

Oncological outcome after lung metastasis in patients presenting with localized chondrosarcoma at extremities: Tokai Musculoskeletal Oncology Consortium study

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Abstract: The oncological outcome after lung metastasis in patients with chondrosarcoma of the extremities has not been reported. Between June 2000 and June 2013, 179 patients with chondrosarcoma in the extremities were treated at eleven hospitals. Twenty consecutive patients (11.2%) developed lung metastases after initial treatment of primary chondrosarcoma in the extremities. We investigated the oncological outcome of 20 chondrosarcoma patients with lung metastasis. There were 14 males and six females with a mean age of 49 years. The mean duration between primary surgery and appearance of lung metastases was 34 months. The mean follow-up period was 48 months. We excluded patients with lung metastasis at the time of presentation from this study. At the final follow-up, four of 20 patients had no evidence of disease, four were alive with disease, and twelve had died of disease. The 3- and 5-year survival rates after lung metastasis were 51.5% and 45.7%, respectively. Tumor grade, extrapulmonary metastasis, and treatment for lung metastases including metastasectomy and radiofrequency ablation were identified by univariate analysis to be significant prognostic factors for oncological analysis. In conclusion, this study evaluated the oncological outcome in patients with chondrosarcoma of the extremities with lung metastasis. Although a large-scale study might be required to confirm the results of this study, we suggest that metastasectomy and/or radiofrequency ablation should be considered to improve postmetastatic survival.

Keywords: chondrosarcoma, lung metastasis, radiofrequency ablation, metastasectomy, extremity

Introduction

Chondrosarcoma is the second most frequently observed primary sarcoma of bone.¹ Surgical resection remains the mainstay of treatment owing to the limited effects of radiation therapy and chemotherapy.¹⁻³ While the 5-year survival rate of patients with grade 1 tumors was 90%, only 40%–60% of patients with grades 2 and 3 tumors could survive after 5 years.⁴ Mesenchymal chondrosarcoma is rare but has a relatively better prognosis, with 80% survival rate at 5 years, if the primary tumor is localized.⁵ Dedifferentiated chondrosarcoma is a rare, particularly aggressive subtype of chondrosarcoma and is associated with an even poorer prognosis, with a 20%–30% survival rate at 5 years.^{4,6} Patients with pelvic chondrosarcoma were often reported to have poor prognoses because the surgical treatment of a pelvic lesion is challenging and a chondrosarcoma at the pelvic lesion has a high potential for metastasis.^{7,8} However, it is considered that metastasis is less common in patients with chondrosarcoma of extremities.^{1,2,9} Therefore, there are no reports on oncological outcome after lung metastasis in patients

with chondrosarcoma of the extremities. In this study, we investigated the oncological outcome in 20 chondrosarcoma patients with lung metastasis at the institutions under the Tokai Musculoskeletal Oncology Consortium.

Patients and methods

Tokai Musculoskeletal Oncology Consortium was formed in 2014 to improve the care of patients with musculoskeletal tumors and to improve the knowledge in all aspects of the biology of these tumors, including basic and clinical research. All the physicians of this consortium consisting of eleven hospitals are specialized in orthopedic oncology.

Between June 2000 and June 2013, 179 patients with chondrosarcoma in the extremities were treated at eleven hospitals. Twenty consecutive patients (11.2%) developed lung metastases after the initial treatment of primary chondrosarcoma of the extremities. We excluded patients with lung metastasis at the time of presentation from this study. There were 14 males and six females with a mean age of 49 years (range, 27–81 years). The details on the number and diameter of lung metastases are summarized in Table 1. The distribution of chondrosarcoma subtype was as follows: conventional chondrosarcoma (n=14; grade 2 in eleven patients and grade 3 in three patients), dedifferentiated chondrosarcoma (n=5), and mesenchymal chondrosarcoma (n=1). Local recurrence occurred in six patients. Two patients developed local recurrence after the diagnosis of lung metastasis. Six patients developed extrapulmonary metastasis at the diagnosis of lung metastasis (pelvis, n=2; pleural, n=1; lymph node, n=1; soft tissue, n=1; vertebrae, n=1). The mean follow-up period was 48 months.

The primary purpose of this study was to elucidate the prognostic factors associated with patient survival after first lung metastasis using univariate and multivariate analyses. The variables included nine characteristics. Age and sex were selected to represent individual clinical covariates. Tumor grade and development of local recurrence were selected for the assessment of primary sarcoma lesions. The maximum metastatic tumor size and number of metastasis at the time of initial diagnosis, extrapulmonary metastasis, chemotherapy, and surgical treatment were also chosen as variables. We defined that the treatment for lung metastases included metastasectomy and radiofrequency ablation (RFA).

The resectability of the lung metastases and indications for RFA were judged by a multidisciplinary team consisting of orthopedic surgeons, thoracic surgeons, and interventional radiologists after considering the number of tumors, location, the patient's lung function, comorbidities, and patient's prognosis.

Table 1 Patient characteristics

Variables	
Age (years)	
Mean	49
Range	27–81
Sex (n)	
Male	14
Female	6
Primary site	
Femur	7
Tibia	5
Humerus	4
Scapula	3
Fibula	1
No of lung metastasis	
Single	7
Multiple	13
Size of lung metastasis (mm)	
Range	2–45
Tumor grade	
G2	11
G3	4
Dedif	5
Local recurrence before metastasis (n)	
Yes	4
No	16
Extrapulmonary metastasis (n)	
Yes	6
No	14
Duration between primary surgery and appearance of lung metastases (months)	
Mean	34
Median	25
Range	1–89

Abbreviation: Dedif, dedifferentiated.

The statistical association of the clinicopathological factors was evaluated using Mann–Whitney *U*-test for quantitative data and Fisher's exact test or χ^2 test for qualitative data. Overall survival was defined as the time from initial diagnosis of lung metastasis to the date of death or last follow-up. Survival curves were constructed using the Kaplan–Meier method. The log-rank test was used to compare the disease-specific survival of the patients. A value of $P < 0.05$ was considered to be significant in all statistical analyses. The statistical software package Stat View Version 5.0 (SAS Institute, Cary, NC, USA) was employed for analysis. This study was approved by the Mie University Hospital review board, and written informed consent was obtained from all patients.

Results

Nine of 20 sarcoma patients underwent metastasectomy (n=8) or RFA (n=1) for the initial lung metastasis (Table 2). There was a significant difference in the number of metastases in the patients who underwent metastasectomy or RFA and

Table 2 Comparison between patients with or without surgical treatment for all 20 patients

Variables	Patients with surgical treatment ^a	Patients without surgical treatment	P-value
Number (n)	9	11	–
Mean age (years)	48	51	0.79
Sex			
Male	7	7	0.64
Female	2	4	
Mean size of metastasis (mm)	13	19	0.18
Mean number of metastasis	2	9	0.01
Initial surgical treatment			
Wedge resection	7	–	–
Lobectomy	1	–	–
RFA	1	–	–

Notes: ^aSurgical treatment includes metastasectomy and RFA. –, Not available.

Abbreviation: RFA, radiofrequency ablation.

those who did not (Mann–Whitney *U*-test, $P=0.01$). In the patients with initial metastasis, the number of tumors treated varied from one to four. Complete resection was achieved in all nine patients. Seven of nine patients developed second relapse. One patient underwent metastasectomy and three patients underwent RFA. One patient was followed without treatment due to small size of relapsed metastasis. The remaining two patients had best supportive care because of difficulty with radical treatment. Chemotherapy for lung metastasis was administered in six of 20 patients. In five patients, adriamycin and ifosfamide were administered. Partial response occurred in one patient, stable disease in two, and progressive disease in one. One patient received chemotherapy as adjuvant therapy after metastasectomy. In one patient, combination therapy with adriamycin, cisplatin, and ifosfamide was administered; however, progressive disease occurred. Seven patients received no surgical treatment and chemotherapy because of their advanced disease. We examined the factors that indicated surgical treatment. The presence of extrapulmonary metastasis was a significant negative indicator for surgical treatment (Fisher's exact test, $P=0.01$). The six patients with extrapulmonary metastasis received no surgical treatment, while nine of 14 patients without extrapulmonary metastasis underwent surgical treatment. The size of lung metastasis and age did not affect the decision for surgical treatment (Table 3).

Regarding the oncological results at the final follow-up, four of 20 patients had no evidence of disease, four were alive with disease, and twelve had died of disease. The 3-year, 5-year, and 10-year survival rates after lung metastasis were 51.5%, 45.7%, and 31.4%, respectively.

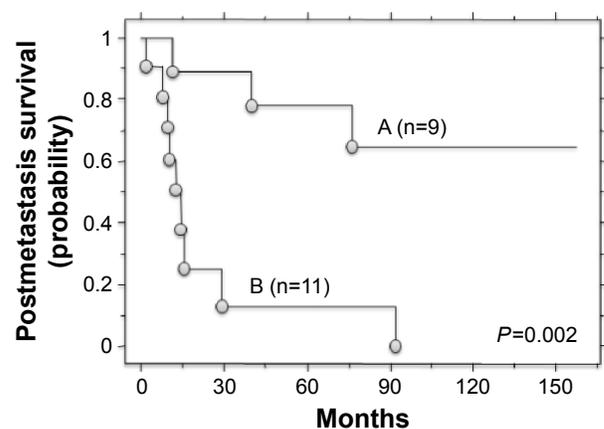
Table 3 Comparison between patients with or without surgical treatment in 14 patients who developed lung metastasis alone

Variables	Patients with surgical treatment ^a	Patients without surgical treatment	P-value
Number (n)	9	5	–
Mean age (years)	48	38	0.29
Sex			
Male	7	1	0.99
Female	2	4	
Mean size of metastasis (mm)	13	23	0.09
Mean number of metastasis	2	7	0.01
Median survival time (months)	Not reached	9.5	0.01
Initial surgical treatment			
Wedge resection	7	–	–
Lobectomy	1	–	–
RFA	1	–	–

Notes: ^aSurgical treatment includes metastasectomy and RFA. –, Not available.

Abbreviation: RFA, radiofrequency ablation.

Tumor grade, extrapulmonary metastasis, and the treatment for lung metastases, which included metastasectomy and RFA, were significant prognostic factors in the univariate analysis (Figure 1; Table 4). We also examined survival after lung metastasis in 14 patients who did not develop extrapulmonary metastasis. The treatment for lung metastases was also a significant prognostic factor (log-rank test, $P=0.002$). The 3-year and 5-year disease-specific survival estimates for those who underwent metastasectomy and/or RFA were 88.9% and 77.8%, respectively, and the estimates for those who did not undergo were 12.6% and 12.6%, respectively. There was a significant difference in the number of metastases in the patients who underwent metastasectomy

**Figure 1** Kaplan–Meier curve showing overall survival in 20 patients.

Notes: A, Patients treated with metastasectomy and/or RFA. B, Patients who were not treated.

Abbreviation: RFA, radiofrequency ablation.

Table 4 Relationship between variables and overall survival in 20 patients with lung metastasis

Variables	n	3-year survival (%)	P-value
Age (years)			0.14
≥50	11	44.4	
<50	9	60	
Sex			0.2
Male	14	60.6	
Female	6	33.3	
No of metastasis			0.48
Single	8	75	
Multiple	12	33	
Size of metastasis (cm)			0.13
≥1.5	10	36	
<1.5	10	67.5	
Tumor grade			0.03
G2	11	71.6	
G3 or dedif	9	25.4	
Local recurrence			0.53
Yes	4	25	
No	16	51.6	
Extrapulmonary metastasis			0.04
Yes	6	16.7	
No	14	69.2	
Surgical treatment ^a			0.002
Yes	9	88.9	
No	11	12.6	
Relapse-free period (years)			0.26
≥2	11	60	
<2	9	41.7	

Note: ^aSurgical treatment includes metastasectomy and RFA.

Abbreviations: dedif, dedifferentiated; G, grade; RFA, radiofrequency ablation.

and/or RFA and those who did not undergo (Mann–Whitney *U*-test, $P=0.01$). The size of lung metastasis and age did not affect the decision of surgical treatment (Table 3).

Discussion

Approximately 22%–32% of patients with chondrosarcoma develop metastasis.^{1,2,9} The rate of metastasis is related to histological tumor grade.^{1–4,9} Moreover, patients with large tumors, pelvic lesions, high-grade tumors, and local recurrence have been reported to be at high risk for metastasis and poor survival.^{1–4,9} Patients with chondrosarcoma of the extremities have shown superior survival and low incidence of metastasis because it is potentially considered to have a lower histological tumor grade and adequate surgical margin, compared to pelvic lesions. Probably due to the rarity of metastasis, there are no reports on survival and prognostic factors for survival after lung metastasis in patients with chondrosarcomas of the extremities. In the 13-year study period, 20 of 179 patients with chondrosarcoma of the extremities who were treated at our hospitals developed lung metastasis.

Therefore, the lung metastasis in chondrosarcoma patients with extremity may be relatively rare in comparison to the incidence in patients with pelvic chondrosarcoma. In this study, treatment for lung metastasis, which included metastasectomy and RFA, extrapulmonary metastasis, and tumor grade were prognostic factors for survival after lung metastasis in univariate analysis; however, a multivariate analysis was not performed due to the small number of patients. Furthermore, we also examined the survival in 14 patients who developed pulmonary metastasis alone and found that treatment for lung metastases, which included metastasectomy and RFA, was also a significant prognostic factor. The number of lung metastases affected the decision to perform metastasectomy and/or RFA. The 3-year and 5-year survival rates after lung metastasis were 51.5% and 45.7%, respectively. This result is better than that for osteosarcoma patients.¹⁰ Although it may be partially because our cases included eleven patients with grade 2 tumor, metastasectomy and/or RFA would be considered to improve postmetastatic survival for selected patients.

The presence of extrapulmonary metastasis was a significant negative indicator for surgical treatment, and postmetastatic survival was identified as a significant prognostic factor by univariate analysis. To date, the presence of extrapulmonary metastasis as a prognostic factor in chondrosarcoma patients with lung metastasis was not investigated. Furthermore, this topic remains to be studied in patients with osteosarcoma and soft tissue sarcoma.^{11,12} Our results possibly suggested that the indicators for the treatment of lung metastasis should be carefully determined if extrapulmonary sites are uncontrolled. However, if the extrapulmonary sites can be controlled, we believe surgical treatment should be considered.

Recently, RFA has been accepted as a relatively safe and useful therapeutic option for the treatment of unresectable non-small-cell lung cancer and lung metastases.^{13–17} It has been demonstrated that RFA does not significantly decrease the lung function parameters and is therefore repeatable.¹⁸ The local control rate after RFA in patients with sarcoma is reported to be 89.6%–95%;^{16,19,20} however, Lanuti et al²¹ reported that RFA is associated with increased rates of local failure in tumors ≥3 cm and in contact with larger segmental vessels. Therefore, we recommend that patients with lung metastasis should be examined by a multidisciplinary team that includes thoracic surgeons, interventional radiologists, and orthopedic oncologists so that the most appropriate treatment approach can be identified for each patient.

There were some limitations in our study. The small sample size is a study limitation. The retrospective study

is another study limitation. The positive results achieved in patients who underwent metastasectomy and/or RFA might be influenced by selection bias because patients who underwent metastasectomy and/or RFA have better lung conditions or more indolent tumors, compared to those who did not undergo.

Conclusion

This study showed the oncological outcome in patients with chondrosarcoma of the extremities with lung metastasis. Although a large-scale study might be required to confirm these results, metastasectomy and/or RFA should be considered to improve postmetastatic survival for selected patients.

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Disclosure

The authors report no conflicts of interest in this work.

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