Clinical Study

Metastasectomy of Pulmonary Metastases from Osteosarcoma: Prognostic Factors and Indication for Repeat Metastasectomy

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Purpose. To identify prognostic factors for metastatic osteosarcoma patients and establish indication for repeat metastasectomy. **Methods.** Data from 37 patients with pulmonary metastasis from osteosarcoma who underwent metastasectomy in our institute from 1979 to 2013 were retrospectively reviewed. **Results.** Prognostic factors analyzed were age, sex, maximal diameter of the tumor at first pulmonary metastasectomy, total number of resected pulmonary metastases at first metastasectomy, number of surgeries, and disease free interval. In our analysis, characteristics associated with an increased overall survival were age > 15 years and fewer metastases (≤ 3). Of the 37 patients, 13 underwent repeat metastasectomy after the first metastasectomy. Of the 7 patients that underwent only two metastasectomies, three remained disease-free. In contrast, all six patients that underwent three or more metastasectomies died of relapse. Patients who had five or less lesions at second metastasectomy showed better survival compared to those who had six or more lesions. **Conclusion.** Age > 15 years and number of metastases at first metastasectomy were independent prognostic factors. Metastasectomy may provide curative treatment even in cases requiring repeat surgery. The number of metastases at second metastasectomy may be a potential predictor of the need for repeat surgery.

1. Introduction

Osteosarcoma is the most common malignant bone sarcoma in children and adolescents. The long-term survival of patients with osteosarcoma has dramatically improved with the use of combination chemotherapy, local treatment, and aggressive metastasectomy [1, 2]. Approximately 50% of patients with osteosarcoma develop synchronous or metachronous metastatic lung disease [3]. The prognosis of patients with synchronous or metachronous metastatic osteosarcoma has improved over the last two decades, with the 5-year disease-free survival rate increasing from 0–17% to 30–50% [4].

Complete metastasectomy is the best predictor of survival in osteosarcoma patients with pulmonary metastases [1, 5, 6].

The purpose of this study was to identify patient and tumor characteristics that are associated with improved survival.

Recent reports recommend repeat surgery for pulmonary metastasis for osteosarcoma; however, there remain no definitive indication criteria for repeat surgery [7, 8]. Therefore, we also investigated possible indications for repeat metastasectomy.

2. Patients and Methods

From 1979 to 2013, 37 patients with pulmonary metastasis from osteosarcoma underwent metastasectomy at Kumamoto University Hospital. The diagnosis of metastatic lesions in the lung was made by chest computed tomography (CT). We analyzed the 37 patients retrospectively by review of medical records. We excluded the patients with metastases of other organs without lungs.

Characteristics of the 37 patients with lung metastasis from osteosarcoma are shown in Table 1. Of the 37 patients,

TABLE 1: Patient characteristics.

Patient characteristics	n (%)	Mean (range)
Gender		
Male	22 (60)	
Location of primary tumor		
Femur	25 (68)	
Tibia	5 (14)	
Humerus	4 (11)	
Other (pubis, fibula, costa)	3 (8)	
Age at first lung metastasectomy (year)		22 ± 14 (5–66)
Number of metastases at first metastasectomy		3.8 ± 3.9 (1–16)
Total number of metastases throughout treatment		4.6 ± 4.1 (1–16)
Maximal diameter of the tumor (cm)		1.4 ± 1.0 (0.4–3.6)
Number of metastasectomies (times)		1.7 ± 1.0 (1–4)
DFI (months)		12.3 ± 11.6 (0–45)

Mean follow-up: 67 ± 64 months (range, 10–270).

DFI: disease-free interval.

22 were men. Primary tumors were located in the femur in 25 patients, the tibia in five patients, the humerus in four patients, the pubis in one patient, the fibula in one patient, and the costa in one patient. The mean age at first metastasectomy was 22 ± 14 years (range, 5–66 years). The mean time from first pulmonary metastasectomy to second pulmonary relapse was 13 months. The mean number of metastases at first metastasectomy was 3.8 ± 3.9 (range, 1–16). The mean total number of metastases throughout treatment was 4.6 ± 4.1 (range, 1–16). The mean maximal diameter of the tumor at first metastasectomy was 1.4 ± 1.0 cm (range, 0.4–3.6 cm). The mean number of metastasectomies required was 1.7 ± 1.0 times (range, 1–4 times). The mean disease-free interval (DFI) was 12.3 ± 11.6 months (range, 0–45 months). The mean time to follow-up since the first pulmonary metastasectomy was 67 ± 64 months (range, 10–270 months).

Of the 37 patients, 21 died of osteosarcoma, 14 were disease free at last follow-up, and two were alive with disease (brain/lung metastases) (Figure 1). Among the 26 relapsed patients, 13 underwent further resections of lung metastases, and 10 died (eight of pleural dissemination, one of cervical spine metastases, and one of unknown causes).

Of the 37 patients, 26 were initially operated unilaterally while 11 underwent bilateral surgery (six patients underwent staged operations). Overall, we performed 39 unilateral wedge resections, eight bilateral wedge resections, six lobectomies or segmentectomies, and six lobectomies or segmentectomies and wedge resections.

In terms of prognostic significance after first pulmonary metastasectomy, age, sex, maximal diameter of the tumor at the first pulmonary metastasectomy, total number of resected pulmonary metastases at first metastasectomy, number of surgeries, and DFI were analyzed for associations with survival. Staged resection for patients with simultaneous bilateral pulmonary metastases was considered as one operation. DFI was defined as the duration between resection of the primary osteosarcoma and the first pulmonary metastasectomy.

FIGURE 1: Iterative pulmonary metastases, patient selection. Of the 37 patients, 21 died of osteosarcoma, 14 were disease free at last follow-up, and two were alive with disease (brain/lung metastases). Among the 26 relapsed patients, 13 underwent further resections for lung metastases of whom 11 died (eight of pleural dissemination, one of cervical spine metastases, and two of unknown causes). Meta: metastasis; DFS: disease-free survival.

2.1. Statistical Analysis. Statistical analysis was performed using SPSS version 18 (SPSS Inc., Chicago, IL). The survival curve was depicted by the Kaplan-Meier method. Receiver operating characteristics (ROC) curves were used to determine the cut-off value of total number of resected pulmonary metastases at first metastasectomy for 1-year survival after metastasectomy. Univariate and multivariate analyses were

TABLE 2: Univariate analysis and multivariate analysis.

Factor	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Age (>15 vs. ≤15)	0.38 (0.14–0.97)	0.04*	0.24 (0.08–0.68)	0.01*
Sex (male vs. female)	1.33 (0.54–3.30)	0.53		
Maximal diameter of the tumor at first metastasectomy	1.55 (0.83–2.90)	0.17		
Total number of resected pulmonary metastases at first metastasectomy (≤3 vs. >3)	0.28 (0.11–0.70)	0.01*	0.18 (0.06–0.51)	<0.01*
Number of surgeries	1.16 (0.77–1.75)	0.47		
Disease-free interval	0.99 (0.96–1.02)	0.53		

HR: hazard ratio; CI: confidence interval.

*P value less than 0.05.

FIGURE 2: Kaplan-Meier curve of cumulative overall survival. Survival curve generated from the time of first metastasectomy showed 2-year and 5-year survival rates of 59% and 41%.

performed with Cox regression model. The log-rank test was used to compare survival. *P* value less than 0.05 was considered statistically significant. All values in the text and tables are presented as mean ± standard deviation.

3. Results

Survival curve measured from the time of first metastasectomy showed 2-year and 5-year survival rates of 59% and 41% (Figure 2). The optimal cut-off value of total number of resected pulmonary metastases at first metastasectomy was determined to be 3.5 using ROC curve, which was associated with the sensitivity and specificity values of 0.90 and 0.85, respectively. The area under the ROC curve value is 0.92 (Figure 3). We set the cut-off value of total number of resected pulmonary metastases at first metastasectomy as 3. Table 2 shows univariate and multivariate analyses of factors influencing overall survival. In univariate analysis, characteristics associated with an increased overall survival were

FIGURE 3: The Receiver operating characteristics (ROC) curve of total number of resected pulmonary metastases at first metastasectomy for 1-year survival after metastasectomy. The optimal cut-off value is determined to be 3.5, which was associated with the sensitivity and specificity values of 0.90 and 0.85, respectively. The area under the ROC curve value is 0.92.

age > 15 years (hazard ratio [HR] 0.38, 95% confidence interval [CI] 0.14–0.97, *P* = 0.04) and fewer metastases (≤3) (HR 0.28, 95% CI 0.11–0.70, *P* = 0.01). In multivariate analysis, age > 15 years (HR 0.24, 95% CI 0.08–0.68, *P* = 0.01) and fewer metastases (≤3) (HR 0.18, 95% CI 0.06–0.51, *P* < 0.01) remained significantly associated with survival. Patients aged > 15 years showed significantly better outcome with a mean survival time of 152 months compared to 32 months for patients aged ≤ 15 years (*P* = 0.04). Patients with ≤3 metastases at first metastasectomy also showed better outcome with a mean survival time of 138 months compared to 54 months for patients with >3 lung lesions (*P* < 0.01). No statistically significant difference in overall survival was found based on sex, tumor size, number of surgeries, or DFI.

Of the 37 patients, 13 underwent repeat metastasectomy. Of the seven patients who underwent only two metastasectomies, three remained disease free at last follow-up.

However, all six patients who underwent three or more metastasectomies died of relapse. Patients with ≤ 5 metastases at second metastasectomy showed better outcome with a mean survival time of 83 months compared to 17 months for patients with > 6 lung lesions ($P = 0.04$).

4. Discussion

The aim of this study was to identify patient and tumor characteristics that are associated with improved survival. To this end, we assessed the impact of age, sex, number of metastases at first metastasectomy, maximal diameter of the tumor at first pulmonary metastasectomy, number of surgeries, and DFI on survival. In a previous systematic review of reported outcome in approximately 1,800 osteosarcoma patients with pulmonary metastases from 1939 to 2007, the main prognostic factor affecting survival was found to be complete surgical remission [1, 4–6, 8]. In addition, DFI, as well as number and localization of metastases, has also been found to be significantly associated with survival [3, 5–7, 9–11].

Our results showed that age and the number of metastases at first metastasectomy were prognostic factors for patients with metastatic osteosarcoma. Some reports show that there was no difference in survival between younger and older people [1, 3, 5, 8]. But our results show that patients aged > 15 years had a better prognosis than patients aged ≤ 15 years. The number of metastases has been a matter of interest since the study by Putnam et al. who described an association between decreased survival and more than three metastases on pre-operative CT [12]. However, most studies do not describe how the cut-off point for the number of nodules was determined, and therefore cut-offs range between “more than one” and “six nodules or more” [1–3, 5–8].

In the present study, seven patients underwent repeat metastasectomy, three of whom remained disease free. This indicates that metastasectomy may be a curative treatment strategy even in cases of repeat surgery. Patients who had five or less lesions at second metastasectomy showed better survival compared to those with more than five lesions. This may act as criteria for indication for repeat surgery.

There are several limitations in our analysis. Firstly, chemotherapeutic regimens ranged widely in our study, and we therefore were unable to assess the effect of regimen on survival. Chemotherapeutic regimens have evolved substantially and rapidly over the last 20 years and continue to be highly individualized based on unique patient and tumor characteristics, along with institutional experience. In recent years, multiagent chemotherapy using methotrexate, doxorubicin, cisplatin, and ifosfamide has become a standard of care for osteosarcoma [13]. Secondly, we could not analyze pathological findings due to a lack of accurate data. In the 37 patients, we were only able to obtain detailed pathological findings in 27 patients, of whom 26 achieved complete resection. The remaining patient underwent S8/9 segmentectomy as a first metastasectomy but underwent repeat lobectomy 1 week later due to positive margins. This patient died of brain metastases 25 months after first metastasectomy. Thirdly, this report may be subject to patient selection bias, as not all cases of pulmonary metastases for osteosarcoma were included in

the analysis. Finally, surgeries were performed by various surgeons, leading to minor technique variability, as there was no attempt to standardize the procedures.

In conclusion, age older than 15 years and the number of metastases (3 or less) at first metastasectomy were independent prognostic factors in patients with pulmonary metastasis from osteosarcoma. Metastasectomy may be a curative treatment strategy even in cases of repeat surgery. The number of metastases is a potential criterion for indication of repeat operations. Our study is limited by the small number of patients and prospective clinical trials are needed to confirm these retrospective observations.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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