,¹ Zachary DC Burke, MD,¹ Anthony M. Griffin MSc,¹ Kim Tsoi, MD, PhD^{1*}, Peter C Ferguson MD,¹ Jay S Wunder, MD, MSc¹,

1. University of Toronto Musculoskeletal Oncology Unit, Mount Sinai Hospital, Division of Orthopaedic Surgery, Department of Surgery, University of Toronto, Toronto, ON, Canada
2. Sarcoma Department, Moffitt Cancer Center, Tampa, FL

Background:

As many as 20-30% of patients with soft tissue sarcoma will develop pulmonary metastatic disease. These metastases occur most often within the first 2 years and presentation is typically in the lungs. Despite this, a subset of patients will develop later metastatic disease beyond 2 years. However, it remains unclear what factors differentiate patients presenting with early as opposed to late pulmonary metastases and how their outcomes differ.

The purpose of the present study was 1) to compare the survival of patients with early vs. late sarcoma metastases in the lungs and 2) to compare the differences between the two groups.

Methods:

A retrospective review of a prospectively maintained institutional database was performed of all patients undergoing surgical treatment of a soft tissue sarcoma of the extremities or pelvis between January 1st, 1992 and November 15, 2020. We included all patients with a soft tissue sarcoma of the pelvis and extremities who developed pulmonary metastases (PM) after definitive resection, defined as progressive pulmonary nodules >1 cm on CT chest imaging or biopsy proven pulmonary metastasis. Exclusion criteria included patients with metastatic disease at presentation.

The primary outcome measure was disease specific survival (DSS) from metastatic disease. Comparisons were made between patients with early vs. late metastatic disease, defined as

presentation less than or greater than 2 years respectively. Survival analyses were performed utilizing the Kaplan Meier method. Continuous and categorical variables were compared in univariate measures before constructing a multivariable analysis to control for potentially confounding variables.

Results:

We identified 584 patients who developed PM following surgical treatment of a soft tissue sarcoma of the extremity or pelvis. 459 patients (79%) developed metastases within 2 years of surgery while 125 patients (21%) developed metastases more than 2 years from surgery. Median time to PM was 9 months (range 0-265 months). Overall, 5-year DSS from presentation of PM was 15.2%.

Considering the treatment of PM, patients presenting with early metastatic lung disease were more likely to receive chemotherapy than those presenting with late disease (35% vs. 22%, $p=0.004$). There was no difference in rates of surgical excision or utilization of radiotherapy. 5-year DSS from presentation of PM was significantly worse for patients who developed early PM compared to those with late PM (12.2% vs. 27.5% respectively, $p<0.001$). Amongst patients undergoing surgical excision of PM, 5-year DSS from presentation was significantly worse for patients who developed early PM (27.2% vs. 48.7%, $p=0.014$). Similarly, 5-year DSS from presentation was significantly worse for patients who developed early PM, even when controlling for utilization of chemotherapy (11.9% vs. 29.3%, $p=0.017$) and radiotherapy (3.4% vs. 43.1%, $p=0.007$).

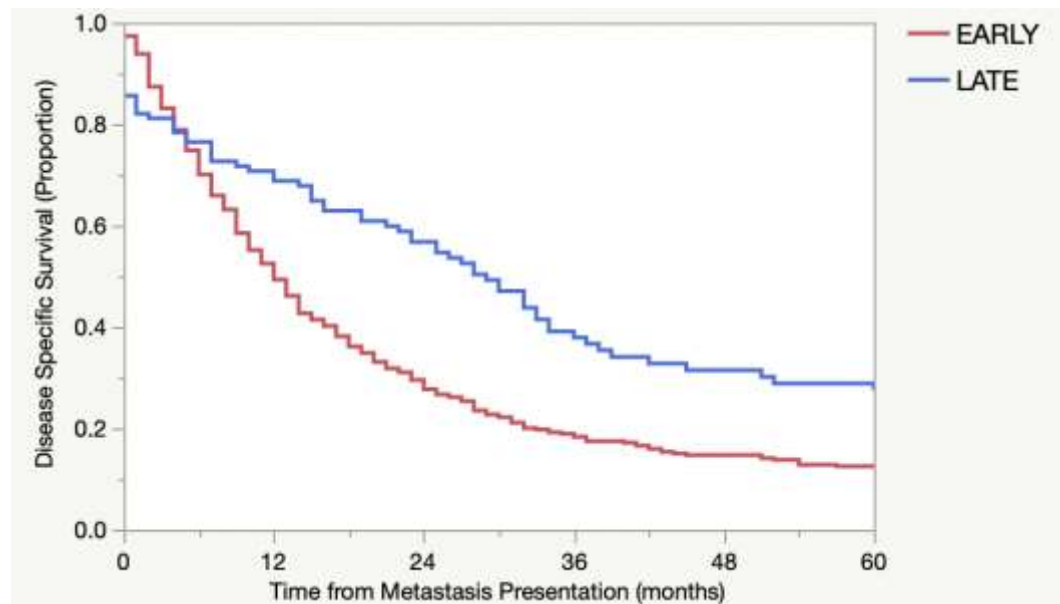
When comparing patient factors between groups, early PM tended to occur in older patients (59 vs. 53 years, $p<0.001$) and were more commonly associated with male gender (58% vs. 48%, $p=0.042$). Regarding tumor factors, late PM were associated with a histological diagnosis of clear cell sarcoma, leiomyosarcoma and liposarcoma while early PM were associated with angiosarcoma, soft tissue osteosarcoma and UPS ($p<0.001$). Early PM were associated with high grade tumors (76% vs. 61%, $p=0.001$) and with larger tumors (mean 12.2 cm vs. 9 cm, $p<0.001$).

When considering treatment of the primary tumor, surgery type, use of radiation therapy and chemotherapy did not differ between patients who subsequently developed an early vs. late PM. However, patients who developed a late PM were more likely to have also developed a prior local recurrence (25% vs 10%, $p < 0.001$).

Multivariable analysis revealed that older age (HR 1.02, $p = 0.001$), larger tumor size (HR 1.1, $p < 0.001$) and higher tumor grade (HR 2, $p = 0.002$) were associated with an increased risk of early PM while prior local recurrence was associated with an increased risk of late PM (HR 3.3 $p < 0.001$).

Discussion:

Disease specific survival is poor following the development of pulmonary metastatic disease after treatment for extremity or pelvic soft tissue sarcoma; however, survival is worst for patients with early presentation (within 2 years). Older age, larger tumor size and higher tumor grade are independently associated with the development of early PM while local recurrence is associated with risk of late PM. Treatment factors did not appear to be associated with risk of developing early vs. late lung metastatic lung disease.



Test	Prob>ChiSq
Log-Rank	<.0001*

Test	Prob>ChiSq
Wilcoxon	0.0054*

Figure 1. Kaplan Meier survival curve comparing early versus late pulmonary metastatic disease specific survival from first pulmonary metastasis presentation (12.2% 5-year DSS for early presentation versus 27.5% 5-year DSS for late presentation).