Impact of Primary Tumor Resection on Metastasis to the Lung in Patients With Bone and Soft-tissue Sarcoma

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Abstract. *Background:* Few reports have investigated the effect of primary tumor resection on lung metastasis and prognosis in patients with bone and soft-tissue sarcoma, and we evaluated its effect on lung metastasis and prognosis. *Patients and Methods:* We retrospectively identified patients with lung metastasis from bone and soft-tissue sarcoma. We examined the factors affecting prognosis and the rate of lung metastasis increase. *Results:* A total of 48 patients were included. The multivariate analysis revealed that poor prognosis was significantly associated with a large maximum diameter of lung metastasis at the first visit and a rapid rate of increase ($p=0.0400$ and $p=0.0003$, respectively). The multivariate logistic regression analysis revealed that the rate of increase of size of lung metastases was only significantly associated with a large maximum diameter at the first visit ($p=0.0245$). *Conclusion:* Primary tumor resection of bone and soft-tissue sarcoma in patients with lung metastasis was not shown to affect their prognosis.

Bone and soft-tissue sarcomas, although relatively rare diseases, have various histological subtypes, including liposarcoma, synovial sarcoma, osteosarcoma, and Ewing sarcoma. Treatment is based on radical resection with adequate margins, regardless of the histological subtype, in order to prevent local recurrence. However, there is a consensus that the presence of distant metastases, particularly in the lungs, strongly influences prognosis (1-3). Chemotherapy is commonly used in patients with bone and

soft-tissue sarcomas with lung metastases, especially those with numerous ones. The primary tumor is not aggressively resected in these patients. However, if the primary tumor interferes significantly with the patient's quality of life in terms of pain, neuropathy, and breaking of the skin, resection or even amputation may be required. Therefore, it is possible to remove only the primary tumor in these patients.

In recent years, prognosis has been shown to improve in certain malignancies, such as gastric and colorectal cancer with multiple metastases, when the primary tumor is removed (4-6). However, very few reports have investigated the effect of primary tumor resection on the prognosis of patients with bone and soft-tissue sarcomas with distant metastases (7, 8). Furthermore, to our knowledge, no reports have examined how excision of the primary tumor affects metastasis to the lungs, which is the most common type. This study aimed to examine the impact of primary tumor resection on lung metastasis and prognosis in patients with bone and soft-tissue sarcoma.

Patients and Methods

Patients. We retrospectively identified patients with bone and soft-tissue sarcoma involving the extremities or trunk with lung metastasis at the first visit treated at our two hospitals between 1994 and 2020. Patients with lung metastasis confirmed at the same time as local primary tumor recurrence were also included. Since we aimed to assess the impact of primary tumor treatment, those who did not receive radiotherapy or surgical treatment for lung metastasis were also included. Patients' records were searched to collect data regarding age, sex, malignancy and histological subtype, anatomical tumor location, size, lung and other metastasis, primary tumor treatment, follow-up period, and outcomes. Specimens of soft-tissue sarcoma were classified using the French Federation of Cancer Center Sarcoma Group system, which includes the mitotic index, extent of necrosis, and histological differentiation (9). The maximum diameter and the number of lung metastases at the first visit were evaluated. In addition, the maximum diameter of lung-metastatic lesions in each of the first and last chest computed tomography images were measured, and the average rate of increase

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Key Words: Sarcoma, lung metastasis, primary tumor, prognosis.

Table I. Comparison between patients based on surgical resection of the primary tumor.

		Surgical resection (n=13)	Not resected (n=35)	p-Value
Age, years	Mean±SD	44.0±27.5	60.3±22.2	0.0393
Gender, n (%)	Male	8 (61.5)	17 (48.6)	0.6354
	Female	5 (38.5)	18 (51.4)	
Location, n (%)	Extremity	7 (53.8)	24 (68.6)	0.5429
	Axial	6 (46.2)	11 (31.4)	
Size of the primary tumor, mm	Mean±SD	81.1±48.6	118.7±69.6	0.0807
Tumor, n (%)	First time	8 (61.5)	26 (74.3)	0.6127
	Recurrence	5 (38.5)	9 (25.7)	
Origin, n (%)	Soft-tissue	10 (76.9)	26 (74.3)	0.8513
	Bone	3 (23.1)	9 (25.7)	
Histological grade, n (%)	Low	1 (7.7)	2 (5.7)	0.6750
	High	12 (92.3)	33 (94.3)	
Number of lung metastases at first visit, n (%)	≤3	6 (46.2)	12 (34.3)	0.3363
	>3	4 (30.8)	21 (60.0)	
	Unknown	3 (23.0)	2 (5.7)	
Maximum diameter of lung metastasis at first visit, mm	Mean±SD	7.5±3.7	16.2±16.1	0.0068
Average rate of lung metastasis increase, mm/month	Mean±SD	1.8±1.3	4.8±5.9	0.0142
Distant metastasis other than lung at the first visit, n (%)	Yes	4 (30.8)	9 (25.7)	0.9879
	No	9 (69.2)	26 (74.3)	
Distant metastasis other than lung that appeared later, n (%)	Yes	1 (7.7)	4 (11.4)	0.8768
	No	12 (92.3)	31 (88.6)	
Radiation for primary tumor, n (%)	Yes	5 (38.5)	11 (31.4)	0.9086
	No	8 (61.5)	24 (68.6)	
Chemotherapy, n (%)	Yes	7 (53.8)	21 (60.0)	0.9562
	No	6 (46.2)	14 (40.0)	
Follow-up period, months	Mean±SD	17.8±11.5	12.6±12.2	0.1915
Status at the last follow-up, n (%)	Alive with disease	2 (15.4)	4 (11.4)	0.9023
	Dead	11 (84.6)	31 (88.6)	

per month (mm/month) was defined. We additionally collected information regarding the type of local therapy and surgical margins (Enneking staging system) for patients who underwent surgery (10). In the absence of any events, patients were censored at the last follow-up. Overall survival (OS) was defined from the date of diagnosis to the date of death or the last follow-up.

Clinical characteristics and outcomes were compared based on primary tumor resection status, and the factors affecting prognosis were examined. In addition, we evaluated the factors affecting the average rate of increase in the size of lung metastases.

Statistical analysis. All continuous variables were expressed as the mean±standard deviation. Student's *t*-tests, Welch *t*-tests, and chi-squared tests were used to compare characteristics between the two groups. A Cox proportional hazards model was used to identify the factors that were associated with OS. OS was compared using the Kaplan–Meier method, and differences were analyzed using the generalized Wilcoxon test.

We were able to measure the rate of increase in size of lung metastases more than once in 39 of the patients. The mean rate was 4.08±5.37 mm/month (range=−0.2–29.2 mm/month) and the patients were divided into fast and slow increase groups based on this average. Multivariate logistic regression analysis was used to examine the factors associated with the rate of lung metastasis size. A *p*-value of less than 0.05 was used to denote statistical significance.

Ethics. This study was approved by the Institutional Review Board for Clinical Research at the Akita University (approval number: 2636) and was conducted in accordance with the 1975 Declaration of Helsinki and its 1983 revision.

Results

A total of 48 patients with bone and soft-tissue sarcoma were included in this study, 25 of whom were male and 24 were female. The mean age was 55.9 years (range=10–91 years), and the mean duration of follow-up was 14.0±12.1 months (range=1–46 months). The histological diagnoses of soft-tissue sarcoma were malignant peripheral nerve sheath tumor in eight, undifferentiated pleomorphic sarcoma in seven, synovial sarcoma in six, dedifferentiated liposarcoma in four, myxoid liposarcoma in two, pleomorphic liposarcoma in one, leiomyosarcoma in two, epithelioid sarcoma in two, extraosseous Ewing sarcoma in two, myxofibrosarcoma in one, and alveolar rhabdomyosarcoma in one. The histological diagnoses of bone malignant tumors were conventional osteosarcoma in seven, small-cell osteosarcoma in one, chondrosarcoma in two, and Ewing sarcoma in two.

Table II. Univariate and multivariate analyses of potential prognostic predictors.

Factor	Univariate			Multivariate		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Age	1.000	0.988-1.012	0.9604			
Gender (female)	1.197	0.641-2.238	0.5725			
Location (axial)	0.736	0.375-1.444	0.3733			
Size of the primary tumor	1.003	0.999-1.008	0.1598			
Local recurrence	0.598	0.302-1.185	0.1405			
Malignant bone tumor	1.026	0.504-2.089	0.9428			
Histological grade (high)	1.579	0.869-2.870	0.1335			
Maximum diameter of lung metastasis at first visit	1.039	1.017-1.062	0.0005	1.028	1.001-1.056	0.0400
Number of lung metastasis at first visit (>3)	1.575	0.794-3.124	0.1939			
Distant metastasis other than lung at the first visit	1.044	0.520-2.039	0.9042			
Surgical treatment for primary tumor	0.738	0.367-1.482	0.3926			
Inadequate surgical margins	1.974	0.504-7.728	0.3289			
Radiation for primary tumor	0.988	0.522-1.869	0.9703			
Chemotherapy	1.145	0.601-2.181	0.6812			
Average rate of lung metastasis increase	1.156	1.075-1.242	<0.0001	1.149	1.066-1.238	0.0003
Distant metastasis other than lung that appeared later	1.117	0.392-3.180	0.8364			

CI: Confidence interval; OR: odds ratio.

The sites these primary lesions were the extremities in 64.6% (n=31) and axial sites in 35.4% (n=17). The mean tumor size was 108.5±66.3 mm (range=25-370 mm), and histological grade was low in three and high in 45 patients.

The mean maximum diameter of lung metastases at first visit was 14.1±14.6 mm (range=2-80 mm) and 30 patients (27.1%) had already developed them in the bones in seven cases, lymph nodes in four, liver in three, intraperitoneal space in two, brain in one, and the stomach in one. In addition, five patients (10.4%) developed extra-pulmonary metastasis later, four in bone, and in a lymph node in one, pancreas in one, adrenal gland in one, and the thoracic cavity in one.

Surgical treatment for the primary tumor was performed in 13 patients (27.1%), and adequate tumor-free margins were achieved in six of these. Radiotherapy for the primary tumor was performed in 16 patients (33.3%), which included proton-beam radiation (6.3%, n=1) and radiotherapy plus surgery (25.0%, n=4). Chemotherapy was administered to 28 patients (58.3%) and included doxorubicin, ifosfamide, dacarbazine, gemcitabine, docetaxel, methotrexate, cisplatin, carboplatin, vincristine, cyclophosphamide, etoposide, actinomycin D, eribulin, trabectedin, and pazopanib. In terms of outcomes, six patients were alive with the disease and 42 patients had died because of it at the last follow-up. No patients died due to complications during the perioperative period.

Patients who had their primary tumor resected had significantly smaller lung metastases at the first visit and a slower rate of increase than those who did not undergo surgical resection ($p=0.0068$ and $p=0.0142$, respectively) (Table I). The multivariate analysis revealed that the

maximum diameter of lung metastases and the average rate of increase were significant prognostic predictors ($p=0.04$ and $p=0.0003$, respectively), yet primary tumor resection did not affect the outcome (Table II). The Kaplan–Meier curve revealed that patients with slow-growing lung metastases had a significantly better prognosis than those with fast-growing ones ($p=0.0003$) (Table III and Figure 1).

Patients in the fast-growing group had a significantly larger maximum diameter of lung metastasis at the first visit ($p=0.0419$) (Table IV). The multivariate logistic regression analysis revealed that the rate of increase was significantly associated with the maximum diameter of lung metastasis at the first visit ($p=0.0245$) and that surgical resection of the primary tumor did not affect the rate of increase (Table V).

Discussion

This study found that patients whose primary tumor was resected were significantly more likely to have smaller lung metastases at the first visit and a slower rate of increase than those who did not undergo surgical resection. The maximum diameter and average rate of increase of size of lung metastases were prognostic predictors, whereas primary tumor resection did not significantly affect the outcome.

Various factors such as histological grade have been reported as poor prognostic predictors for bone and soft-tissue sarcoma (11-13), but few have been reported for patients with distant metastases. Lung metastasis has a worse prognosis than lymph node metastasis, irrespective of therapeutic intervention (1). In our previous study, large

Table III. Significance of prognostic predictors of survival from the Kaplan–Meier curve.

Evaluated items		p-Value
Gender	Male vs. female	0.5815
Location	Extremity vs. axial	0.5068
Tumor	First time vs. recurrence	0.0613
Origin	Soft-tissue vs. bone	0.4278
Histological grade	Low vs. high	0.5797
Number of lung metastasis at first visit	≤3 vs. >3	0.2026
Distant metastasis other than lung at the first visit	Yes vs. no	0.4240
Surgical treatment for primary tumor	Yes vs. no	0.1118
Radiation for primary tumor	Yes vs. no	0.6209
Chemotherapy	Yes vs. no	0.6745
Average rate of increase in lung metastasis	≥4.08 vs. <4.08 mm/month	0.0003
Distant metastasis other than lung that appeared later	Yes vs. no	0.6718

primary tumor diameter and malignant peripheral nerve sheath tumor were poor prognostic predictors (14), and recently, Zhang *et al.* showed that tumor size, histological malignancy, and undifferentiated pleomorphic sarcoma were additional ones (8). In our study of patients with only lung metastases, the size at the first visit and the rate of increase were predictors of poor prognosis. Although distant metastases of the lung are the most common, as far as we are aware, there have been no reports that have evaluated only this subset of patients as we have in our study. Thus, when examining the prognosis of bone and soft-tissue sarcoma, it is necessary to focus on lung-metastatic lesions.

A few studies have examined the effect of interventions on patients with bone and soft-tissue sarcoma with distant metastasis. Although some have shown that resection of the distant metastasis improves the prognosis (2, 8, 15-17), only a few reports have examined the effects of primary lesion resection (4, 5). Nakamura *et al.* showed that prognosis improved after primary lesion excision, but this was through a univariate analysis and they did not examine the treatment for distant metastatic lesions (7). However, Zhang *et al.* studied more than 1,000 registered cases and reported that primary tumor resection, especially with wide margins, improved prognosis, along with resection of distant metastasis in multivariate analysis (8). In our study, although the analysis was limited to patients with lung metastasis and the number of cases was small, the prognosis was not significantly affected after primary tumor resection. It is important to note that the primary tumor may be aggressively resected to improve the patient's distress, even if there are distant metastases.

The rate of increase in the size of lung metastases was the factor that most affected the prognosis in our study, and it was only associated with the maximum diameter at the first visit. Since the rate of growth of lung metastases is high,

Figure 1. Kaplan–Meier overall survival curves for patients with bone and soft-tissue tumors according to the monthly rate of growth of lung metastases, using a cut-off of 4.08 mm/month. These curves revealed that patients with slow-growing lung metastases had a significantly better prognosis than those with fast-growing ones ($p=0.0003$).

lung metastases may already be large when the primary tumor is diagnosed.

In this study, primary resection was not shown to significantly affect the rate of increase in the size of lung metastases. Yet both the odds ratio and the p -value were low. Given the reports that primary tumor resection is a prognostic predictor, it may be possible that it affects the rate of increase in lung metastasis size. However, in this study, the size of lung metastases at the first visit was significantly smaller in patients who had undergone surgical resection. Although we conducted a multivariate analysis, it is possible that the rate of lung metastasis increase was low due to the large number of surgeries performed on patients with small lung-metastatic lesions at the time of the initial diagnosis. In order to better clarify this, more cases need to be examined.

Table IV. Comparison between patients with fast- and slow-growing lung metastases.

		Fast-growing (n=15)	Slow-growing (n=24)	p-Value
Age, years	Mean±SD	53.2±20.9	59.0±26.5	0.4736
Gender, n (%)	Male	9 (60.0)	12 (50.0)	0.7800
	Female	6 (40.0)	12 (50.0)	
Location, n (%)	Extremity	11 (73.3)	13 (54.2)	0.3905
	Axial	4 (26.7)	11 (45.8)	
Size of the primary tumor, mm	Mean±SD	108.4±53.7	99.6±58.5	0.6413
Tumor, n (%)	First time	11 (73.3)	17 (70.8)	0.8439
	Recurrence	4 (26.7)	7 (29.2)	
Origin, n (%)	Soft-tissue	11 (73.3)	20 (83.3)	0.7302
	Bone	4 (26.7)	4 (16.7)	
Histological grade, n (%)	Low	1 (6.7)	1 (4.2)	0.6879
	High	14 (93.3)	23 (95.8)	
Number of lung metastases at first visit, n (%)	≤3	4 (26.7)	13 (54.2)	0.1760
	>3	11 (73.3)	11 (45.8)	
Maximum diameter of lung metastasis at first visit, mm	Mean±SD	19.7±18.8	8.5±6.9	0.0419
Average rate of lung metastasis increase, mm/month	Mean±SD	8.6±6.3	1.2±1.0	0.0005
Distant metastasis other than lung at the first visit, n (%)	Yes	3 (20.0)	6 (25.0)	0.9760
	No	12 (80.0)	18 (75.0)	
Distant metastasis other than lung that appeared later, n (%)	Yes	2 (13.3)	3 (12.5)	0.6770
	No	13 (86.7)	21 (87.5)	
Surgical treatment for primary tumor	Yes	1 (6.7)	8 (33.3)	0.1254
	No	14 (93.3)	16 (66.7)	
Radiation for primary tumor, n (%)	Yes	3 (20.0)	10 (41.7)	0.2950
	No	12 (80.0)	14 (58.3)	
Chemotherapy, n (%)	Yes	12 (80.0)	13 (54.2)	0.1960
	No	3 (20.0)	11 (45.8)	
Follow-up period, months	Mean±SD	7.1±6.7	19.9±12.8	0.0002
Status at the last follow-up, n (%)	Alive with disease	1 (6.7)	4 (16.7)	0.6770
	Dead	14 (93.3)	20 (63.3)	

Table V. Multivariate logistic regression analysis for the rate of increase in lung metastasis size.

Factor	OR	95% CI	p-Value
Age	0.943	0.866-1.028	0.1805
Gender (female)	2.182	0.214-22.272	0.5104
Location (axial)	0.145	0.009-2.468	0.1817
Size of the primary tumor	1.001	0.980-1.022	0.9220
Local recurrence	1.220	0.090-16.552	0.8811
Malignant bone tumor	1.049	0.051-21.430	0.9754
Histological grade (high)	4.564	0.454-45.853	0.1896
Maximum diameter of lung metastasis at first visit	1.199	1.024-1.404	0.0245
Number of lung metastasis at first visit (>3)	1.818	0.137-24.052	0.6499
Distant metastasis other than lung at the first visit	0.352	0.023-5.478	0.4561
Surgical treatment for primary tumor	0.076	0.003-2.274	0.1374
Radiation for primary tumor	0.288	0.013-6.151	0.4256
Chemotherapy	0.218	0.006-7.682	0.4018

CI: Confidence interval; OR: odds ratio.

The size of lung metastases at the first visit and the rate of size increase were found to be poor prognostic predictors, whilst the number of lung metastases was not. Although Ferguson *et al.* showed that patients have a better prognosis

when the number of lung metastases is three or fewer, that was the result of a univariate analysis (10). In our study, we investigated lung metastasis in detail by conducting a multivariate analysis, and there have been no reports in the past

regarding the rate of lung metastasis increase. It is considered to be a very effective index for evaluation, but the method used for its delamination needs to be improved. It is important to note that the rate of increase was calculated only using the first and last computed tomography images. The rate of increase in the size of lung metastases is not always uniform and they may increase rapidly after tumor progression. Therefore, it is necessary to consider a more detailed evaluation method.

The strength of this study is that it is the first to examine the relationship between primary tumor resection and lung metastasis in detail in patients with bone and soft-tissue sarcoma. However, there are some limitations that should be mentioned. Since the number of patients with bone and soft-tissue sarcoma with lung metastases was small, they were analyzed together in this study, as were patients with initial and recurrence disease. Although a multivariate analysis was performed, it is better to analyze each group separately. In addition, it was not possible to examine various other histological and chemotherapy types in this analysis. Therefore, further detailed studies are needed with a larger number of patients included.

In conclusion, this study evaluated the impact of primary tumor resection and revealed it to have no effect on the prognosis of patients with lung metastasis of bone and soft-tissue sarcoma. Thus, the primary tumor should be excised only if it is necessary to improve the patient's quality of life. In addition, it may be necessary to consider detailed evaluation of lung metastases such as the rate of increase in size, since it was shown to affect the prognosis in these patients. Future studies should focus on validating these results by conducting larger studies and improving this evaluation index.

Conflicts of Interest

The Authors report no conflicts of interest.

Authors' Contributions

All Authors were involved in the planning and revising for this research. Tsuchie H, Nagasawa H, Emori M, Murahasi Y, Mizushima E, and Shimizu J collected the clinical data. Tsuchie H analyzed the raw data. Tsuchie H wrote the article. Miyakoshi N and Yamashita Y reviewed the article.

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