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Research paper

Clinical characteristics and risk factors analysis of lung metastasis from benign giant cell tumor of bone☆

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A B S T R A C T

Pulmonary metastasis of benign giant cell tumor of bone is very rare, and its biological behavior is difficult to predict. In the present study, we analyzed the clinical characteristics of and related risk factors for pulmonary metastasis from this tumor. Forty-six patients with lung metastasis were analyzed. In total, 60.9% of the primary tumors were located around the knee joint. The Campanacci stage of all tumors was stage 3. Surgery of the primary tumor included curettage in 37 patients, resection in 8, and amputation in 1. Local recurrence after the primary surgery occurred in 34 patients. The recurrence rate, Campanacci stage, and surgical method were significant risk factors for lung metastasis. The median postoperative metastasis times in the lower limbs, upper limbs, and axial skeleton were 20.1, 7.9, and 1.4 months, respectively ($p = 0.010$). The median metastasis times in patients with and without recurrence were 13.7 and 43.2 months, respectively ($p = 0.018$). Eighteen patients had unilateral metastasis and 28 had bilateral metastasis. Most lesions ($n = 38$) were located in the peripheral lung. Nineteen patients received treatment, and 12 of them underwent tumor resection. The 5-year overall survival rate was 94.4%. This study showed that local recurrence, a high Campanacci stage, and curettage were possible high-risk factors for pulmonary metastasis. The primary lesion site and local recurrence may be related to the metastasis time. The survival rate of patients with pulmonary metastasis was high.

1. Introduction

Giant cell tumor of bone (GCTB) is an invasive benign bone tumor consisting of proliferative mononuclear cells and osteoclast-like multinucleated giant cells. It has the tendency to relapse. GCTB accounts for 4–5% of primary bone tumors. The incidence of lung metastasis in patients with GCTB is about 1–9% [1–5]. Viswanathan et al. [3] reported that two mechanisms are related to lung metastasis: a self-limiting process of transformation and vascular transfer. Because both lung tissue and GCTB tissue have a rich blood supply, the tumor cells may invade the interstitium and destroy the vessel walls, facilitating hematogenous metastasis to the lung.

Studies and reports of lung metastasis of GCTB are rare because of the low incidence of lung metastasis. The biological behavior and clinical features of GCTB are difficult to predict [6,7]. Some researchers have attempted to analyze related clinical factors of lung metastasis, such as age, sex, primary tumor site, tumor stage, primary tumor treatment, and recurrence. However, the numbers of patients were small, and different results were reported among the studies. High-level evidence from large-sample data is lacking. Therefore, the present study focused on a large number of patients with lung metastasis in a single center. The purpose was to elucidate the clinical characteristics and risk factors for pulmonary metastasis of GCTB.

2. Materials and methods

2.1. General characteristics

This study was a retrospective clinical case analysis. All cases were from the clinical database of our center. The inclusion criteria were a pathological diagnosis of benign GCTB, lung metastasis as confirmed by pathology or computed tomography (CT) (lesion diameter of > 1 cm and dynamically increasing), and no evidence of any other tumor. According to the above conditions, 46 patients were enrolled in this study from January 1983 to February 2014 (Table 1). The following possible risk variables were analyzed: sex and age of patient, tumor location, Campanacci stage, treatment of the primary tumor [8], and number of local recurrences. The following metastatic characteristics were reviewed: duration of time from initial treatment of primary lesion to diagnosis of metastasis and number and location of metastases.

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Table 1
Profile of patients with lung metastasis of GCTB.

Case	Gender	Age	Location of Primary lesion	Campanacci stage	Treatment of Primary lesion	No. of Local Recurrences	Interval from Treatment of Primary lesion to Diagnosis of Metastasis (Month)	No. of metastasis	Location of Metastasis
1	Female	22	Distal femur	3	Curettage and cementation	1	16.7	2	Bilateral lung
2	Male	20	Distal radial	3	Curettage and grafting	2	0	> 10	Bilateral lung
3	Male	30	Proximal tibia	3	Amputation	0	0	1	Unilateral lung
4	Female	17	Proximal humerus	3	Curettage and grafting	1	51.1	1	Unilateral lung
5	Male	24	Proximal tibia	3	Curettage and cementation	2	35.5	2	Bilateral lung
6	Male	29	Distal femur	3	Curettage and cementation	2	42.4	> 10	Bilateral lung
7	Female	37	Proximal femur	3	Resection	2	334.5	1	Unilateral lung
8	Male	48	Proximal tibia	3	Curettage and grafting	2	91.6	1	Unilateral lung
9	Male	44	Proximal tibia	3	Curettage and cementation	2	65.7	4	Bilateral lung
10	Male	30	Distal femur	3	Curettage and cementation	0	21	4	Bilateral lung
11	Female	24	Distal femur	3	Curettage and grafting	2	51.8	5	Bilateral lung
12	Female	40	Proximal femur	3	Curettage and grafting	1	13.7	1	Unilateral lung
13	Male	38	Distal radius	3	Curettage and cementation	1	6	1	Unilateral lung
14	Female	58	Ischium	3	Resection	0	0	2	Bilateral lung
15	Female	31	Distal femur	3	Resection	0	3.1	1	
16	Female	29	Distal femur	3	Curettage and cementation	1	89.5	> 10	Bilateral lung
17	Male	27	Proximal tibia	3	Curettage and cementation	1	18	9	Bilateral lung
18	Male	21	Distal femur	3	Curettage and cementation	1	6.1	2	Unilateral lung
19	Female	53	Proximal tibia	3	Curettage and grafting	1	107.8	1	Unilateral lung
20	Male	42	Proximal femur	3	Curettage and cementation	0	0	2	Unilateral lung
21	Female	34	Distal radius	3	Curettage and grafting	1	7.9	> 10	Bilateral lung
22	Male	23	Distal femur	3	Curettage and grafting	1	32	1	Unilateral lung
23	Male	39	Distal femur	3	Curettage and cementation	1	0	2	Unilateral lung
24	Female	30	T12 vertebra	3	Curettage and cementation	0	0	> 10	Bilateral lung
25	Male	26	Proximal femur	3	Resection	1	3.2	> 10	Bilateral lung
26	Female	61	Proximal tibia	3	Curettage and grafting	1	20.1	1	Unilateral lung
27	Male	32	Proximal humerus	3	Resection	2	154.9	1	Unilateral lung
28	Female	28	Distal femur	3	Curettage and grafting	0	0	4	Bilateral lung
29	Female	25	Distal radius	3	Curettage and cementation	2	0	> 10	Bilateral lung
30	Male	28	Distal radius	3	Curettage and grafting	2	13.7	> 10	Unilateral lung
31	Female	33	Proximal femur	3	Curettage and grafting	2	21.8	8	Bilateral lung
32	Female	33	Proximal tibia	3	Curettage and grafting	1	105.1	7	Bilateral lung
33	Male	32	Distal femur	3	Curettage and grafting	1	23.3	10	Bilateral lung
34	Male	36	Distal femur	3	Curettage and grafting	1	6	10	Bilateral lung
35	Male	45	Sacrum	3	Curettage alone	1	4.2	1	Unilateral lung
36	Female	58	Distal femur	3	Resection	0	12.2	6	Bilateral lung
37	Male	25	Proximal femur	3	Resection	0	48	3	Bilateral lung
38	Male	25	Distal femur	3	Curettage and grafting	1	7	3	Bilateral lung
39	Male	29	Proximal humerus	3	Curettage and grafting	0	15	> 10	Bilateral lung
40	Male	21	Proximal tibia	3	Curettage and grafting	0	0	> 10	Bilateral lung
41	Female	19	Proximal femur	3	Curettage and cementation	0	26.8	2	Unilateral lung
42	Male	38	Proximal tibia	3	Curettage and grafting	1	69.9	2	Unilateral lung
43	Male	33	Distal femur	3	Curettage and cementation	1	0	> 10	Bilateral lung
44	Male	26	Distal femur	3	Curettage and grafting	1	17.2	> 10	Bilateral lung
45	Female	32	Proximal tibia	3	Curettage and cementation	1	24	> 10	Bilateral lung
46	Male	26	Distal femur	3	Resection	1	8	> 10	Bilateral lung

Table 2
Risk factors analysis of lung metastasis of GCTB (compared with our database).

Factors	Cases	P value
Gender	Male: 27 Female: 19	0.983
Age	Mean: 32.6 (17–61)	0.581
Primary tumor site	Upper limbs: 8 Lower limbs; 35	0.968
Campanacci stage	Stage 3: 46	0.000
Surgical method of primary tumor	Curretage: 37 Resection: 8	0.001
Recurrence	Recurrence: 34 No recurrence: 12	0.000

2.2. Diagnosis

All patients underwent radiographic and CT examinations of the primary site, a whole-body bone scan, radiographic and CT examinations of the chest, and biopsy before operation of the primary site. The above examinations with the exception of biopsy were also performed every 3 months postoperatively. All chest CT examinations showed evidence of lung metastases. The lung CT scans were evaluated by experienced musculoskeletal surgeons and radiologists. In all cases, the maximum diameter of the metastatic lesions was > 1 cm and/or the lesions had progressed as confirmed by growth of the lesions on serial CT images; other possible diagnoses with the exception of metastasis were excluded. Eleven patients underwent biopsy or resection of the lung lesions, and the biopsy specimens were evaluated by experienced musculoskeletal pathologists. Pathological examination of the lung tissues provided definitive diagnoses in all 11 patients.

2.3. Statistical analysis

The data analysis was performed with SPSS software (version 19.0; IBM Corp., Armonk, NY). The survival rate was calculated and plotted by the Kaplan–Meier method. The log-rank test was performed between different groups. Continuous variables were compared by the *t*-test, and categorical variables were compared by the chi-square test or Fisher's exact test. Pearson's correlation analysis was used for continuous parameters, and Spearman's correlation analysis was used for non-parametric factors. The relationship between each variable and the occurrence of pulmonary metastasis was evaluated, and a p value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of primary lesions

The patients comprised 27 males and 19 females. Their mean age was 32.6 (range, 17–61) years. The primary tumor site was the femur in 24 patients, tibia in 11, radius in 5, humerus in 3, sacrum in 1, thoracic vertebra in 1, and ischium in 1. All patients had stage 3 tumors according to the Campanacci staging system [8].

In total, 60.9% (28/46) of the primary tumor sites were located around the knee joint, including the distal femur in 17 patients and the proximal tibia in 11. A total of 93.5% (43/46) of the primary tumors occurred in the extremities, including 17.4% (8/46) in the upper limbs and 76.1% (35/46) in the lower limbs; the proximal limbs (femur and humerus) were affected in 23.2% (10/43) of these patients. Three primary tumors occurred in the axial skeleton.

Three patients had a pathological fracture of the primary tumor site. The surgery of the primary tumor involved curettage in 37 patients, tumor resection in 8, and thigh amputation in 1. Local recurrence occurred in 34 patients (once in 23 patients and twice in 11). The average time of recurrence was 29.4 (range, 1–207) months postoperatively. Kaplan–Meier analysis of recurrence revealed a 5-year recurrence-free survival rate of 25.8% and a median recurrence-free survival time of 25 months (95% confidence interval, 18.1–31.9).

3.2. Characteristics of metastatic lesions

Unilateral metastasis occurred in 18 patients, and bilateral metastases occurred in 28 patients. Twelve patients had a single lesion and 34 had multiple lesions. Fourteen patients had > 10 lung lesions, and 32 had < 10 (average, 3.1; median, 2). Most lesions (38 patients) were located in the peripheral lung. The imaging features showed calcification in four patients and cavitation in two.

3.3. Risk factors for lung metastasis

The male: female sex ratio in this study was 1.4:1.0 (27:19), which was the same as that of large sample from our database [9]. The mean age was 32.6 years in this study and 31.7 years in our database [9] ($p = 0.581$) (Table 2).

The primary tumor sites in the present study included the upper limbs in 18.6% of patients and the lower limbs in 81.4% (excluding the axial skeleton). Our database showed that the primary tumor sites were in the upper limbs in 18.4% and lower limbs in 81.6% of patients; no significant difference was shown (chi square = 0.002, $p = 0.968$) (Table 2). A total of 65.1% of the lesions (excluding the axial skeleton) were around the knee in the present study, and 66.0% were around the knee in our database; no significant difference was shown (chi square = 0.015, $p = 0.903$). The proximal limbs (femur and humerus) accounted for 23.2% of tumors in the present study and 18.0% in our database (chi square = 0.731, $p = 0.393$). The proximal femur accounted for 16.3% of tumors in the present study and 10.6% in our database (chi square = 1.312, $p = 0.252$). A total of 11.6% of the primary lesions were located in the distal radius in the present study versus 8.2% in our database (chi square = 0.607, $p = 0.436$).

The recurrence rate was 73.9% (34/46) in the present study and 12.4% in our database [9]; there was a significant difference (chi square = 90.430, $p = 0.000$). The Campanacci stage was 3 in all patients in the present study and in 31.1% (87/280) in our database; there was a significant difference (chi square = 77.718, $p = 0.000$). Curettage was performed in 80.4% of the patients in the present study and in 55.5% (157/283) in our database; there was a significant difference (chi square = 11.494, $p = 0.001$) (Table 1).

3.4. Metastasis time analysis

Ten patients had initial pulmonary metastasis and 36 had postoperative metastasis at an average of 43.7 (median, 21.4; range, 3.1–334.5) months postoperatively. Kaplan–Meier analysis showed that the 5-year metastasis-free survival rate was 17.4% and that the median metastasis-free survival time was 15 months (95% confidence interval, 8.6–21.4) (Fig. 1).

Analysis of related factors showed that sex ($p = 0.265$), age ($p = 0.786$), and surgical method (curettage or resection) ($p = 0.279$) were not significant factors. The primary site was a significant factor ($p = 0.010$). The median metastasis time was 20.1, 7.9, and 1.4 months in the lower limbs, upper limbs, and axial skeleton, respectively (Fig. 2). Recurrence was also a significant factor ($p = 0.018$). The median metastasis time was 13.7 and 43.2 months in patients with and without recurrence, respectively (Fig. 3).

3.5. Treatment and survival

Nineteen patients received treatment, and 12 of them underwent tumor resection. Twelve patients received chemotherapy and four received denosumab. After an average of 72.4 months of follow-up (range, 21–396 months), five patients died at an average of 62.2 (range,

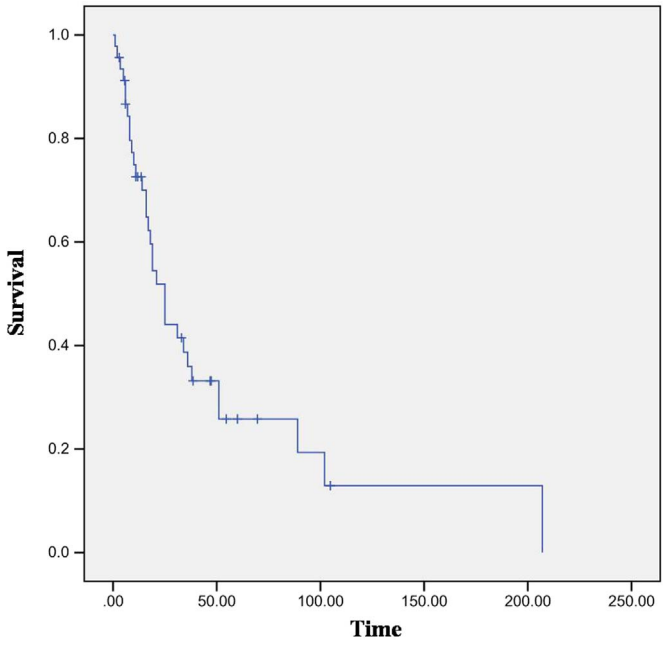

Fig. 1. The metastasis free survival curve.

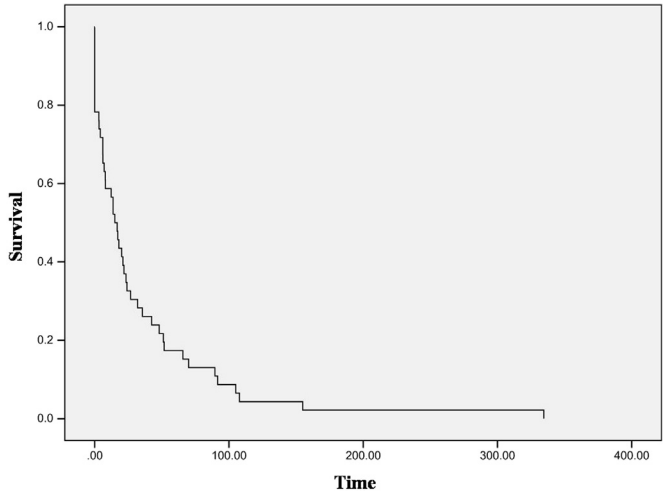

Fig. 2. The metastasis free survival curves in different primary site (1 for lower limb, 2 for upper limb and 3 for axial skeleton).

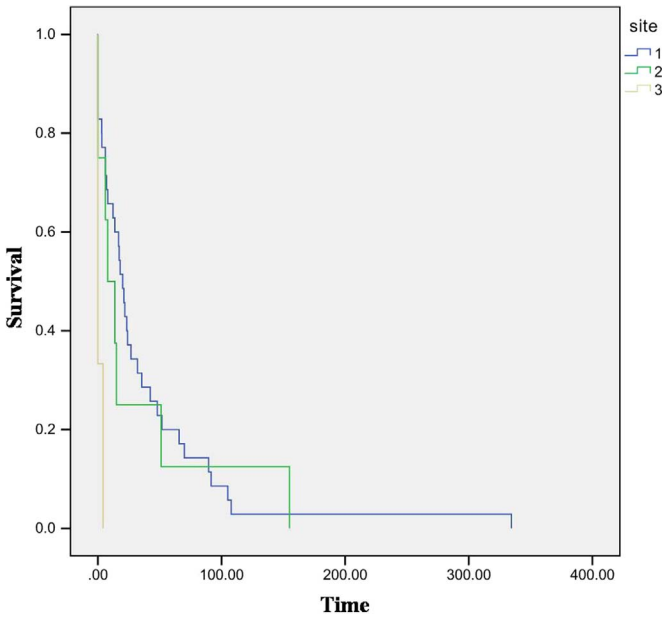

Fig. 3. The metastasis free survival curves in recurrence and no recurrence group (0 for recurrence and 1 for no recurrence group).

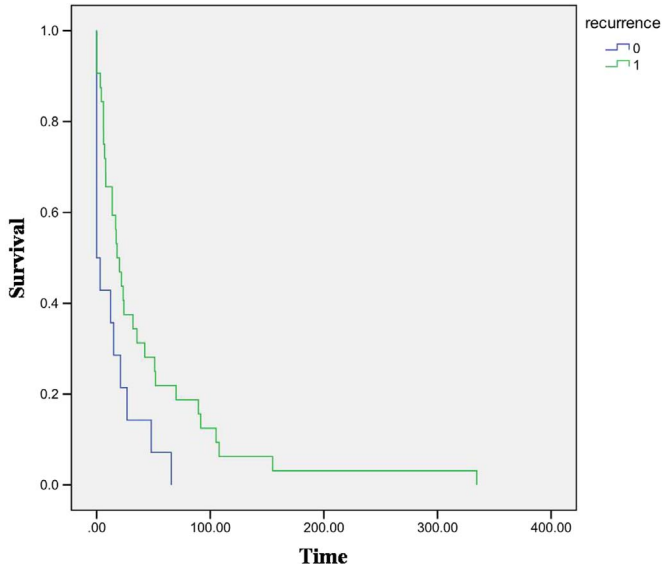

Fig. 4. The overall survival curve.

22–103) months. Four patients received no treatment for the metastatic lesions, and one patient progressed after receiving chemotherapy. The 5-year overall survival rate was 94.4% (Fig. 4).

4. Discussion

Finch and Gleave [10] reported pulmonary metastasis of benign GCTB for the first time in 1926. Initial pulmonary metastases are rare, and most appear after the operation of the primary tumor. Previous studies have shown that most pulmonary metastases were found several months to 3 years postoperatively [3,11,12]. However, some metastases occurred more than 10 years postoperatively [6,7]; the longest occurred at 49 years postoperatively [13]. Such case reports are very rare.

The rate of lung metastasis from GCTB is very low, and only small samples of affected patients have been reported in the literature. Campanacci et al. [1] reported 280 cases of GCTB in 1987, and the lung metastasis rate among these cases was 2.1%. Dominkus et al. [4] reported 649 cases of GCTB, and 2.1% of them had lung metastasis. In 2010, Errani et al. [5] reported 349 cases of GCTB, and the lung metastasis rate was 4.0%. In our center, Sung et al. [14] reported that 6 of 111 patients with GCTB had pulmonary metastasis in 1982, and Niu et al. [9] reported that the rate of lung metastasis was 3.4% among 621 cases of GCTB in 2012.

The clinical characteristics of lung metastatic lesions were analyzed in the present study. Most lesions were multiple and located in the bilateral lungs, and they were mainly distributed in the peripheral lung. These characteristics are similar to those of metastases of other malignant tumors. However, the biological behavior of pulmonary metastasis of GCTB differs from that of other tumors. In general, the vast majority of GCTB metastases progress slowly. The doubling time of GCTB lung metastasis is significantly longer than that of other tumors [15].

The male: female sex ratio was 1.4:1.0 in the present study, which is the same as that in our database [9]. This indicates no sex-related tendency of lung metastasis. There was also no significant difference in the age distribution between the present study and our database. A previous study [16] also suggested that the patient's age and sex as well

as the characteristics of the primary lesion (such as the presence of a pathological fracture, the range of bone involvement, and the distance from the joint) were not significantly related to lung metastasis.

In terms of location, 81.4% of the primary tumors in this study were located in the lower limbs and 18.6% were in the upper limbs. No significant difference was present between these results and those in our database. The proportions of tumors around the knee joint were also similar. The proximal extremities (femur and humerus) accounted for 23.2% of the tumor sites in the present study, which is 5.2% higher than that in our large-sample report. However, a significant difference was not shown. Therefore, our analysis does not indicate a correlation between lung metastasis and the distribution of the primary lesion. Errani et al. [5] reported a higher rate of lung metastasis in patients with primary tumors located in the proximal femur and distal radius. The small number of cases involving tumors in the proximal femur and humerus in our study may have accounted for the lack of a significant difference.

We also analyzed the factors related to the metastasis time and found some positive results. The metastasis time was shortest for primary tumors located in the axial skeleton, second shortest for the upper limbs, and longest for the lower limbs. Donthineni et al. [17] reported that spinal GCTB had a high metastasis rate at 13.7%. In 2015, Chan et al. [13] also reported that a primary tumor located in the axial skeleton was a risk factor for lung metastasis. However, most of the literature does not support that the primary tumor site is associated with lung metastasis.

In this study, all tumors were Campanacci stage 3, which is a significantly higher proportion than in our database [9]. Such a high stage usually suggests that a tumor is highly aggressive and may be a high-risk factor for lung metastasis. Previous reports have also suggested that the stage of a GCTB may be related to lung metastasis. Chan et al. [13] reported that all patients with lung metastasis had stage 3 tumors, and Dominkus et al. [7] reported that most patients with lung metastasis had stage 3 tumors. Faisham et al. [18] reported that the metastasis rate of Campanacci stage 3 GCTB was as high as 30%.

The recurrence rate in our database [9] was 12.4%, and that in the present study was 73.9%. This significant difference suggests that local recurrence is correlated with pulmonary metastasis. Niu et al. [9] reported that the metastasis rate was 8.6% in patients with recurrence and only 2.4% in those without recurrence. Rock [19] reported that the metastatic risk in patients with recurrence was six times higher than that in patients without recurrence. Many other reports [5,16,20–22] have also supported that the recurrence is a high-risk factor. A study at the Rizzoli Institute [4] revealed a 71% recurrence rate among patients with metastasis and only a 29% recurrence rate among those without metastasis. Therefore, monitoring of the pulmonary condition is very important for patients with postoperative recurrence.

Some authors [23,24] have suggested that pulmonary metastases are related to the type of surgery performed for the primary tumor. The surgery itself, not the invasiveness of the tumor, might lead to vascular differentiation because surgical manipulation enables implantation of tumor cells in the lung. Most pulmonary metastases occur postoperatively, but this does not occur for several years or even > 10 years postoperatively in some patients. Therefore, there is not enough evidence to prove the relationship between surgery and metastasis. Kay et al. [25] suggested that the surgical method was a risk factor. All six patients with pulmonary metastasis had undergone curettage of the primary tumor, but not resection. The present study showed similar results in that the patients who underwent resection of the primary lesion had a lower metastasis rate. This should be related to the lower rate of local recurrence among patients who underwent resection. In our previous study [9], the local recurrence rate in the resection group (1.6%) was significantly lower than that in the curettage group (8.6%). A low local recurrence rate is related to a low lung metastasis rate. Curettage is currently the most common and effective method for the treatment of GCTB. We applied extended curettage for GCTB and achieved satisfactory local control. Therefore, even if an association between surgery and pulmonary metastasis exists, the benefits (good local control and retention of the articular surface) are obvious.

With respect to the relationship between vascular invasion and lung metastasis, Sladden [26] reported five patients with tumor invasion of blood vessels, but no metastasis was found. Other studies [27,28] have shown that the presence of an intravascular tumor thrombus did not increase the risk of pulmonary metastasis.

Our study had some limitations. First, it was a retrospective study covering a long span of time period, and the incidence of lung metastasis was very low. Second, only 11 patients had pathologic evidence of lung metastasis. Both biopsy and resection are traumatic operations with risks and complications. Many patients in our study had multiple metastases that could not be completely removed by surgery or benefit from surgery; there was no effective treatment method even if the lesions were confirmed by pathological examination. Therefore, these patients did not undergo surgery based on ethical considerations and the wishes of the patients. Growth of the lesions was confirmed on serial images in all patients, and other possible diseases such as tuberculosis, infection, or fibrous tissue hyperplasia were excluded.

In conclusion, local recurrence, a high Campanacci stage, and curettage of the primary lesion are possible high-risk factors for pulmonary metastasis. The primary lesion site and local recurrence may be related to the time of metastasis. The survival rate of patients with pulmonary metastasis in this study was high.

Conflict of interest statement

Each author certifies that he or she has no commercial associations (eg, consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Ethical review committee statement

Each author certifies that his or her institution approved the reporting of this case report and that all investigations were conducted in conformity with ethical principles of research.

Conflict of interest statement

The authors declare no conflict of interest.

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