A simple prognostic benefit scoring system for sarcoma patients with pulmonary metastases: Sarcoma Lung Metastasis Score

Haruchika Yamamoto[1], MD, PhD, Hiromasa Yamamoto[1], MD, PhD, Junichi Soh[1], MD, PhD, Etsuji Suzuki[2], MD, PhD, Kei Namba[1], MD, PhD, Ken Suzawa[1], MD, PhD, Kentaroh Miyoshi[1], MD, PhD, Shinji Otani[1], MD, PhD, Mikio Okazaki[1], MD, PhD, Seiichiro Sugimoto[1], MD, PhD, Masaomi Yamane[1], MD, PhD, Takashi Yorifuji[2], MD, PhD, Katsuhito Takahashi[3], MD, PhD, Shinichi Toyooka[1], MD, PhD.

[1]Department of Thoracic Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama, 700-8558, Japan.

[2]Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama, 700-8558, Japan.

[3]Center for Multidisciplinary Treatment of Sarcoma, Department of Sarcoma Medicine, Kameda Medical Center, 929 Higashi-cho, Kamogawa-city, Chiba, 296-8602, Japan.

Correspondence to:

Hiromasa Yamamoto, MD, PhD

Department of Thoracic Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama-city, Okayama, 700-8558, Japan.

E-mail: h.yamamoto@md.okayama-u.ac.jp

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Conflict of interest statement

None of the authors has a financial relationship with commercial entity that has interest in the

subject of the presented manuscript or other conflict interest.

Synopsis: We proposed a simple prognostic benefit scoring system for sarcoma patients (the Sarcoma Lung Metastasis Score) created from preoperatively measured prognostic clinical factors and demonstrated its usefulness for sarcoma patients with pulmonary metastases.

Abstract

Background: Pulmonary metastasectomy could be considered as one of the treatment options for disease control in sarcoma patients with pulmonary metastases. However, there is little consensus about the suitable criteria for predicting the likely outcomes in these patients. The aim of this study was to establish a prognostic benefit scoring system based on preoperatively examined prognostic factors for sarcoma patients with pulmonary metastases.

Methods: This was a single-center retrospective cohort study conducted in a cohort of 135 sarcoma patients who underwent the first pulmonary metastasectomy at Okayama University Hospital between January 2006 and December 2015. Based on the results of a multivariable logistic regression analysis performed to determine the factors influencing the 3-year mortality, a Sarcoma Lung Metastasis Score was created and its correlation with the 3-year survival was analyzed.

Results: The results of the multivariate analysis revealed significant differences in the disease-free interval (< 2 years vs. ≥ 2 years; odds ratio (OR):4.22; 95% confidence interval (CI):1.67-10.70), maximum tumor diameter (≥ 15 mm vs. < 15 mm; OR:3.86; 95%CI:1.75-8.52), number of pulmonary metastases (≥ 6 vs. < 6; OR:2.65; 95%CI:1.06-6.620). The Sarcoma Lung Metastasis Score, which was defined as the total score on these three factors, reliably predicted the 3-year survival (Score: 0: 89.5%; 1: 63.2%; 2: 39.0%; 3: 10.5%).

Conclusions: Our newly proposed simple Sarcoma Lung Metastasis Score appears to be a useful prognostic predictor for sarcoma patients with pulmonary metastases, in that it could be helpful for the selection of appropriate treatments for these patients.

Introduction

Sarcoma, in general, is a disease that responds poorly to treatment, and often metastasizes to the lung [1, 2]. Since only limited effects of chemotherapy and treatment with molecular-targeted agents can be expected in sarcoma patients with pulmonary metastases, pulmonary metastasectomy could be considered as one of the treatment options for control of the disease [3-5]. It is a matter of vital importance for physicians and surgeons engaged in the treatment of sarcomas to be able to predict the prognosis of sarcoma patients with pulmonary metastases, so that they can select appropriate candidates that might benefit from surgical resection; however, there is little consensus about the suitable criteria for predicting the likely outcomes in these patients.

Previous studies have shown that the disease-free interval (DFI), tumor diameter, and number of pulmonary metastases could be predictive of the prognosis after resection in sarcoma patients with pulmonary metastases [2, 5, 6]. However, there is no clear evidence yet as to the possibility of preoperative prediction of the prognostic impact of surgical treatment in sarcoma patients with pulmonary metastases. Therefore, the surgical indications in sarcoma patients with pulmonary metastases are determined by each treating institution. At our institution, we consider surgical treatment for pulmonary metastases in sarcoma patients when the following factors are applicable: the primary lesion and lesions other than those in the lung are controlled or potentially controllable, the patient is a low risk candidate for surgery, and life-threatening situations can be avoided [7-9].

Scoring systems to predict the postoperative outcomes have been developed for other diseases [10]. Therefore, we attempted to develop a simple beneficial scoring system for sarcoma patients with pulmonary metastases 1) to allow physicians and surgeons to assess the potential benefit of metastasectomy in sarcoma patients with pulmonary metastases, and 2) to appropriately apprise sarcoma patients with pulmonary metastases prior to surgery. Herein, we

propose a simple beneficial scoring system using factors identified by multivariate regression analyses in the previous studies for sarcoma patients with pulmonary metastases.

Materials and Methods

Patients

This was a single-center retrospective cohort study conducted in a total of 158 patients who underwent lung metastasectomy at Okayama University Hospital between January 2006 and December 2015 [11]. Among these, 20 patients who had undergone the first lung resection in other hospitals and 3 patients who had undergone radiofrequency ablation (RFA) therapy prior to lung resection, were excluded from this study. The remaining 135 patients were divided into 2 groups according to the 3-year survival status from the first pulmonary metastasectomy: the survivor group (n = 66), and the non-survivor group (n = 69) (**Figure 1**). Patients were diagnosed as having sarcoma by histological examination of the primary lesion and the presence of pulmonary metastasis was confirmed by histological examination of the resected lung specimens.

This retrospective study protocol (No. K1612-033) was approved by the Institutional Review Board of Okayama University Hospital. The need for written informed consent from each patient was waived. All of the methods used for the study were in compliance with the relevant guidelines and regulations. Two authors, ES and TY, supervised the statistical analyses of this study and contributed to this research as biostatisticians.

Univariate, multivariate and survival analyses

Univariate and multivariate analyses were performed for identifying the differences in prognostic factors between the 3-year survivor group and non-survivor group using the following factors : age, sex, site of the primary tumors, histology, extent of primary disease at initial diagnosis, presence of local recurrence and/or extrapulmonary metastasis diagnosed with or

before the diagnosis of pulmonary metastasis, DFI, lung tumor location, maximum tumor diameter, number of pulmonary metastases, surgical procedure employed, and performance of two-stage operation. DFI was defined as period between primary tumor resection and diagnosis of the lung metastases.

We created a Sarcoma Lung Metastasis Score from the factors that were identified as being significant factors influencing the 3-year mortality by a multivariate analysis of preoperative prognostic clinical factors. These clinical factors were dichotomized (0/1) as explained below, and the sum of the scores for the three factors was calculated as the Sarcoma Lung Metastasis Score. In addition, the correlation between the Sarcoma Lung Metastasis Score and the survival period after the first lung metastasectomy was analyzed.

Statistical analyses

Differences in patient characteristics between the two groups were tested by Pearson's chi-square test for categorical variables. Univariate and multivariate analyses were performed using Pearson's chi-square test and logistic regression analysis by the backward stepwise elimination method, respectively. Discrimination for continuous variable factors were evaluated with a concordance index (c-index), which was identical to the area under the receiver operating characteristic (ROC) curve for the 3-year mortality. The 3-year survival rate was analyzed using the Kaplan–Meier method, and the log rank test was used for statistical comparison of the differences among the groups. Pearson's product-moment correlation coefficient was calculated in the correlation analysis. Differences were considered significant at $P < 0.05$ (two-sided).

All statistical analyses were performed using EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).[12] Specifically, the software is a modified version of R commander designed to add statistical functions frequently used in biostatistics. GraphPad Prism 7.04 software program (San Diego, CA, USA) was used for graph

editing.

Results

The patient characteristics are shown in **Table 1**. Among the 135 patients, 101 were female and 34 were male, the median age was 55 years (range, 14 to 88). Of the patients, 86 (64%) had bilateral lung metastases at the first lung metastasectomy. The median DFI was 369 days (range, 0 to 8985). The median maximum diameter of the lung tumors and median number of pulmonary metastases were 15 mm (interquartile range (IQR), 9.25-27.75 mm) and 3 (IQR, 1-5), respectively. The median observation period in the survivor group was 1568.5 days (IQR, 1266-2190 days). The overall 3-year survival rate was 48.8% (66/135). As for the surgical procedures, wedge resection of the lung was defined as “Wedge”, and segmentectomy, lobectomy, or pneumonectomy was defined as “Anatomical”. The cut-off values for age, maximum tumor diameter and number of pulmonary metastases were determined to be 56 years (c-index 0.52), 15 mm (c-index 0.70), and 6 (c-index 0.64), respectively, by ROC analysis for the 3-year mortality. For DFI, 2 years (730 days) was determined as the cut-off value on the basis of the results of a preliminary ROC analysis for the 3-year mortality, which showed 723 days as the optimal cut-off value, with a c-index of 0.63.

Univariate analyses to identify factors influencing the 3-year mortality risk identified factors including the DFI (< 2 years, $P = 0.00038$), maximum tumor diameter (≥ 15 mm, $P = 0.000052$), and number of pulmonary metastases (≥ 6, $P = 0.0050$) as significant factors (**Table 2**). Multivariate analysis also identified the DFI ($P = 0.0023$), maximum tumor diameter ($P = 0.00082$) and number of pulmonary metastases ($P = 0.037$) as significant factors influencing the 3-year survival rate (**Table 3**). Based on this result, the Sarcoma Lung Metastasis Score was calculated as the total score for the following three factors, with a score of 1 assigned to each of DFI, maximum tumor diameter, and number of pulmonary metastases. Each of these three factors was

significantly associated with overall survival after the pulmonary metastasectomy (**Supplementary Figure**).

Figure 2 shows the ROC curve drawn to determine the ability of the Sarcoma Lung Metastasis Score to predict the 3-year mortality risk. The Sarcoma Lung Metastasis Score was found to be moderately discriminatory, with a c-index of 0.75. As shown in **Figure 3**, the Sarcoma Lung Metastasis Score reliably predicted the 3-year survival rate (Sarcoma Lung Metastasis Score: 0: 89.5%; 1: 63.2%; 2: 39.0%; 3: 10.5%; P = 0.000000019). The survival period after lung metastasectomy was also correlated with the Sarcoma Lung Metastasis Score (**Figure 4**, r = -0.38, P = 0.0000068).

Discussion

In this study, we proposed the Sarcoma Lung Metastasis Score created from preoperatively measured prognostic clinical factors and demonstrated its usefulness for sarcoma patients with pulmonary metastases. In order to precisely select prognostic factors for an accurate Sarcoma Lung Metastasis Score, the analysis was performed only in patients who underwent the initial intervention at our hospital for pulmonary metastases. Despite previous reports about the usefulness of lung metastasectomy in sarcoma patients, there were no methods to predict the postoperative prognosis in the patients prior to the performance of metastasectomy [2-6]. For this reason, there was no clear consensus in respect of the surgical indications for pulmonary metastases in sarcoma patients, and the indications were determined arbitrarily by each institution. Our newly proposed Sarcoma Lung Metastasis Score is calculated on the basis of three factors alone that are determined at the time of diagnosis of the pulmonary metastasis, and is useful for selecting the most appropriate and viable treatments for patients with metastatic sarcomas, from the perspective of both the patients and their physicians.

Various therapies (e.g., chemotherapy, hormonal therapy, radiotherapy, RFA, and molecular-targeted therapy) have been reported for the treatment of pulmonary metastases in patients with sarcomas. However, each of the therapies is known to exert only limited effect, and surgical resection may need to be considered as a therapeutic option for disease control [13-15]. As per previous reports, surgical resection could be expected to prolong the overall survival in sarcoma patients with pulmonary metastases [2, 5, 6]. Since no randomized controlled trials have been reported, however, the accurate outcomes of resection are still unknown. This study also found that certain preoperative factors were associated with prognosis. However, this cohort analyzed only the surgery group and there is no control group for comparison. Thus, it is still unclear whether surgery itself improves prognosis. To prove the effectiveness of pulmonary metastasectomy, the prospective randomized study is warranted, although it may be difficult to find a group of patients who are just observed. There is a previous study that attempted to perform the randomized clinical trial comparing pulmonary metastasectomy versus continued active monitoring in colorectal cancer [16], resulting in the termination because of recruitment difficulties.

Among the preoperative prognostic predictors reported hitherto that are considered prior to metastasectomy in colorectal cancer patients with pulmonary metastases, there are two that are common with the factors suggested in this study: DFI and the number of pulmonary metastases. The reported 3-year survival rate after pulmonary metastasectomy in colorectal cancer patients is 53.0-54.1% [17-19], which is consistent with the percentage of 48.9% in our entire cohort. Therefore, it would appear that surgical treatment would be acceptable in sarcoma patients with pulmonary metastases, if the patients are appropriately selected on the basis of reliable prognostic factors. Each of the three factors of the Sarcoma Lung Metastasis Score, namely, the DFI, tumor size, and number of pulmonary metastases are considered to be predictors of the degree of malignancy. In sarcoma patients with pulmonary metastases, because the 3-year survival after metastasectomy is lower than 50% in patients with a Sarcoma Lung Metastasis Score of 2 or more, the indications for pulmonary metastasectomy should be carefully considered.

The present study had several limitations. First, this was a retrospective study conducted at a single center, and the number of patients was relatively small. Thus, we need to carefully consider the generalizability of our findings. Second, we did not take the effect of chemotherapy into consideration. However, because it is expected to be of very limited benefit [5, 20], we believe this limitation is negligible. Last, as a feature of sarcomas per se, our cases also showed heterogeneity from the viewpoint of the primary lesions and tissue types involved. The usefulness of the Sarcoma Lung Metastasis Score may need to be carefully considered depending on the background of the patients with each type of sarcoma. External validation would be desirable to determine the accuracy of the Sarcoma Lung Metastasis Score using a different cohort.

In conclusion, as a preoperative-measurements-based scoring system to determine the prognostic benefit of surgery for sarcoma patients with pulmonary metastases, we have proposed the simple but useful Sarcoma Lung Metastasis Score, which can be calculated from only three factors measured preoperatively, namely the DFI, tumor size, and number of pulmonary metastases. This score not only enables the treating doctors to predict the prognosis at the time of diagnosis in sarcoma patients with pulmonary metastases, but also allows them to offer the most appropriate treatment, from both the patients' and the physicians' perspective, for metastatic sarcoma patients.

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FIGURE LEGENDS

Figure 1: Flow-diagram of this study cohort. Lung resection was performed in 158 sarcoma patients with pulmonary metastases during the study period at Okayama University Hospital. Twenty-three patients, including 20 patients who had undergone the first lung metastasectomy at another hospital and 3 patients who had undergone radiofrequency ablation (RFA) therapy before the lung resection were excluded from this study. Of the remaining 135 patients, the 69 patients who died within 3 years after the metastasectomy were designated as the 3-year non-survivor group (n = 69), and the 66 patients who survived for at least 3 years after the metastasectomy were designated as the survivor group (n = 66). Abbreviations: RFA, radiofrequency ablation.

Figure 2: Receiver operating characteristic (ROC) curve to determine the ability of the Sarcoma Lung Metastasis Score to predict the 3-year mortality risk. The Sarcoma Lung Metastasis Score was moderately discriminatory, with a concordance index of 0.75.

Figure 3: Three-year survival after lung metastasectomy according to the Sarcoma Lung Metastasis Score. Good correlation was observed between the Sarcoma Lung Metastasis Score and the 3-year survival rate (Sarcoma Lung Metastasis Score: 0: 89.5%; 1: 63.2%; 2: 39.0%; 3: 10.5%; $P = 0.000000019$)

Figure 4: Plot showing the relationship between the survival period after lung metastasectomy and the Sarcoma Lung Metastasis Score. Pearson product-moment correlation coefficient was calculated between the Sarcoma Lung Metastasis Score and the survival time after lung metastasectomy, and a significant correlation was observed between these two factors (r = -0.38, $P = 0.0000068$).

Table 1. Patient characteristics

Patient characteristics		N = 135
Age in yr, median (range)		55 (14-88)
Sex, female		101 (75%)
Site of primary tumor	Uterus	54 (40%)
	Lower extremity	33 (24%)
	Retroperitoneum	16 (12%)
	Inguinal region	6 (4%)
	Others	26 (19%)
Histology	Leiomyosarcoma	72 (53%)
	Synovial sarcoma	9 (7%)
	Osteosarcoma	11 (8%)
	Others	43 (32%)
Extent of primary disease at initial diagnosis	Localized	113 (84%)
	Metastatic	22 (16%)
Local recurrence and or extrapulmonary metastasis diagnosed with or before the diagnosis of pulmonary metastasis, yes		42 (31%)
Disease-free interval, days, median (range)		369 (0-8985)
Lung tumor location	Unilateral	49 (36%)
	Bilateral	86 (64%)
Maximum tumor diameter, mm, median (range)		15 (3-110)
Number of pulmonary metastases, median (range)		3 (1-19)
Surgical procedure	Wedge only	95 (70%)
	Anatomical	40 (30%)
Two-stage operation, yes		37 (27%)
Curative resection (all detected tumors)	Curative	102 (76%)
	Non-curative	33 (24%)
Median observation period for survivor, days, median (range)		1568.5 (1095-4697)

Table 2. Results of univariate analysis to identify factors influencing the 3-year mortality risk

Factor		3-year survivors (N = 66)	3-year non-survivors (N = 69)	*P* value
Age (yr)	< 56	32	38	0.49
	≥ 56	34	31	
Sex	Female	51	50	0.56
	Male	15	19	
Site of primary tumor	Uterus	24	30	0.48
	Others	42	39	
Histology	Leiomyosarcoma	35	37	0.99
	Others	31	32	
Extent of primary disease at initial diagnosis	Localized	57	56	0.49
	Metastatic	9	13	
Local recurrence and or extrapulmonary metastasis diagnosed at the time or before the diagnosis of pulmonary metastasis	No	41	52	0.14
	Yes	25	17	
Disease-free interval	< 2 years	39	60	0.00038
	≥ 2 years	27	9	
Lung tumor location	Unilateral	29	20	0.077
	Bilateral	37	49	
Maximum tumor diameter	< 15mm	38	16	0.000052
	≥ 15mm	28	53	
Number of pulmonary metastases	< 6	57	45	0.0050
	≥ 6	9	24	
Surgical procedure	Wedge only	49	46	0.35
	Anatomical	17	23	
Two-stage operation	No	47	51	0.85
	Yes	19	18	

Table 3. Scores assigned on the Sarcoma Lung Metastasis Score system for factors identified as influencing the 3-year mortality risk identified by a multivariate analysis

Factors	Odds. ratio	95% CI	*P* value	Sarcoma Lung Metastasis Score
Disease-free interval **< 2 years** vs. ≥ 2 years	4.22	1.67-10.70	0.0023	1
Maximum tumor diameter **≥ 15 mm** vs. < 15 mm	3.86	1.75-8.52	0.00082	1
Number of pulmonary metastases **≥ 6** vs. < 6	2.65	1.06-6.620	0.037	1

Abbreviation: CI: confidence interval