Original Article

A Retrospective Analysis of Surgical Outcomes After Resection of Pulmonary Metastases from Bone and Soft Tissue Sarcomas

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Abstract: Background: Bone and soft tissue sarcomas often give rise to pulmonary metastases, for which surgical resection is indicated in most cases.

Methods: A retrospective study was conducted of 38 surgeries performed on 22 patients within a 14-year period between March 2001 and March 2014 for curative resection of bone and soft tissue sarcomas followed by surgical resection of pulmonary metastases. For all cases, high-resolution computed tomography (HRCT) was performed for preoperative staging prior to orthopedic surgery, at the end of adjuvant chemotherapy, and after radical orthopedic surgery. During outpatient follow-up, CT examinations were performed every 6 months for 5 years. When pulmonary metastases were detected, each patient was carefully examined and determined to be a suitable candidate for complete metastasectomy. If the metastatic lesion was not easily distinguished from the visceral pleura, lipiodol marking was performed to clearly identify the tumor lesions with C-arm X-ray fluoroscopy during video-assisted thoracoscopic surgery. For this procedure, a radiologist injected 0.2 mL lipiodol percutaneously through a 21-gauge needle under CT fluoroscopic guidance in the vicinity of the target pulmonary tumor. Survival was analyzed with respect to number of metastatic lesions, primary tumor site, tumor pathology, tumor depth, and timing of pulmonary metastasis identification.

Results: Thirty-eight surgeries were performed on 22 patients to resect pulmonary metastases from bone and soft tissue sarcomas. There were no intraoperative complications and no perioperative deaths. Postoperatively, the 1-year, 2-year, and 5-year survival rates were 60.7%, 40.5%, and 34.7%, respectively. Patients with an isolated, single pulmonary metastasis at the time of surgery had a significantly better prognosis than those who had multiple metastases.

Conclusion: Patients with a single isolated pulmonary metastasis at the time of surgery tend to have a better prognosis than those with multiple metastases. For patients with primary osteosarcoma or soft tissue sarcoma, follow-up with HRCT to detect small lung metastasis, lipiodol marking to delineate the lesions, and precise partial pulmonary

Received: July 4, 2014. Accepted: August 26, 2014
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resection of the metastases are important procedures for improving prognosis.

Key Words: Bone tumors, Soft tissue tumors, Lung metastases, Resection, Prognosis.

Introduction

For patients with primary osteosarcomas and soft tissue sarcomas, curative surgical resection is the treatment of choice. Computed tomography (CT) is performed to detect systemic metastases and to assess disease progression after surgery. In most cases, pulmonary metastatic foci are detected. Although various methods are used for the treatment of the metastases, the prognosis of these patients is currently very poor.

Osteosarcomas occur most often in young patients, the incidence of pleomorphic sarcoma peaks in patients in their 60s, whereas synovial sarcomas often develop in the limbs of patients in their 20s and 30s. Thus, the three types of sarcomas present in individuals in different age groups. Bone and soft tissue sarcomas of the limbs are most likely to metastasize to the lungs, and complete surgical resection of these metastases is the only treatment that can improve prognosis and prolong survival[1)2)].

Osteosarcomas are malignant tumors that arise from the bones. In Japan, osteosarcoma is the most frequently encountered osteogenic primary malignant tumor, occurring most commonly in adolescents. In addition, soft tissue sarcomas show various metastatic patterns, including gastrointestinal metastasis[3)] and disseminated lesions in the pleural surface, undetectable on CT[4)5)]. The 5-year survival rate after resection of pulmonary metastases from osteosarcomas and soft tissue sarcomas is 36.0-50.9%[6-8)]. Partial lung resection is the main surgical approach for metastatic lung tumors. However, surgical resection of the pulmonary lesions is indicated only when the primary tumor has been controlled [7)]. In this study, the therapeutic outcomes of patients with bone and soft tissue sarcomas with pulmonary metastases treated with metastasectomy in our department were evaluated.

Method

We reviewed 38 surgeries performed on 22 patients within a 14-year period between March 2001 and March 2014 for curative resection of bone and soft tissue sarcomas. In all patients, the presence of pulmonary metastatic foci was confirmed during postoperative outpatient follow-up, an indication for metastatic lung tumor resection. For all patients, high-resolution CT (HRCT) with a 1-mm slice thickness was performed preoperatively as a staging examination before orthopedic surgery, at the end of adjuvant chemotherapy after radical orthopedic surgery, and every 6 months for 5 years during outpatient follow-up. When pulmonary metastases were detected, each patient was carefully examined and determined to be a suitable candidate for complete metastasectomy. If the metastatic tumor lesion was not easily distinguished from the visceral pleura during video-assisted thoracoscopic surgery (VATS), lipiodol marking was performed to clearly identify the tumor lesions under C-arm X-ray fluoroscopy. For this procedure, a radiologist injected 0.2 mL lipiodol percutaneously through a 21-gauge needle under CT fluoroscopic guidance in the vicinity of the target pulmonary tumor.

Patient prognosis after pulmonary metastasectomy and the predictive indicators of prognosis were assessed retrospectively. The survival rates at 1, 2, and 5 years after surgery for pulmonary metastases

(on both lungs in patients with bilateral pulmonary metastases) were calculated using the Kaplan-Meier method. The survival rates between groups were compared using the log-rank test, and a p-value of <0.05 was considered statistically significant.

For the 18 patients with resected masses confirmed by CT, the distance from the pleural surface was measured, and lesions were classified as deep or superficial. This determination was based on whether tumors could be gripped and treated easily with a ringed forceps during partial lung resection; lesions were considered superficial if they were located <3 cm from the pleural surface and deep if located ≥ 3 cm from the pleural surface.

Results

A total of 22 patients, 16 men and 6 women, were evaluated. The mean age at the time of lung surgery was 50 years (range, 18-76 years), 48 years for men and 54 years for women. The mean age at the time of primary lesion development was 47 years. Excluding 3 patients in whom lung metastases were apparent at the time of initial diagnosis, the mean duration between primary lesion surgery and the diagnosis of metastatic lung tumors was 23 months, and the mean duration between primary lesion detection and the initiation of treatment for metastatic lung tumors was 21 months.

The mean patient age at the time of primary lesion diagnosis was 47 years, and the mean age at referral to the department of respiratory surgery was 50 years. The mean age at diagnosis of the 6 patients who achieved 5-year survival was 39 years, and elderly patients tended to have an unfavorable prognosis.

1. Overall survival rate

For all 22 patients who underwent pulmonary metastasectomy, the 1-year, 2-year, and 5-year survival rates were 60.7%, 40.5%, and 34.7%, respectively (Fig. 1). Survival did not differ significantly according to sex or age. Five of the 18 patients who were followed-up for at least 5 years after lung resection were still alive.

2. Number of lung metastases and lipiodol markings

Six patients had a single, isolated lung metastasis, and the remaining 16 patients had multiple lung metastases. Prognosis was better in patients with a single, isolated metastasis ($p=0.04$) (Fig. 2).

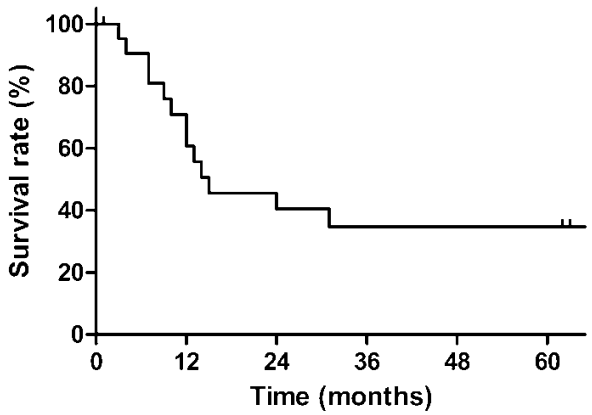

Fig. 1. Survival rate for all 22 patients

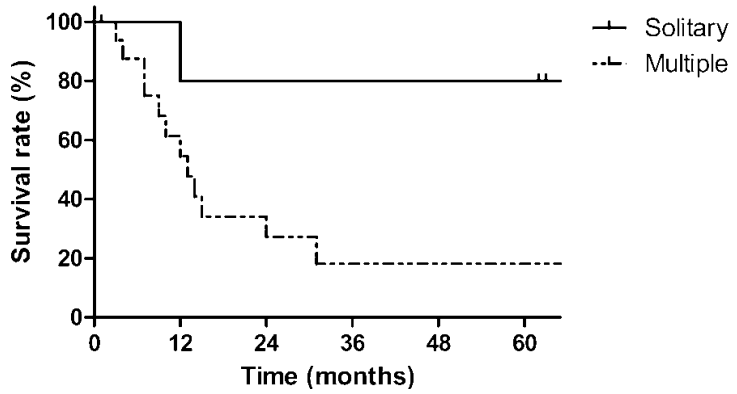

Fig. 2. Survival rate for patients with a solitary tumor versus multiple tumors

Lipiodol marking was performed in 12 patients. Of 38 surgeries, 21 were performed with lipiodol marking. Lipiodol marking was performed between 1 and 5 times for each patient. Of the 12 patients who had lipiodol marking, 10 patients had a single lipiodol marking.

3. Primary tumor site

The primary tumor occurred in the extremities in 17 patients and in the trunk in 5 patients. The survival rate did not differ significantly according to tumor site (Fig. 3).

4. Histological examination of the metastases

The pathological diagnoses of the resected lung metastases were as follows: undifferentiated pleomorphic sarcoma in 5 patients, osteosarcoma in 4 patients, synovial sarcoma in 4 patients, leiomyosarcoma in 3 patients, epithelioid sarcoma in 2 patients, myxofibrosarcoma in 2 patients, extraskeletal chondrosarcoma in 1 patient, and alveolar soft part sarcoma in 1 patient. There was no difference in survival between the 4 patients diagnosed with osteosarcoma and the 18 patients diagnosed with other sarcomas (Fig. 4).

5. Distance between the metastatic foci and the visceral pleura

Ten patients had superficial lesions, and 8 patients had deep lesions, which made it difficult to

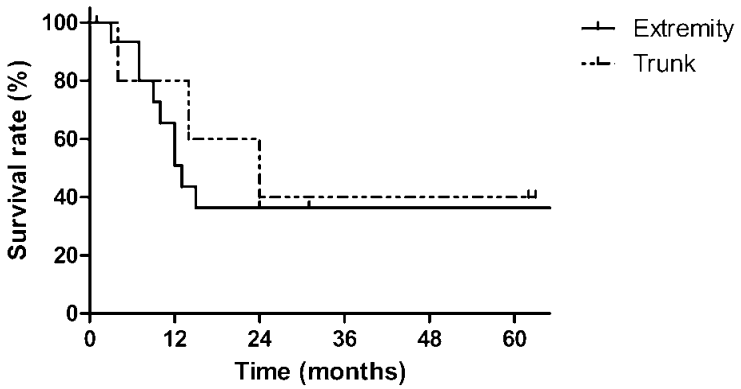

Fig. 3. Survival rate for patients according to the primary tumor site

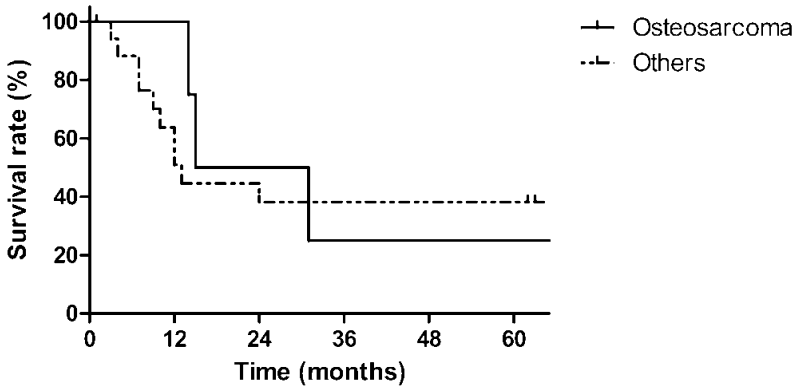

Fig. 4. Survival rate for patients with osteosarcoma versus non-osteosarcoma

perform partial resection. Prognosis was poorer in patients with deep lesions, but the difference was not significant ($p = 0.23$; Fig. 5).

6. Timing of metastatic foci detection

Lung metastases had been detected at the time of primary tumor treatment in 3 patients. In the remaining 19 patients, lung metastases were identified during the follow-up period after surgery for the primary tumor. The 5-year survival rate was higher among patients previously detected lung metastases than in patients with lung metastases identified after the primary surgery, although this difference was not significant (Fig. 6).

7. Recurrence after resection of the pulmonary metastatic foci

Sixteen patients had recurrence after resection of pulmonary metastases; the sites of recurrence were the lung (12 patients), bone (2 patients), liver (1 patient), brain (1 patient), and pancreas (1 patient). Thirteen patients died after recurrence. The mean age at death was 56 years (range, 19-76 years). The original disease was the cause of death in all patients who died after recurrence. The pathological diagnoses of the original disease were undifferentiated pleomorphic sarcoma in 4 patients, osteosarcoma in 3 patients, synovial sarcoma in 1 patient, leiomyosarcoma in 1 patient, epithelioid

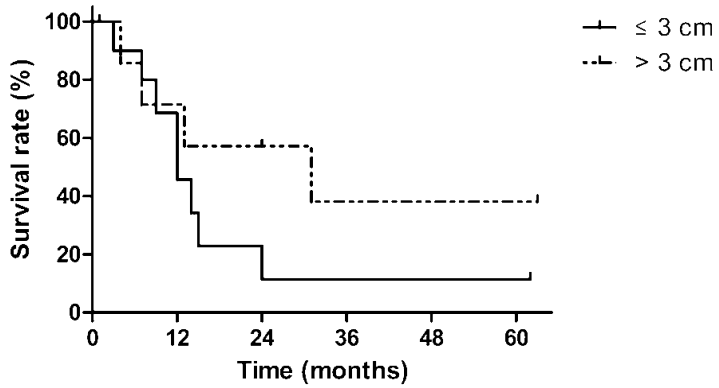

Fig. 5. Survival rate for patients according to tumor depth

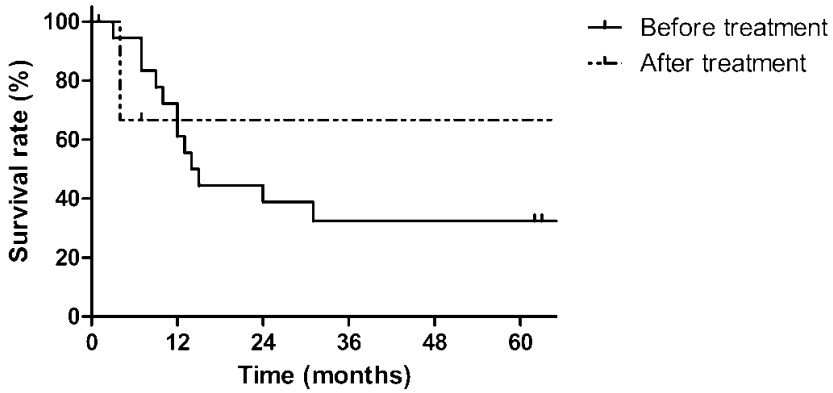

Fig. 6. Survival rate for patients according to the timing of lung metastasis detection

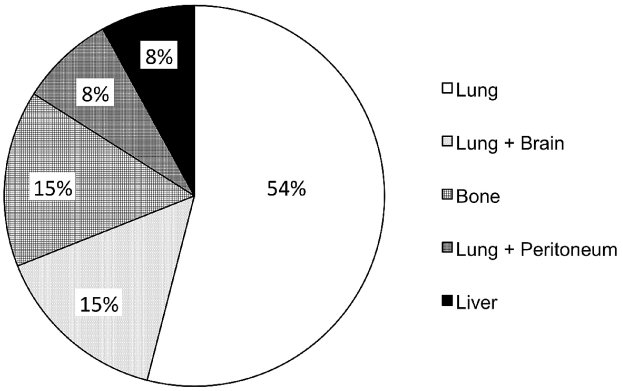

Fig. 7. Site of recurrence causing death after lung metastasectomy for bone and soft tissue sarcomas

sarcoma in 2 patients, extraskeletal chondrosarcoma in 1 patient, and alveolar soft part sarcoma in 1 patient. Death was due to pulmonary metastases in 7 patients, a combination of pulmonary and brain metastases in 2 patients, bone metastases in 2 patients, pulmonary and peritoneal metastases in 1 patient, and liver metastasis in 1 patient. Respiratory failure due to progression of pulmonary metastases was the most common immediate cause of death (77%; Fig. 7).

Discussion

For patients with bone and soft tissue sarcomas with pulmonary metastases, our results showed that patients with a single isolated metastatic lung tumor had a significantly better prognosis than those with multiple metastatic lung tumors. Previous studies of pulmonary metastases from colon and rectal cancer have shown that a solitary pulmonary metastatic lesion was associated with a good prognosis[9]; similarly, in cases of bone and soft tissue sarcomas, an isolated single metastasis might be a favorable prognostic factor[10]. Further, pulmonary metastases from osteosarcomas in the trunk have been

reported to have an unfavorable prognosis; in this study, we classified patients according to the primary cancer site (trunk versus extremities). However, there was no difference in prognosis according to primary lesion site.

The similar survival rates between patients with osteosarcomas and those with other soft tissue sarcomas might be related to the fact that both tumor types originate from soft tissue, muscle, or bone marrow, all of which are rich in blood vessels. In fact, all patients in this study developed pulmonary metastatic foci through hematogenous metastasis.

For synovial sarcomas, the 5-year survival rate has been reported to be 36-76%. Pulmonary, bone, and lymph node metastases are commonly associated with synovial sarcomas[6]. Among the 4 patients with pulmonary metastases from synovial sarcoma in our study, 2 of the 3 patients who could be followed-up for at least 5 years survived, corresponding to a 5-year survival rate of 66.6%, which is within the expected range. We believe that the prognosis of patients with pulmonary metastases from synovial sarcoma can be relatively favorable if the metastases are able to be resected surgically.

For partial lung resection via VATS, the tumor is gripped with a grasping forceps and is often resected using an end stapler. A ring-shaped grasping forceps with a diameter of 3 cm is use. Therefore, we analyzed prognosis according to tumor depth: lesions located within 3 cm of the pleura and lesions that extended deeper than 3 cm into the lungs. In patients with deep tumors, the pulmonary artery (which has a larger inner diameter) is likely to be infiltrated by the metastatic tumor. Therefore, we initially hypothesized that the prognosis of patients with deep tumors would be unfavorable. However, survival rate of patients with a tumor depth of $\leq$3 cm was in fact lower. One patient with deep metastasis had to undergo right pulmonary lobectomy. However, recurrence after lobectomy was not observed even in patients with deep metastases, suggesting that the treatment may have helped improve prognosis.

Survival did not differ according to the timing of pulmonary metastasis detection (at the time of primary tumor diagnosis versus after primary tumor resection). The prognosis of osteosarcoma has been reported to be unfavorable if metastatic lung foci are confirmed during postoperative chemotherapy[10]; however, a single-factor analysis of the 5-year survival rate among the relatively few subjects in this study showed no significant difference.

The presence or absence of pulmonary metastases has previously been described as an important prognostic factor in bone and soft tissue tumors; similarly, in this study, it was the most common cause of death. Therefore, careful follow-up examination for pulmonary metastases is needed, even after surgical treatment for pulmonary lesions. Positron emission tomography CT has previously been reported to be of no value in the early detection of pulmonary metastases; currently, thin-slice CT is believed to be the most useful test, because it provides better resolution.

During the 14-year study period, lipiodol marking was adopted as a method for marking the location of lung tumors. Pulmonary metastasis resection may potentially increase the 5-year survival to 60% in some types of sarcomas, such as pulmonary metastases from synovial sarcoma; therefore, accurate partial pulmonary resection with the aid of lipiodol marking is important. This is especially true for patients with chemotherapy side effects who are under intensive postoperative management for complications such as thrombosis.

As the accuracy of CT improves considerably, we expect an increase in the number of cases in which microscopic pulmonary metastases are detected. With lipiodol marking under CT fluoroscopy,

surgical treatment can be performed with greater precision, thus minimizing the volume of lung that needs to be removed.

Conclusions

In our study, the 1-year, 2-year, and 5-year survival rates after surgery for pulmonary metastases from bone and soft tissue sarcomas were 60.7%, 40.5%, and 34.7%, respectively. Patients with a single, isolated pulmonary metastasis at the time of surgery tended to have a better prognosis. For patients with primary osteosarcoma or soft tissue sarcoma, follow-up with HRCT to detect small lung metastasis, lipiodol marking to delineate the lesions, and precise partial pulmonary resection of the metastasis are important procedures for improving prognosis.

The authors declare no potential conflicts of interest.

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〈和文抄録〉

原発性悪性骨・軟部腫瘍の肺転移巣に対する手術成績の検討

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背景：原発性悪性骨・軟部腫瘍は肺転移を来すことが多く，また外科切除の適応とされることが多い．方法：2001 年 3 月から 2014 年 3 月までの 14 年間に原発性悪性骨・軟部腫瘍の治癒切除と，肺転移巣に対して外科切除を行った 22 症例を後ろ向きに検討した．転移性肺腫瘍の診断のため，整形外科での手術前や手術の化学療法の直後やその後の外来検査時に胸部 CT を行った．肺腫瘍摘出時に臓側胸膜からの病変特定が困難な症例では，VATS 手術前に CT 透視下に経皮的に 21G の針穿刺から造影剤としてリピオドールを腫瘍近傍に注入してマーキングして手術を行った．

結果：22 症例の原発性悪性骨・軟部腫瘍の肺転移病巣に対して 38 回の手術を施行した．術死は認めず安全に施行された．術後 1 年生存率，2 年生存率，5 年生存率は，それぞれ，60.7%，40.5%，34.7%あった．手術時の肺転移が単発の症例の予後は多発症例より有意に良好であった．結論：原発性悪性骨・軟部腫瘍の肺転移は，長期の生存を得るには肺転移のコントロールが重要であるので，積極的に転移巣の切除を目指していくことが重要である．

キーワード：骨腫瘍，軟部腫瘍，肺転移，切除，予後．