Similar outcomes with first-line observation versus metastasectomy for bone giant cell tumor lung metastases

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Abstract

Background: The outcome of lung metastases in patients with giant cell tumor of bone (GCTB) varies from spontaneous regression to uncontrolled growth. To investigate whether observation is an appropriate first-line management for patients with lung metastases from GCTB, we compared the outcomes of patients initially treated with observation with those treated with metastasectomy.

Methods: We retrospectively reviewed the data of 29 patients with lung metastases from histologically confirmed GCTB. The median follow-up period was 114 months. We evaluated progression-free survival, which was defined as the time from the date of occurrence of lung metastases to the date of disease progression in the observation or incomplete metastasectomy group, disease recurrence in the complete metastasectomy group, or the last follow-up.

Results: Disease progression or recurrence occurred in 14 patients (48.3%). Progression-free survival did not vary significantly between the observation and metastasectomy groups ($p=0.373$). The total number of metastasectomies was significantly higher in the initial metastasectomy group than in the observation group ($p=0.017$).

Conclusions:

The number of patients included in this study is small, however the data suggests that observation can be used safely as first-line management for patients with lung metastases from GCTB with an outcome similar to that of metastasectomy. It is necessary to confirm our result in multi-institutional study with sufficient number of patients.

Background

Giant cell tumor of bone (GCTB) accounts for approximately 5% of all primary bone tumors [1]. It usually involves the metaphyseal-epiphyseal region of long bones [2] and its incidence peaks in the third and fourth decade [3]. The main treatment modality is surgery, consisting of curettage or en block resection.

Although benign, GCTB is known to be locally aggressive with a tendency for local recurrence with occasional metastatic potential [4]. GCTBs metastasize in up to 4% of cases, mainly to lung [5–16]. Treatment recommendations of lung metastasis vary; the most common is metastasectomy [8,17–22], but chemotherapy (cytotoxic agents [21,23], denosumab [24–26], interferon- α [27], or bisphosphonates [28]), radiation [17,29,30], and observation [20] have each been reported with varying effectiveness. Some patients with lung metastasis have been reported to experience uncontrolled growth, eventually resulting in death [31]. Other patients with lung metastases can spontaneously regress or present growth arrest [31]; therefore, these patients would benefit from a wait-and-see policy without the use of surgical or medical treatments. Before 2010, many authors recommended, when feasible, an immediate metastasectomy [11,16,32–35]. Recently, some authors have proposed that metastasectomy should only be recommended when accompanied by disease progression or developing a symptom [12,36–38]. The

aim of the wait-and-see policy was to determine with observation the biologic behavior of lung metastases and determine further treatment, based on disease progression. However, there is limited information regarding the ideal treatment approach of patients with metastatic GCTB.

Therefore, to confirm whether observation is appropriate as a first-line approach for patients with lung metastases from GCTB, we performed a retrospective study to compare the outcomes between patients initially treated with observation and those treated with metastasectomy.

Methods

We retrospectively reviewed the medical records of 496 patients diagnosed with histologically confirmed GCTB in a single institution between 1984 and 2019. Of the 496 patients, 32 experienced lung metastases as evident by computed tomography (CT) of the chest. Three of the 32 patients were excluded due to malignant transformation of GCTB. 14 patients who received metastasectomy were histologically diagnosed with lung metastases from benign GCTB. The other 15 patients were diagnosed with lung metastases from benign GCTB when chest CT shows nodular, rounded, well-defined opacities [11,38]. The remaining 29 patients were included in this study for further analysis. We evaluated the primary tumor characteristics as shown in Table 1. Tumors were graded radiographically according to the Campanacci classification system for GCTB [9]. Primary tumor surgeries were performed with curettage or resection. The tumor cavity after curettage was left alone or packed with bone allografts, cement, or cement with bone allografts, as reported in previous study [39–41]. Resection was indicated for large tumors with soft tissue extension, pathological fractures with joint invasion or an unstable fracture pattern, multiple recurrences, or involvement of expendable bones (head of the fibula or distal end of the ulna), as previously reported [39].

After primary tumor treatment, the patients were followed every four months for the first 2 years, every 6 months for the next 3 years, and then annually. Follow-up evaluation included radiographs of the primary tumor area and CT of the chest. We evaluated the lung metastases characteristics including number of lung nodules, size of maximum nodule, solitary or multiple lesion, and laterality (unilateral or bilateral) as shown in Table 1. Seven of the 29 patients had lung metastases at presentation and the remaining patients had metachronous metastases. The median interval between surgery of primary tumor and occurrence of lung metastasis was 22 months (interquartile range [IQR], 5 to 37.5 months). Twenty-three patients underwent observation as the first-line approach. Eight of them received metastasectomy and 2 of them received denosumab treatment (120mg) for 1 year and 11 years, respectively, due to progression of lung metastases. One of the 2 patients received chemotherapy (ifosfamide, adriamycin, interferon, or cyclophosphamide) before starting denosumab treatment. The median interval between occurrence of lung metastasis and metastasectomy in the 8 patients who received metastasectomy following initial observation was 14 months (IQR, 6 to 15 months; range, 4 to 69 months). Six patients received metastasectomy as the first line approach. One patient received stereotactic radiotherapy due to a recurrent tumor following metastasectomy (Figure 1).

Lung lesion size was assessed by CT as complete response, partial response, stable disease, or progressive disease, as measured by the modified Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) that assess tumor extent on the basis of the sum of the longest diameter of a lesion [42]. The Fisher's exact test was used to compare 2 variables. The difference between 2 independent samples was statistically analyzed using the Mann-Whitney U test for nonparametric analyses. Progression free survival was defined as the time from the date of occurrence of lung metastases to the date of lung lesion progression in observation or incomplete metastasectomy group, lung lesion recurrence in complete metastasectomy group, or the last follow-up. Progression-free survival was evaluated with the Kaplan-Meier survival analysis; survival curves were compared with a log-rank test. Analyses were performed with JMP® 14 (SAS Institute Inc., Cary, NC, USA).

Results

Progression-free survival was not significantly different between the observation and metastasectomy groups ($p=0.373$; Figure 2) (Table 2). There were no significant differences between any variables in progression-free survival (Table 2). There was no significant difference between the observation and metastasectomy groups in patient characteristics (Table 1). Patient outcomes are summarized in Figure 1. Two patients received denosumab treatment due to disease progression. In 1 of the two patients, CT showed disease progression one year after occurrence of lung metastases and the patient was treated with chemotherapy (ifosfamide, adriamycin, and interferon). CT showed continued disease progression 4 months after chemotherapy commencement and so the patient underwent cyclophosphamide; however, the lung lesions progressed. Denosumab was started 4 years after occurrence of lung metastases and continued for 11 years and the disease remained stable. In the other patient, chest CT showed lung lesion progression 3 years after the curettage for the primary tumor and the patient was treated with denosumab for 1 year and was observed with stable disease until last follow up. The denosumab therapy was rechallenge because the patient had denosumab treatment before and after curettage of the primary tumor. The patient had no side effects related to the denosumab treatment (Figure 3). In the observation group (23 patients), 15 patients did not undergo metastasectomy (65.2%), 4 patients underwent metastasectomy once (17.4%), and 3 patients had several metastasectomies (13.0%). The total number of metastasectomies in patients treated with initial metastasectomy was 1 in 5 patients (83.3%) and 2 in 1 patient (16.7%). Thus, the total number of metastasectomies was significantly higher in the initial metastasectomy group than in the observation group ($p=0.017$).

Overall, disease progression or recurrence occurred in 14 patients (48.3%). The median follow-up period from surgery for primary tumor was 113.9 months (IQR, 80.9 to 140.6 months)(observation group, median 78.6 months [IQR, 43.5 to 119.5 months]; metastasectomy group, median 75.8 months [IQR, 45.1 to 113.9 months]). The median follow-up period from occurrence of lung metastases was 72 months (IQR, 48 to 124 months)(observation group, median 72 months [IQR, 48 to 124 months]; metastasectomy group, median 79 months [IQR, 51 to 129.3 months]). With respect to the oncologic results, 12 had no evidence of disease and 17 patients were alive with lung metastases. None experienced spontaneous regression among the 13 patients who did not receive any treatment in the overall therapeutic process.

None of the patients died due to the disease. None of the patients had pleural effusion or respiratory symptoms. None of the patients experienced metastases anywhere but the lungs. All patients with metastasectomy had histological confirmation of their GCTB lung metastases.

Discussion

The results of our study revealed similar progression-free survival with the observation approach when compared to metastasectomy as a first-line approach in patients with metastatic GCTB. Before 2010, many authors stressed the importance of early detection of metastasis in GCTB with regular long-term follow up and recommended, where possible, appropriate immediate surgical resection, such as metastasectomy, wedge resection, or lobectomy, to prevent progressive pulmonary dysfunction [11,16,32–35]. On the other hand, a few authors suggested that pulmonary metastases has a good long-term prognosis and should be kept under observation, avoiding aggressive treatment such as lobectomy, chemotherapy, and radiotherapy [20,43]. Since 2015, authors have suggested that it is unnecessary to perform lung metastasectomy immediately after the diagnosis of metastasis and it is more appropriate to perform metastasectomy only when there is disease progression in terms of volume and number of lung metastases [12,36–38]. According to a recent systematic review regarding prognosis of metastatic GCTB, spontaneous regressions were observed in 4.5% of patients [44]. Lung metastasis of GCTB often exhibits no changes in volume [36]. Because it is impossible to predict the behavior of lung metastases from GCTB [38], it is reasonable to evaluate the tumor biology with observation in each case in order to determine further treatments such as metastasectomy or medical treatment.

The mortality of the patients who had metastases from GCTB and received metastasectomy ranged between 0% and 50% [2,12–14,20,31,32,34,37,45–50]. The recurrence rate of the patients who had metastases from GCTB and received metastasectomy ranged between 0% and 50% [2,13,14,20,31,32,37,45,46,49]. The outcome following metastasectomy varied due to unpredictable tumor behavior of lung metastases from GCTB. Literature showed that aggressive lung metastasectomy might fail to produce a cure [51].

Although the efficacy of cytotoxic chemotherapy for lung metastases from GCTB has been scarcely reported [34,52], its role is loosely determined. Thus, considering that GCTBs are borderline tumors, they are not responsive to chemotherapy even after the appearance of the lung metastases [48].

There is anecdotal evidence that interferon α -2a can be effective in stabilizing progressive GCTB refractory to other modalities such as surgery, radiation and cytotoxic chemotherapy [53–55]. Interferon may have activity in GCTB via its antiangiogenic properties. Interferon is not well-tolerated and is associated with numerous side effects, including depression and ischemic events [56].

Feigenberg et al. [57] reported 3 patients with lung metastases from GCTB who were treated with whole-lung radiotherapy. One patient's lung metastasis progressed after treatment, and the patient soon died. The 2 other patients were long-term survivors (7.5 years and 13 years) with complete resolution of detectable disease. However, radiotherapy may induce (secondary) malignant transformation, which is of

concern especially because most patients are usually relatively young. The reported risk of malignant transformation varies between 0% and 5% [58–62].

Denosumab was able to stop the progression of lung metastases in 2 patients. In 1 of the 2 patients, lung metastases progressed despite chemotherapy but denosumab halted the progression of lung metastases. Palmerini et al. [26] reported a series of 15 patients with metastatic GCTB treated with denosumab and all patients achieved tumor control under denosumab treatment. Engellau et al. [63] reported that 38 patients with metastatic GCTB, who had tumor control under denosumab treatment. Thus, denosumab could halt the disease progression in most metastatic GCTBs. In our study, 2 patients underwent denosumab treatment and achieved tumor control of lung metastases without side effects. One of these 2 patients was treated with denosumab twice before surgical treatment of the primary lesion and then for the treatment of lung nodules. To date, there has been no evidence that denosumab rechallenge could be effective.

Balke et al. [28] reported a series of 12 patients with metastatic GCTB who had a stable disease following bisphosphonate treatment. Li et al. [64] conducted a randomized study comparing the efficacy and safety of denosumab and zoledronic acid treatment in patients with surgically unsalvageable GCTB, including GCTB of the sacrum and spine, and multifocal tumor including lung metastases. In their study, 29 of 125 patients who were administered denosumab had lung metastasis, compared to 25 of 125 patients who were administered zoledronic acid. Zoledronic acid halted the progression of lung metastases as well as denosumab, with relatively manageable adverse effects [64].

This study has some limitations. Firstly, a power analysis was not performed, and there was a risk of type II error due to the small sample size. If an adequate number of patients is gathered in the future, significant differences may appear regarding the variables in this study. However, lung metastases from GCTBs are very rare. Secondly, the study was retrospective and thus had inherent limitations and risk of selection bias. Multivariable analysis was impossible due to the small sample and we were not able to correct of the influence of confounding factors. Moreover, there are still concerns of negative effect in terms of disease control or survival by delaying metastasectomy in patients who showed progression later. Future prospective randomized controlled trials with an endpoint of not only traditional oncologic metrics such as local recurrence, progression disease by imaging and death but also impact on quality of life and respiratory function are needed to confirm the similar outcome between the patients initially treated with observation and those treated with metastasectomy at presentation. As no randomized trials have been performed yet, well-designed cohort and observational studies with strong effects may provide reliable information. Thirdly, we have a histological documentation for the lung nodules only for the patients who underwent resection of their lung metastases. However, most patients with GCTB are young patients and it is not frequent among healthy young patients to have lung lesions; therefore, these lung lesions when observed in imaging studies of GCTB patients most likely represent GCTB lung metastases.

Conclusions

The number of patients included in this study is small, however the data suggests that observation can be safely used as first-line management for patients with lung metastases from GCTB with an outcome similar to that of metastasectomy. In these patients, the goal of observation is to evaluate the tumor biology in each case to determine further treatment such as metastasectomy or medical treatment. It is necessary to confirm our result in multi-institutional study with sufficient number of patients.

Abbreviations

GCTB, giant cell tumor of bone; CT, computed tomography; IQR, interquartile range; RECIST, Response Evaluation Criteria in Solid Tumors

Declarations

Ethics approval and consent to participate

All patients gave written informed consent for their data to be included in any possible future scientific study. This study was approved by the Institutional Review Board/Ethics Committee of the senior author's institution (ClinicalTrials.gov Identifier: NCT02996734).

Consent for publication

All patients gave written informed consent for their data to be included in any possible future scientific study.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to privacy problem but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' contributions

ST designed this study, analyzed the data and wrote this manuscript. CG gathered the data. MA performed statistical analyses. AFM, CF, YT, MR, AL, DMD integrated this study. CE designed this study and revised this manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Details of the patients included in this study at baseline.				
		First-line approach		
Variables	Patients (n = 29, %)	Observation (n = 23, 79.3%)	Metastasectomy (n = 6, 20.7%)	<i>p</i> <i>value</i>
Age (years)				0.080
Median	28.2	31.3	23.4	
IQR	24.4- 36.6	26.0-36.8	20.8-36.3	
Sex				0.258
Male	9, 31.0%	6, 26.1%	3, 50.0%	
Female	20, 69.0%	17, 73.9%	3, 50.0%	
Site				0.869 [#]
Distal radius	7, 24.1%	5, 21.7%	2, 33.3%	
Proximal femur	1, 3.4%	0	1, 16.7%	
Distal femur	4, 13.8%	3, 13.0%	1, 16.7%	
Proximal tibia	6, 20.7%	6, 26.1%	0	
Proximal fibula	1, 3.4%	1, 4.3%	0	
Proximal humerus	2, 6.9%	1, 4.3%	1, 16.7%	
Ilium	1, 3.4%	1, 4.3%	0	
Ischium	1, 3.4%	1, 4.3%	0	
Vertebra	2, 6.9%	1, 4.3%	1, 16.7%	
Phalanx	1, 3.4%	1, 4.3%	0	
Metacarpal	2, 6.9%	2, 8.7%	0	
Metatarsal	1, 3.4%	1, 4.3%	0	
Campanacci classification				0.363
Stage II	6, 20.7%	4, 17.4%	2, 33.3%	
Stage III	23, 79.3%	19, 82.6%	4, 66.7%	
Previous surgery				0.114
No	21,	15, 65.2%	6, 100.0%	

	72.4%			
Yes	8, 27.6%	8, 34.8%	0	
Lung metastasis at presentation				0.157
No	22, 75.9%	16, 69.6%	6, 100.0%	
Yes	7, 24.1%	7, 30.4%	0	
Pathological fracture at presentation				0.944
No	20, 69.0%	17, 73.9%	3, 50.0%	
Yes	9, 31.0%	6, 26.1%	3, 50.0%	
Surgery for primary tumor				0.843
Curettage	7, 24.1%	6, 26.1%	1, 16.7%	
Resection	22, 75.9%	17, 73.9%	5, 83.3%	
Pre- and postoperative denosumab treatment				0.373
No	25, 86.2%	19, 82.6%	6, 100.0%	
Yes	4, 13.8%	4, 17.4%	0	
Local recurrence				0.931
None	15, 51.7%	13, 56.5%	2, 33.3%	
1£	14, 48.3%	10, 43.5%	4, 66.7%	
Interval between surgery of primary tumor and occurrence of lung metastasis (months)				0.431
Median	22	22	25	
IQR	5-37.5	0-40	11-54.8	
Number of lung nodules				0.394
Median	4	4	6	
IQR	3-7	3-6.8	4-8	
Size of maximum nodule (mm)				0.599
Median	5	5	10	

IQR	5-10	5-9	3-12	
Lung lesion				0.144
Solitary	4, 14.8%	2, 9.1%	2, 40.0%	
Multiple	23, 85.2%	20, 90.9%	3, 60.0%	
Laterality				0.221
Unilateral	5, 18.5%	3, 13.6%	2, 40.0%	
Bilateral	22, 81.5%	19, 86.4%	3, 60.0%	
#Comparison of distal end of the radius and the others. IQR, interquartile range				

Table 2. Univariate analysis for progression-free survival			
Variable	No. of patients	Five-year progression-free survival (95% CI) (%)	<i>p</i> value
Age (years)			0.436
<30	16	50.0 (27.3-72.7)	
≥30	13	59.3 (31.4-82.3)	
Sex			0.108
Male	9	77.8 (42.1-94.4)	
Female	20	42.9 (22.8-65.6)	
Site			0.896
Distal radius	7	42.9 (14.4-77.0)	
Other sites	22	59.1 (38.2-77.2)	
Campanacci classification			0.631
Stage II	6	50.0 (16.8-83.2)	
Stage III	23	55.8 (35.4-74.4)	
Previous surgery			0.896
No	15	53.3 (29.3-75.9)	
Yes	14	55.1 (29.0-78.7)	
Lung metastasis at presentation			0.620
No	22	59.1 (38.2-77.2)	
Yes	7	38.1 (10.5-76.3)	
Pathological fracture at presentation			0.264
No	20	48.9 (28.0-70.1)	
Yes	9	66.7 (33.3-88.9)	
Surgery for primary tumor			0.801
Curettage	7	57.1 (23.0-85.6)	
Resection	22	54.5 (34.1-73.5)	
Pre- and postoperative denosumab treatment			0.226
No	25	60.0 (40.3-77.0)	
Yes	4	25.0 (3.4-76.2)	

Local recurrence			0.896
None	15	53.3 (29.3-75.9)	
³ 1	14	55.1 (29.0-78.7)	
Interval between surgery of primary tumor and occurrence of lung metastasis (months)			0.610
<24	17	45.4 (23.6-69.1)	
24£	12	66.7 (37.6-86.9)	
Number of nodules			0.435
<4	7	57.1 (23.0-85.6)	
4£	11	45.5 (20.3-73.2)	
Lung lesion			0.302
Solitary	4	75.0 (23.8-96.6)	
Multiple	23	47.0 (27.8-67.1)	
Laterality			0.625
Unilateral	5	60.0 (20.0-90.0)	
Bilateral	22	49.1 (29.1-69.3)	
Size of maximum nodule (mm)			0.060
<6	12	66.7 (37.6-86.9)	
6£	7	14.3 (2.0-58.1)	
First-line approach			0.373
Observation	23	50.9 (30.8-70.6)	
Metastasectomy	6	66.7 (26.8-91.6)	

Figures

Figure 1

Diagram of patient outcomes. a, The two patients showed stop of progression afterwards; b, One of the two patients received chemotherapy before starting denosumab treatment. Lung lesions progressed under the chemotherapy; c, One patient received metastasectomy again due to slow progression and never experienced recurrence. The other patient received metastasectomy 3 more times due to slow progression and never experienced recurrence since then; d, The patient had lung lesion with slow progression; e, One of the 3 patients experienced recurrence, received stereotactic radiotherapy and the lung lesion regressed. Another patient experienced recurrence, underwent metastasectomy, and no further recurrence was observed; f, Two patients experienced recurrences; g, The patient showed stop of progression afterwards. NED, no evidence of disease; AWD, alive with disease;

Figure 2

A Kaplan-Meier curve showing the similar progression-free survival in patients treated with observation and those treated with metastasectomy.

Figure 3

A case of 33-year-old woman with giant cell tumor of bone and lung metastases treated with denosumab rechallenge. She was referred to our institute for the local recurrence following curettage and cementing for distal radius giant cell tumor of bone. Radiograph showed osteolytic lesions (arrow) surrounding the cement (a). Chest CT showed lung metastasis on the left lung (arrow) at presentation (b). She received preoperative denosumab therapy for 4 months and radiograph showed sclerotic formation (arrow) surrounding the cement (c). Then she received curettage and cementing and postoperative denosumab therapy for one month. However, she experienced local recurrence 14 months after the operation and received en bloc resection and reconstruction with allograft. Follow up chest CT showed a new lesion on the right lung (arrow) 3 years after the initial operation at our institute (d). She was treated with denosumab for 1 year and the lung lesions were stable (arrows) thereafter (e).