Received:
07 October 2019

Revised:
08 June 2020

Accepted:
15 June 2020

<https://doi.org/10.1259/bjr.20190856>

Cite this article as:

Isidro U, O'Brien LM, Sebro R. Linear mixed-effects models for estimation of pulmonary metastasis growth rate: implications for CT surveillance in patients with sarcoma. *Br J Radiol* 2020; **93**: 20190856.

FULL PAPER

Linear mixed-effects models for estimation of pulmonary metastasis growth rate: implications for CT surveillance in patients with sarcoma

¹ULYSSES ISIDRO, MPH, ²LIAM M O'BRIEN, PhD and ^{1,3,4,5}RONNIE SEBRO, MD, PhD

¹Department of Radiology, University of Pennsylvania, 3400 Civic Center, Philadelphia, PA 19104, USA

²Department of Mathematics and Statistics, Colby College, Waterville, ME 04901, USA

³Department of Orthopaedic Surgery, University of Pennsylvania, 3737 Market Street, Philadelphia, PA 19104, USA

⁴Department of Genetics, University of Pennsylvania, 415 Curie Blvd, Philadelphia, PA 19104, USA

⁵Department of Biostatistics, Epidemiology and Informatics University of Pennsylvania, 423 Guardian Drive, Philadelphia, PA 19104, USA

Address correspondence to: Dr Ronnie Sebro

E-mail: ronnie.sebro@uphs.upenn.edu

The authors Ulysses Isidro and Ronnie Sebro contributed equally to the work.

Objectives: Sarcoma patients often undergo surveillance chest CT for detection of pulmonary metastases. No data exist on the optimal surveillance interval for chest CT. The aim of this study was to estimate pulmonary metastasis growth rate in sarcoma patients.

Methods: This was a retrospective review of 95 patients with pulmonary metastases (43 patients with histologically confirmed metastases and 52 with clinically diagnosed metastases) from sarcoma treated at an academic tertiary-care center between 01 January 2000 and 01 June 2019. Age, sex, primary tumor size, grade, subtype, size and volume of the pulmonary metastasis over successive chest CT scans were recorded. Two metastases per patient were chosen if possible. Multivariate linear mixed-effects models with random effects for each pulmonary metastasis and each patient were used to estimate pulmonary metastasis growth rate, evaluating the impact of patient age, tumor size, tumor grade, chemotherapy and tumor subtype. We estimated the pulmonary metastasis volume doubling time using these analyses.

Results: Maximal primary tumor size at diagnosis (LRT statistic = 2.58, df = 2, $p = 0.275$), tumor grade (LRT statistic = 1.13, df = 2, $p = 0.567$), tumor type (LRT statistic = 7.59, df = 6, $p = 0.269$), and patient age at diagnosis (LRT statistic = 0.735, df = 2, $p = 0.736$) were not statistically significant predictors of pulmonary nodule growth

from baseline values. Chemotherapy decreased the rate of pulmonary nodule growth from baseline (LRT statistic = 7.96, df = 2, $p = 0.0187$). 95% of untreated pulmonary metastases are expected to grow less than 6 mm in 6.4 months. There was significant inpatient and interpatient variation in pulmonary metastasis growth rate. Pulmonary metastasis volume growth rate was best fit with an exponential model in time. The volume doubling time for pulmonary metastases assuming an exponential model in time was 143 days (95% CI (104, 231) days).

Conclusions: Assuming a 2 mm nodule is the smallest reliably detectable nodule by CT, the data suggest that an untreated pulmonary metastasis is expected to grow to 8 mm in 8.4 months (95% CI (4.9, 10.2) months). Tumor size, grade and sarcoma subtype did not significantly alter pulmonary metastasis growth rate. However, chemotherapy slowed the pulmonary metastasis growth rate.

Advances in knowledge: CT surveillance intervals for pulmonary metastases can be estimated based on metastasis growth rate. There was significant variation in the pulmonary metastasis growth rate between metastases within patient and between patients. Pulmonary nodule volume growth followed an exponential model, linear in time.

INTRODUCTION

Sarcomas are rare heterogeneous tumors, thought to be of mesenchymal origin, with over 50 different subtypes.¹⁻³ Approximately 16,000 patients are diagnosed with bone

and soft tissue sarcoma every year.⁴ Patients with localized sarcomas have poor prognosis with an estimated median 5-year overall survival of 65%.⁴ Sarcomas have the propensity to metastasize to the lungs.^{5,6} Patients with

pulmonary metastases have stage IV disease and have an even worse prognosis with a 5-year median survival rate of 16%.⁷⁻⁹ As a result, patients with newly diagnosed sarcoma undergo staging and surveillance chest radiographs (CXR) or CT.^{10,11} CT is more accurate than CXR, but has increased costs and results in increased radiation dose to the patient.^{10,11} There is considerable variation in clinical care regarding which imaging modality to use (CXR versus CT) and how often surveillance for pulmonary metastases should occur.^{10,11} The United States National Cancer Center Network (NCCN) (https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf) recommends chest imaging every 6–12 months with CXR or CT for patients with stage I disease; every 3–6 months for 2–3 years, every 6 months for the next 2 years, then annually for patients with stage II/III; every 2–6 months for 2–3 years, then every 6 months for the next 2 years, then annually for patients with stage IV disease.¹²

Excessive chest imaging results in increased cost, increased patient anxiety and detection of pulmonary nodules that may not be metastases, or detection of pulmonary nodules that are too small for an actionable intervention (too small to biopsy or too small to be reliably evaluated by positron emission tomography (PET), too small for radiation therapy, or too small to find for video-assisted thoracic surgery (VATS)).^{10,11} A recent manuscript showed no substantial difference in the overall survival of patients with sarcoma undergoing surveillance imaging with CXR compared to those imaged with CT, which suggests that although CT is more accurate, the smaller nodules detected by CT may be too small for an actionable intervention.¹⁰⁻¹⁴ However, too infrequent imaging may result in missed opportunities for curative metastectomies.¹⁰⁻¹⁴

The aims of this manuscript were to (1) estimate the average growth rate of sarcoma pulmonary metastases to determine the optimal surveillance interval, (2) to evaluate whether all pulmonary metastases grow at the same rate (intrapersonal variation) and (3) to evaluate whether the pulmonary metastasis growth rate varies by sarcoma subtype.

METHODS AND MATERIALS

The protocol for this retrospective cohort study was reviewed and approved by the local Institutional Review Board (IRB), and the need for signed informed consent from each patient was waived.

Patients with a diagnosis of bone or soft tissue sarcoma were identified by searching the electronic medical record (EMR) using Montage powered by Nuance (Burlington, MA). These patients were evaluated or treated at a single tertiary care academic healthcare center between 01 January 2000 and 06 June 2019. Some of these patients were diagnosed at outside institutions and transferred their care to our academic institution. There were 2976 patients identified. Of the first 1000 patients, 113 patients were duplicates. The first consecutive 887 patients were evaluated because we were interested in the longest interval from the date of diagnosis to the development of pulmonary metastases. Since the primary aim of the study was to estimate the average pulmonary metastasis growth rate, several patients were excluded from the analysis. Patients without pulmonary metastases ($n = 261$,

29.4%); patients with less than two surveillance chest CTs with metastases ($n = 279$, 31.5%); patients without a histologically confirmed sarcoma diagnosis ($n = 246$, 27.7%); patients with already resected pulmonary metastases ($n = 73$, 8.2%); patients with pulmonary metastases but no imaging ($n = 20$, 2.3%); and patients with no/insufficient clinical data ($n = 8$, 0.9%) were excluded from the analysis. There were 95 (10.7%) patients with pulmonary metastases (43 patients with biopsy diagnosed pulmonary metastases *i.e.* metastases diagnosed histologically; and 52 patients with clinically diagnosed pulmonary metastases (*i.e.*, pulmonary metastases grew over time or responded to chemotherapy)) who had at least two surveillance chest CT studies that made them eligible to be in the study.

CT parameters and measurements

Unenhanced chest CTs were performed using Siemens Definition AS40 (128 slice), Siemens Definition AS plus (128 slice) or Siemens Definition Flash (128 slice) CT scanners (Siemens Healthineers, Erlangen, Germany). The following parameters were used: 120 kVp and slice thickness 1.25 mm. The tube current was modulated to limit radiation dose. The CT scanner was calibrated per the American College of Radiology (ACR) guidelines using phantoms, and all patients were imaged in the supine position.

Up to two pulmonary metastases were selected from each patient (with one pulmonary metastasis histologically diagnosed via biopsy and the other pulmonary metastasis clinically diagnosed; or two clinically diagnosed pulmonary metastases). Each pulmonary nodule had to be greater than 0 mm in size and visible on all CT surveillance studies. We retrospectively confirmed that the nodule we measured was the nodule biopsied for patients with histologically confirmed pulmonary metastases, by reviewing the CT-guided biopsy images. In clinical practice, due to the morbidity and potential mortality of lung biopsies, usually only one pulmonary nodule per patient is biopsied. Once a pulmonary nodule is histologically diagnosed as a pulmonary metastasis, then other pulmonary nodules with similar imaging appearance and clinical behavior as the biopsied pulmonary nodule within the same patient are generally clinically diagnosed as pulmonary metastases. In cases where there were more than two pulmonary nodules, the second nodule chosen was one that could be visualized easily on all surveillance scans unobstructed by atelectasis or edema.

The maximum length in millimeters (mm) of each pulmonary metastasis was measured along the same axes using the lung kernel on the baseline CT and on the two subsequent surveillance CT scans (Figure 1a, b and c). The measurement tool from SECTRA (Linköping, Sweden) Picture Archiving and Communication Systems (PACS) was used to obtain measurements. A single reader (advanced medical student) recorded the pulmonary metastasis measurements, which were verified by a board-certified radiologist with 6 years of experience. The PACS software allows measurement of pulmonary metastases up to 0.1 mm. Semi-automated volumetric measurements of each pulmonary metastasis were obtained using ITK-SNAP software¹⁵ (Figure 2). The major outcome of interest was the average

Figure 1. Axial chest CT scan (lung kernel, slice thickness 1.25 mm, 120 kVp, 70 mAs) of a 43-year-old female with Grade 1 myxofibrosarcoma and histologically proven pulmonary metastasis demonstrating (a) no pulmonary metastasis at baseline, (b) development of 5 mm nodule (white arrow) after 157 days (~5 months 1 week) and (c) growth of the nodule to 7 mm (white arrow) after 216 days (7 months 1 week).

rate of change (growth) of the maximum length of the pulmonary metastasis across surveillance CT scans.

Reliability of measurements

A random sample of 120 pulmonary nodules were re-measured and the test-retest reliability of the volumetric measurements was assessed using the correlation coefficient following the guidelines of Cicchetti.¹⁶

Demographic and clinical variables

Patient age at diagnosis, sex, maximum size of the primary sarcoma at diagnosis, sarcoma subtype, tumor grade and time from diagnosis to development of pulmonary metastasis in days were measured. These data were obtained from the EMR.

Statistical methods

Summary statistics were calculated for the key clinical and demographic variables. Linear mixed-effects models for estimation of growth curves were utilized to allow for multiple measures on the same patient (two pulmonary metastases) and repeated measurements over three serial CT scans. Let Y_{ijk} be the length

of pulmonary nodule k at time j in patient i where $k = (1, 2)$, j is the number of days from diagnosis, and $i = (1, \dots, n)$, where n is the number of patients in the study. Let Y be a vector of all outcomes for all patients; let X_i be a matrix of the independent variable(s) for subject i (such as age at diagnosis, maximum size of the primary sarcoma at diagnosis, sarcoma subtype, and tumor grade); let Z_i be a matrix associated with subject-specific random effects (nodule and patient); let ε_i be a vector of random errors, which are distributed as a multivariate normal vector with mean vector 0 and covariance matrix R_i . β is an unknown vector of fixed effects, and γ_i is an unknown vector of random effects with mean $E[\gamma_i] = 0$ and covariance matrix $\text{Var}[\gamma_i] = \Sigma$.^{17,18}

Then, $Y = X_i\beta + Z_i\gamma_i + \varepsilon$, where $\gamma_i \sim N(0, \Sigma)$ and $\varepsilon_i \sim N(0, R_i)$

This model accounts for within-patient variation from CT scan to CT scan and within-patient variability associated with pulmonary metastasis. Linear mixed-effects models were used. Full details of model construction and selection are available in the Appendix.

Maximum pulmonary nodule size

First, the distribution of the change in maximum pulmonary nodule size from baseline at each post-baseline measurement occasion was assessed for normality. This distribution was approximately normal and as a result, the difference scores were not transformed. The baseline maximum pulmonary nodule size was right skewed and not normally distributed (Shapiro Wilks $W = 0.97$, $p = 4.0 \times 10^{-5}$), so was log-transformed. Next, a linear mixed-effects model with random effects (intercepts and slopes) for each pulmonary nodule within each person using restricted maximum likelihood (REML) was used to predict the change in pulmonary nodule size from baseline at each post-baseline measurement occasion using time, log baseline nodule size and the interaction between time and log baseline nodule size as covariates. Two other linear mixed-effects models were built with the same parameters: the first including time, time squared and their interactions with log baseline nodule size as covariates; and the second including time, time squared, time cubed and their interactions with log baseline nodule size as covariates. These models were refitted using maximum likelihood (ML) to compare the models. The model including time

Figure 2. Volumetric segmentation of a 4.5 cm pulmonary nodule in 71-year-old male with Grade 3 undifferentiated pleomorphic sarcoma and a histologically proven pulmonary metastasis.

and time squared was not significantly better than the model with time only (Likelihood-ratio test (LRT) chi-squared = 1.37, df = 2, $p = 0.504$). The model with time, time squared and time cubed was not significantly better than the model with time only (LRT chi-squared = 1.58, df = 4, $p = 0.812$). We then compared the model with time, log baseline nodule size and the interaction between them (time and log baseline nodule size) to a model with only time as a covariate. Log baseline nodule size and the interaction between log baseline nodule size and time were not significant (LRT chi-squared = 2.31, df = 2, $p = 0.316$). The model with time as the only covariate was selected as the best model. We then evaluated different variance-covariance structures for the random errors and found that the optimal variance-covariance matrix for the autocorrelated random errors was one with an uncorrelated variance-covariance matrix (Appendix).

Next, we evaluated whether there were significant random effects by building various random effects models for person and pulmonary nodule. We compared the model with random intercepts and slopes for each pulmonary nodule to the model with random intercepts and slopes for each pulmonary nodule within each person. Similarly, we compared the model with random intercepts and slopes for each person to the model with random intercepts and slopes for each pulmonary nodule within each person. We also compared a model with random intercepts only for each pulmonary nodule within each person to the model with random intercepts and slopes for each pulmonary nodule within each person. Finally, we compared a model with random slopes only for each pulmonary nodule within each person to the model with random intercepts and slopes for each pulmonary nodule within each person.¹⁹ We found that the model with random intercepts only for each pulmonary nodule within each person was the best statistical model (Supplementary Material 1).¹⁹

We then built linear mixed-effects models with random intercepts for each pulmonary nodule within each person, using time as a covariate, and then one additional variable (either maximal primary tumor size at diagnosis, tumor grade (low = Grade I, high = Grade II, III), tumor type (undifferentiated pleomorphic sarcomas (UPS) or leiomyosarcoma, or myxofibrosarcoma), age at diagnosis, or chemotherapy)). The model included that additional variable's interaction with time as well, to evaluate how each additional variable contributed to overall prediction when compared to the model without the additional variable and its interaction (Supplementary Material 1). Chemotherapy decreased the rate of log pulmonary nodule growth (LRT statistic = 7.96, df = 2, $p = 0.0187$). We noted that the interaction between chemotherapy and time was not significant (t-statistic = -0.00294, $p = 0.509$) and subsequently removed it from the model. This is reasonable since the response in this model is the difference from baseline at each post-baseline measurement occasion, thus the main effect of chemotherapy is a test of parallel trajectories for patients treated with chemotherapy and those who were not.

The final fixed effects design matrix, X , was:

$$\text{Difference from baseline} = \beta_0 + \beta_1 \text{time} + \beta_2 \text{chemotherapy in interval} \quad [1]$$

(Supplementary Material 1).

Pulmonary nodule volume

Next, we evaluated pulmonary nodule volume. The nodule volume was not normally distributed ($W = 0.68$, $p < 2.2 \times 10^{-16}$) but was right-skewed, so was log-transformed. The baseline pulmonary nodule volume was also right skewed and not normally distributed ($W = 0.55$, $p < 2.2 \times 10^{-16}$) so was also log-transformed.

Next, a generalized linear mixed-effects model with random intercepts and slopes for each nodule within each person and an uncorrelated variance-covariance matrix for the random errors was used to predict log pulmonary nodule volume (excluding the baseline log pulmonary nodule volume) using time, log baseline nodule volume and their interaction as covariates. Another linear mixed-effects model was built with the same parameters, but including time, time squared and their interactions with the log baseline nodule volume as covariates. A third linear mixed-effects model was built with the same parameters, including time, time squared, time cubed and their interactions with the log baseline nodule volume as covariates.

The model with only time was adequate when compared to the models with time squared (LRT chi-squared statistic = 4.17, df = 2, $p = 0.124$) and time cubed (LRT chi-squared statistic = 4.11, df = 4, $p = 0.391$). The model with time, log baseline pulmonary nodule volume, and their interaction was then compared to a model with only main effects for time and log baseline pulmonary nodule volume, and we found that the interaction was not necessary (LRT chi-squared statistic = 0.104, df = 1, $p = 0.747$). The model with time and log baseline pulmonary nodule volume was chosen as the best model in this step of the analysis.

We evaluated the optimal autocorrelation structure for the random errors and found that uncorrelated random errors were adequate (Supplementary Material 1). Next, we evaluated whether there were significant random effects by building various models with combinations of random effects for person and pulmonary nodule. To test whether there were significant pulmonary nodule random effects, we compared the model with random intercepts and slopes for each pulmonary nodule to the model with random intercepts and slopes for each pulmonary nodule within each person. Similarly, to test whether there were significant random effects for each person, we compared the model with random intercepts and slopes for each person to the model with random slopes for each pulmonary nodule within each person. We found that the model with random intercepts and slopes for each pulmonary nodule within each person was the best statistical model (Supplementary Material 1).

We then built linear mixed-effects models with random intercepts and slopes for each pulmonary nodule within each person, with time and log baseline volume as fixed effects, and then one additional variable and that additional variable's interaction

with time as fixed effects (either maximal primary tumor size at diagnosis, tumor grade (low = Grade I, high = Grade II, III), tumor type (UPS or leiomyosarcoma, or myxofibrosarcoma), age at diagnosis, or chemotherapy in the interval) to evaluate how each additional variable contributed to overall prediction when compared to the model without the additional variable ([Supplementary Material 1](#)). We found that maximal tumor size at diagnosis (LRT chi-squared statistic = 2.78, $df = 2$, $p = 0.250$), tumor grade (LRT chi-squared statistic = 1.02, $df = 2$, $p = 0.600$), tumor type (LRT chi-squared statistic = 5.23, $df = 6$, $p = 0.515$) and age at diagnosis (LRT Chi-squared statistic = 0.73, $df = 2$, $p = 0.679$) were not significant predictors of average log pulmonary nodule volume growth. Chemotherapy in the interval (LRT chi-squared statistic = 8.36, $df = 2$, $p = 0.015$) was a significant predictor of average log pulmonary nodule volume growth. The interaction between time and chemotherapy in the interval was not significant (t -statistic = -4.44×10^{-4} , $p = 0.667$) and was removed from the model.

The final fixed effects model was:

$$\text{Log pulmonary nodule volume} = \beta_0 + \beta_1 \text{time} + \beta_2 \log \text{baseline} + \beta_3 \text{chemotherapy in interval} \quad [2]$$

The volume doubling time of the pulmonary nodule growth was calculated using the best statistical model ([Supplementary Material 1](#)).

Statistics were calculated using Rv3.6 statistical software

RESULTS

Approximately 10.7% (95/887) of patients were included in the study. A total of 185 pulmonary nodules in 95 patients were evaluated. The median age of the patients at diagnosis was 58.0 years (range 16–87), and the majority of patients were female (54.7%). Pulmonary nodules ranged from 2 to 171 mm in size (median 12.7 mm, interquartile range IQR (7.7 mm–23.8 mm)). UPS, myxofibrosarcomas and leiomyosarcomas accounted for 66.3% (63/95) of all sarcomas ([Table 1](#)). The median sarcoma size was 10.3 cm (range 0.8–45.0 cm), and most (62.1%) sarcomas were Grade 3. Of the patients who developed pulmonary metastases in the dataset, 50% developed these pulmonary metastases within 547 days (1 year 6 months), 75% in 1140 days (3 years 2 months) and 90% in 3056 days (8 years 6 months), with one patient with osteosarcoma developing pulmonary metastases approximately 19 years and 11 months after the initial diagnosis. The test–retest reliability of the volumetric measures was excellent ($r = 1.00$, 95% CI (1.00, 1.00), $p < 2.2 \times 10^{-6}$).

Maximum pulmonary nodule size growth from baseline

We found that maximal primary tumor size at diagnosis (LRT chi-squared statistic = 2.58, $df = 2$, $p = 0.275$), tumor grade (LRT chi-squared statistic = 1.13, $df = 2$, $p = 0.567$), tumor type (LRT chi-squared statistic = 7.56, $df = 6$, $p = 0.269$); and age

Table 1. Patient demographic and clinical characteristics

Variable	
Mean Age at diagnosis in years (SD)	56.1 (16.4)
Male sex (%)	43 (45.3%)
Sarcoma subtype (%)	
Chondrosarcoma	5 (5.3%)
Ewing sarcoma	3 (3.2%)
Leiomyosarcoma – non-uterine	21 (22.1%)
Leiomyosarcoma – uterine	16 (16.8%)
Liposarcoma – retroperitoneal	4 (4.2%)
Liposarcoma – non-retroperitoneal	3 (3.2%)
Malignant Peripheral Nerve Sheath Tumor (MPNST)	2 (2.1%)
Myxofibrosarcoma	10 (10.5%)
Osteosarcoma	6 (6.3%)
Synovial sarcoma	9 (9.5%)
Undifferentiated Pleomorphic Sarcoma (UPS)	16 (16.8%)
Tumor grade (%)	
I	7 (10.8%)
II	13 (13.7%)
III	59 (62.1%)
Unreported	16 (16.8%)
Mean primary tumor size in cm (SD)	12.3 (7.5)
Mean time from diagnosis to development of pulmonary metastasis in days (SD)	1019 (1251)

at diagnosis (LRT statistic = 0.735, $df = 2$, $p = 0.736$) were not statistically significant predictors of the difference in nodule size from baseline. Chemotherapy decreased the pulmonary nodule growth (LRT Chi-squared statistic = 7.96, $df = 2$, $p = 0.0187$).

The model with random intercepts and slopes for each pulmonary nodule within each patient was not significantly better than the model with random intercepts and slopes for each patient (LRT Chi-squared statistic = 5.14, $df = 3$, $p = 0.162$), or the model with random intercepts for each pulmonary nodule within each patient (LRT Chi-squared statistic = 1.42, $df = 4$, $p = 0.841$).

The model with random intercepts for each pulmonary nodule within each patient was not significantly worse than the model with random intercepts and slopes for each patient (LRT Chi-squared statistic = 3.72, $df = 1$, $p = 0.054$). This suggests that there is significant variation in the pulmonary nodule growth rate between nodules within patients and between patients.

Pulmonary nodules are expected to grow 6 mm from their baseline size in 252 days (95% CI (148, 307)) or 8.4 months (95% CI

Figure 3. Growth curves for histologically confirmed sarcoma pulmonary metastases

(4.9, 10.2) months). From the bootstrap estimates, 95% of untreated pulmonary metastases are expected to grow less than 6 mm in 6.4 months.

Pulmonary nodule volume

We found that maximal tumor size at diagnosis (LRT chi-squared statistic = 2.78, $df = 2$, $p = 0.250$), tumor grade (LRT chi-squared statistic = 1.02, $df = 2$, $p = 0.600$), tumor type (LRT chi-squared statistic = 5.23, $df = 6$, $p = 0.515$) and age at diagnosis (LRT chi-squared statistic = 0.773, $df = 2$, $p = 0.679$) were not significant predictors of average log pulmonary nodule volume growth. Chemotherapy in the interval (LRT chi-squared statistic = 8.36, $df = 2$, $p = 0.015$) was a significant predictor of average log pulmonary nodule volume growth.

We found that the model with random intercepts and slopes for each pulmonary nodule within each patient was significantly better than the model with only random intercepts for each pulmonary nodule within each patient (LRT chi-squared statistic 11.6, $df = 4$, $p = 0.021$), and better than the model with only random slopes for each pulmonary nodule within each patient (LRT chi-squared statistic = 55.6, $df = 4$, $p < 0.0001$), which suggests that there is significant variation in the pulmonary nodule volume growth rate between nodules and between patients.

Figure 3 shows the individual pulmonary metastases growth curves from patients with histologically confirmed metastases. We found using the exponential model with linear time that the estimated volume doubling time for sarcoma metastases was approximately 143 days (95% CI (104, 231) days).

DISCUSSION

The results suggest that untreated sarcoma pulmonary metastases grow at approximately 0.8 mm per month over 8 months. The data also show that there is significant variation in the pulmonary metastasis growth rate between nodules within a

patient, which means one nodule may show substantial growth relative to another within the same patient. The data also show that there is significant variation in the pulmonary metastasis growth rate between patients. Pulmonary metastases did not show significant differences in growth rate based on the sarcoma subtype. Finally, the data showed that the growth rate decreased after initiation of systemic chemotherapy.

This study has several clinical implications. Prior reports show that percutaneous biopsy, PET/CT and VATS are unreliable in patients with nodules less than 8 mm in size.^{20–25} The Fleischner Society recommends follow-up imaging for nodules less than 8 mm in size rather than percutaneous biopsy or VATS in both low and high-risk patients,^{23,24} therefore an 8 mm pulmonary nodule is thought of as a nodule of actionable size. PET/CT is sometimes informative for the evaluation of pulmonary nodules, however many patients at baseline have pulmonary nodules, especially in areas of endemic granulomatous disease, which can be ¹⁸F-FDG-avid on PET.²⁶ Pulmonary nodules may be infectious or inflammatory, so the development of small pulmonary nodules is often not sufficient to warrant treatment without histological confirmation.²⁶ PET/CT has also been shown to have variable accuracy for pulmonary nodules less than 8 mm in size,^{22,27} so follow-up of these smaller nodules is often recommended. Prior studies have shown that small nodules less than 10 mm or greater than 5 mm from the pleural surface have a 63% chance of non-detection from VATS.²⁸ Another article by Saito et al showed that 52/61 (85.2%) of nodules less than 10 mm could not be identified by VATS without hookwire marking.²⁹ Therefore, VATS is not routinely recommended for the evaluation of subcentimeter pulmonary nodules. However, pulmonary nodules in patients with breast cancer and suspected pulmonary metastases that 47% had confirmed pulmonary metastases, 40% had a second primary (primary malignant lung cancer), and 13% had benign disease.³⁰ Caparica et al, evaluated biopsies of

pulmonary nodules in 228 patients with non-pulmonary cancer and showed that metastases were found in 64%, a secondary primary malignancy (lung cancer) in 26.3%, and 9.6% had benign disease.³¹

The data suggest that assuming a pulmonary nodule is actionable at 8 mm, and assuming the previous CT had a nodule at least 2 mm in size (approximately the lower limits of detection by CT), then in 252 days (approximately 8.4 months; 95% CI (4.9, 10.2) months), an untreated nodule is expected to grow by 6 mm, from 2 to 8 mm. The bootstrap estimates suggest that 95% of pulmonary nodules take greater than 6.4 months to grow 6 mm. Chest CT surveillance for pulmonary metastases in patients with sarcoma could conservatively be done every 6 months. Our model can be modified to predict the surveillance frequency depending on the actionable size of a pulmonary nodule.

The National Comprehensive Cancer Network (NCCN) has guidelines for the frequency of chest CT surveillance for pulmonary metastases in patients with sarcoma. However, this is based on expert opinion. Chest CT surveillance should occur every 3–6 months (NCCN guidelines) for stage II/III disease. Our study shows the expert opinion is close to and conservative relative to the estimates obtained from our data. This difference in chest CT surveillance (every 6 months versus every 3–6 months) over 3 years results in an additional 0–6 chest CT studies, and an estimated increased cost to the patient of \$0 – \$1,056.00 US dollars (USD) (€0 – €935.22 Euro) (Medicare reimbursement for a CT scan of the chest without the administration of contrast material in 2019 is \$176 USD).³² The data also suggest that if a 2 mm pulmonary nodule is identified, and an intervention (biopsy, PET/CT, wedge resection) can only be done on nodules that are at least 8 mm in size, then in 252 days (95% CI (143, 307) days), the nodule is expected to be 8 mm. This has the potential to decrease excess radiation to the patient related to frequent surveillance chest CTs and decrease patient anxiety related to identification of multiple pulmonary nodules that are too small for intervention.

The time from diagnosis to the first development of pulmonary metastases ranged from at the time of diagnosis 3–7265 days, with more than 50% of patients developing pulmonary metastases within 547 days. Prior reports suggest that chest CT surveillance should continue for at least 5 years, with 10% of patients developing pulmonary metastases between 5 and 10 years after diagnosis.^{33,34} Our data showed that 90% of the patients who developed pulmonary metastases developed these metastases within 8 years and 6 months, which is consistent with prior reports.^{33,34} There was substantial inpatient variability in pulmonary metastasis growth rate, which suggests either (a) that the pulmonary metastasis growth rate may vary by nodule location, for example lower lobe nodules may grow faster than upper lobe nodules due to perfusion effects or (b) the local microenvironment of the pulmonary nodule affects pulmonary metastasis growth rate or (c) the pulmonary metastases may be heterogeneous tumor clones and some clones grow faster than others.

Prior reports have investigated sarcoma pulmonary metastasis growth rate.^{35,36} Rösser *et al* evaluated sarcoma pulmonary metastasis growth in 11 patients using CXR. These radiographs were not calibrated to ensure that the measurements were standardized, and volumetric measurements were calculated assuming sphericity of the pulmonary nodules. None of the pulmonary nodules was histologically confirmed. Rösser *et al* estimated tumor doubling time of 8 to 198 days; however, this was not based on statistical theory.³⁵ Like our study, they noted variation in the growth rate between nodules within the same patient, and hypothesized that this was due to tumor cell polyclonality. Blomqvist *et al* also used CXR to evaluate sarcoma pulmonary metastases in 21 patients.³⁶ Similarly, these radiographs were not calibrated to ensure that the measurements were standardized, and volumetric measurements were calculated assuming an elliptic shape of the pulmonary metastasis. None of the pulmonary nodules was histologically confirmed. However, they found interpatient variability was greater than inpatient variability in sarcoma pulmonary metastasis growth rate, similar to this study. A prior CT study investigating 40 patients with sarcoma estimated the median volume doubling time (VDT) at 46 days, however the CT protocols used in this study were suboptimal with 2–5 mm collimation, which could miss pulmonary nodules 1–4 mm in size.³⁷ This analysis did not adjust for treatment, and some patients were treated, whereas others were not.

The study has a few limitations that should be acknowledged. The study is a retrospective study of patients with sarcoma treated at a single tertiary care academic institution and therefore subject to ascertainment bias. In addition, all sarcoma subtypes were not represented in the clinical sample, although the more common sarcomas were well represented. All of the metastases were not histologically diagnosed via biopsy, but were thought to be clinically consistent with pulmonary metastases by an oncologist after discussion at a multidisciplinary tumor board. Analysis of the histologically diagnosed pulmonary metastases resulted in similar estimates for sarcoma pulmonary metastasis growth rates. There was substantial heterogeneity in the chemotherapy regimens administered, and each regimen may have a different effect on the pulmonary metastasis growth rate, but there was insufficient data to evaluate this hypothesis. We do not know whether biopsies affected the growth rate of pulmonary metastases. Our analysis of the time to development of pulmonary metastases was based on a subset of patients who had pulmonary metastases (histologically or clinically confirmed) and appropriate surveillance chest CTs. Because of this study design, the estimates of the time to develop pulmonary metastases may not be generalizable. Because we only included those patients with complete pulmonary nodule growth data, there is a risk of bias in those who were excluded having faster or slower growth rates. Finally, the small sample size limits the ability to detect small differences between the pulmonary metastasis growth rate for sarcoma subtypes. Further research is required to confirm our findings apply to all sarcoma subtypes so that pulmonary metastasis surveillance can be generalized across all sarcoma subtypes.

CONCLUSIONS

In conclusion, small (2 mm) pulmonary metastases from sarcoma have a variable growth rate, with an average growth rate of approximately 0.8 mm/month over 8 months for untreated

nodules. Chemotherapy slowed the pulmonary metastasis growth rate. Finally, the analysis showed that there was significant variability in the pulmonary metastasis growth rate within the same patient, which may be related to underlying polyclonality of the metastasis.

REFERENCES

- Fletcher CDM, Bridge JA, Hogendoorn P, et al. (ed): WHO Classification of Tumours of Soft Tissue and Bone. In: 4th. Lyon, France: IARC Press; 2013.
- Chibon F, Lagarde P, Salas S, Pérot G, Brouste V, Tirode F, et al. Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. *Nat Med* 2010; **16**: 781–7. Epub 2010 Jun 27. doi: <https://doi.org/10.1038/nm.2174>
- Segal NH, Pavlidis P, Antonescu CR, Maki RG, Noble WS, DeSantis D, et al. Classification and subtype prediction of adult soft tissue sarcoma by functional genomics. *Am J Pathol* 2003; **163**: 691–700. doi: [https://doi.org/10.1016/S0002-9440\(10\)63696-6](https://doi.org/10.1016/S0002-9440(10)63696-6)
- Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al. Seer cancer statistics review, 1975–2016, National cancer Institute., 2019; Bethesda, MD April.
- Kang S, Kim H-S, Kim S, Kim W, Han I. Post-metastasis survival in extremity soft tissue sarcoma: a recursive partitioning analysis of prognostic factors. *Eur J Cancer* 2014; **50**: 1649–56. Epub 2014 Apr 3. doi: <https://doi.org/10.1016/j.ejca.2014.03.003>
- Komdeur R, Hoekstra HJ, van den Berg E, Molenaar WM, Pras E, de Vries EGE, et al. Metastasis in soft tissue sarcomas: prognostic criteria and treatment perspectives. *Cancer Metastasis Rev* 2002; **21**: 167–83. doi: <https://doi.org/10.1023/a:1020893200768>
- Digesu CS, Wiesel O, Vaporciyan AA, Colson YL. Management of sarcoma metastases to the lung. *Surg Oncol Clin N Am* 2016; **25**: 721–33. doi: <https://doi.org/10.1016/j.soc.2016.05.005>
- Toulmonde M, Le Cesne A, Mendiboure J, Blay J-Y, Piperno-Neumann S, Chevreau C, et al. Long-Term recurrence of soft tissue sarcomas: prognostic factors and implications for prolonged follow-up. *Cancer* 2014; **120**: 3003–6. Epub 2014 Jun 18. doi: <https://doi.org/10.1002/cncr.28836>
- Statistics adapted from the American Cancer Society's (ACS) publication Cancer Facts & Figures 2017: Special Section – Rare Cancers in Adults and the ACS website. 2019;
- Greenberg DD, Crawford B. Surveillance strategies for sarcoma: results of a survey of members of the musculoskeletal tumor Society. *Sarcoma* 2016; **8289509**. Epub 2016 Jul 13.
- Ries Z, Gibbs CP, Scarborough MT, Miller BJ. Pulmonary surveillance strategies following sarcoma excision vary among orthopedic oncologists: a survey of the musculoskeletal tumor Society. *Iowa Orthop J* 2016; **36**: 109–16.
- National comprehensive cancer network (NCCN) Clinical practice guidelines in oncology soft tissue sarcoma. 2019; Version 2.2019 — February 4.
- Puri A, Gulia A, Hawaldar R, Ranganathan P, Badwe RA. Does intensity of surveillance affect survival after surgery for sarcomas? results of a randomized noninferiority trial. *Clin Orthop Relat Res* 2014; **472**: 1568–75. doi: <https://doi.org/10.1007/s11999-013-3385-9>
- Whooley BP, Gibbs JF, Mooney MM, McGrath BE, Kraybill WG. Primary extremity sarcoma: what is the appropriate follow-up? *Ann Surg Oncol* 2000; **7**: 9–14. doi: <https://doi.org/10.1007/s10434-000-0009-x>
- Yushkevich PA, Piven J, Hazlett HC, Smith RG, Ho S, Gee JC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage* 2006; **31**: 1116–28. Epub 2006 Mar 20. doi: <https://doi.org/10.1016/j.neuroimage.2006.01.015>
- Guidelines CDV. Criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment* 1994; **6**: 284–90.
- Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics* 1982; **38**: 963–74.
- Johnson W, Balakrishna N, Griffiths PL. Modeling physical growth using mixed effects models. *Am J Phys Anthropol* 2013; **150**: 58–67. doi: <https://doi.org/10.1002/ajpa.22128>
- Burnham KP, Anderson DR, Selection M. *Multimodel Inference: A Practical Information Theoretic Approach*. 2nd ed. New York: Springer; 2002.
- Tan BB, Flaherty KR, Kazerooni EA, Iannettoni MD. American College of chest physicians. The solitary pulmonary nodule. *Chest* 2003; **123**(1 Suppl): 89S–96.
- Bar-Shalom R, Valdivia AY, Blafox MD. Pet imaging in oncology. *Semin Nucl Med* 2000; **30**: 150–85. doi: <https://doi.org/10.1053/snuc.2000.7439>
- Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001; **285**: 914–24. doi: <https://doi.org/10.1001/jama.285.7.914>
- Sánchez M, Benegas M, Vollmer I. Management of incidental lung nodules <8 mm in diameter. *J Thorac Dis* 2018; **10**(Suppl 22): S2611–27. doi: <https://doi.org/10.21037/jtd.2018.05.86>
- MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: from the Fleischner Society 2017. *Radiology* 2017; **284**: 228–43. Epub 2017 Feb 23. doi: <https://doi.org/10.1148/radiol.2017161659>
- Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015; **70**(Suppl 2): ii1–ii54.
- Sebro R, Aparici CM, Hernandez-Pampaloni M. Fdg PET/CT evaluation of pathologically proven pulmonary lesions in an area of high endemic granulomatous disease. *Ann Nucl Med* 2013; **27**: 400–5. Epub 2013 Feb 12. doi: <https://doi.org/10.1007/s12149-013-0695-7>
- O JH, Yoo IR, Kim SH, Sohn HS, Chung SK. Clinical significance of small pulmonary nodules with little or no 18F-FDG uptake on PET/CT images of patients with nonthoracic malignancies. *J Nucl Med* 2007; **48**: 15–21.
- Suzuki K, Nagai K, Yoshida J, Ohmatsu H, Takahashi K, Nishimura M, et al. Video-Assisted thoracoscopic surgery for small indeterminate pulmonary nodules: indications for preoperative marking. *Chest*

- 1999; **115**: 563–8. doi: <https://doi.org/10.1378/chest.115.2.563>
29. Saito H, Minamiya Y, Matsuzaki I, Tozawa K, Taguchi K, Nakagawa T, et al. Indication for preoperative localization of small peripheral pulmonary nodules in thoracoscopic surgery. *J Thorac Cardiovasc Surg* 2002; **124**: 1198–202. doi: <https://doi.org/10.1067/mtc.2002.127331>
 30. Matsuura K, Itamoto T, Noma M, Ohara M, Akimoto E, Doi M, et al. Significance of lung biopsy for the definitive diagnosis of lung nodules in breast cancer patients. *Mol Clin Oncol* 2018; **8**: 250–6. Epub 2017 Nov 24 PMID: 29111111. doi: <https://doi.org/10.3892/mco.2017.1511>
 31. Caparica R, Mak MP, Rocha CH, Velho PHI, Viana P, Moura MRL, et al. Pulmonary nodules in patients with Nonpulmonary cancer: not always metastases. *J Glob Oncol* 2016; **2**: 138–44. Collection 2016 Jun. doi: <https://doi.org/10.1200/JGO.2015.002089>
 32. Centers for Medicare and Medicaid Services Physician Fee Schedule look-up tool. , 2019 August 1. Available from: http://www.cms.hhs.gov/pfslookup/02_PFSsearch.asp.
 33. Ferguson PC, Dehesi BM, Chung P, Catton CN, O'Sullivan B, Gupta A, et al. Soft tissue sarcoma presenting with metastatic disease: outcome with primary surgical resection. *Cancer* 2011; **117**: 372–9. Epub 2010 Sep 9. doi: <https://doi.org/10.1002/cncr.25418>
 34. Zagars GK, Ballo MT, Pisters PWT, Pollock RE, Patel SR, Benjamin RS, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. *Cancer* 2003; **97**: 2530–43. doi: <https://doi.org/10.1002/cncr.11365>
 35. Rööser B, Pettersson H, Alvegård T. Growth rate of pulmonary metastases from soft tissue sarcoma. *Acta Oncol* 1987; **26**: 189–92. doi: <https://doi.org/10.3109/02841868709091429>
 36. Blomqvist C, Wiklund T, Tarkkanen M, Elomaa I, Virolainen M. Measurement of growth rate of lung metastases in 21 patients with bone or soft-tissue sarcoma. *Br J Cancer* 1993; **68**: 414–7. doi: <https://doi.org/10.1038/bjc.1993.351>
 37. Nakamura T, Matsumine A, Matsubara T, Asanuma K, Uchida A, Sudo A. Clinical impact of the tumor volume doubling time on sarcoma patients with lung metastases. *Clin Exp Metastasis* 2011; **28**: 819–25. Epub 2011 Jul 30. doi: <https://doi.org/10.1007/s10585-011-9413-9>