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ORIGINAL PAPER

Pulmonary metastasis of giant cell tumour: a retrospective study of three hundred and ten cases

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Abstract

Background Giant cell tumour (GCT) is an invasive benign bone tumour, and the incidence of pulmonary metastasis is rare. We are aiming to analyze risk factors of pulmonary metastasis and clinical prognosis for giant cell tumour patients with pulmonary metastasis.

Method We performed a retrospective study of 310 patients with GCT between December 2004 and December 2016. Risk factors of pulmonary metastasis were analyzed by univariate and multivariate logistic regression analysis. Then, the influence of risk factors of overall LR (local recurrence), recurrent tumor at presentation, LR after our therapy, and with soft tissue mass on the pulmonary metastasis-free survival rates was analyzed.

Results The mean follow-up of the present cohort was 45.6 ± 35.3 months (median, 36.6 months; range, 6.1–193.4 months). Eighteen (5.8%) of 310 patients developed pulmonary metastasis. The average interval from surgery of primary tumour to detection of pulmonary metastasis was 15 months. Multivariate logistic regression analysis showed overall local recurrence was the independent risk factor of developing pulmonary metastasis. Among 18 patients with pulmonary metastasis, sixteen cases had history of local recurrence (88.9%, 16/18), including eleven (68.8%, 11/16) with local recurrence at presentation before receiving our therapy and seven (43.8%, 7/16) with local recurrence after receiving treatment in our hospital. Time to local recurrence had obvious difference between patients with and without pulmonary metastasis. Patients with pulmonary metastasis were prone to recur earlier. Furthermore, overall local recurrence, local recurrence after our therapy, recurrent tumor at presentation, and tumour with a soft tissue mass showed statistical differences in the pulmonary metastasis-free survival rates.

Conclusions Giant cell tumour patients with soft tissue mass and overall local recurrence are prone to develop pulmonary metastasis. Although giant cell tumour is a benign tumor, more attention should be paid to the problem of pulmonary metastatic lesions, and chest CT scan should be recommended during follow-up.

Keywords Giant cell tumour · Pulmonary metastasis · Risk factors · Prognosis

Introduction

Giant cell tumour (GCT) is an invasive benign bone tumor consisting of proliferative mononuclear cells and osteoclast-like multinucleated giant cells. It has been reported that pulmonary metastasis rate of GCT was approximately 1–3.9% in patients without local recurrence and 6–21.1% in patients with local recurrence [1–8].

The overall mortality rate of patients with GCT pulmonary metastasis varies widely. However, metastatic disease of GCT

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is rarely fatal. The aetiology of pulmonary metastasis for GCT has been debated, and various factors have been considered as being associated with pulmonary metastasis [5, 6, 9–12]. To date, there is no consensus and guideline regarding the management of pulmonary metastasis for GCT patients. Treatment recommendations including observation, surgical resection, chemotherapy, radiation, and denosumab have each been reported with different effectiveness [5, 6, 9–12]. Thus, the purpose of present study was to analyze risk factors of pulmonary metastasis and clinical prognosis for GCT patients with pulmonary metastasis.

Patients and methods

We performed a retrospective study of 310 patients with GCT between December 2004 and December 2016. There were 181 males and 129 females with a mean age of 34.0 ± 12.7 years (median, 27 years; range, 11–75 years). Basic characteristics and surgical data including surgery methods, surgery record, pulmonary metastasis, and time between primary operation and pulmonary metastasis were drawn from clinical record. Pulmonary metastasis was diagnosed when radiologic findings met the following criteria: (1) development of abnormal lesions as single or multiple pulmonary nodules, rounded, well-defined opacities on chest CT and (2) growth either in number or size of lesions during follow-up [3].

Risk factors related to the occurrence of pulmonary metastasis for patients with GCT, including gender, age, side, location, overall local recurrence, recurrent tumour at presentation, local recurrence after our therapy, with soft tissue mass, pathological fracture, combined with aneurysmal bone cyst (ABC), multiple GCT, surgery methods, and Campanacci grade were evaluated by univariate and multivariate logistic regression analysis. Overall local recurrence indicated those with local recurrence after receiving our therapy and those who referred from other hospitals because of local recurrence. All the patients which were included in the present study gave written informed consent for their data to be included in this study. This study was approved by the institutional review board/ethics committee of the authors' institution. Patients who met the following inclusion and exclusion criterion were recruited into the present study. The inclusion criteria were as follows: (1) patients with GCT at the extremity, spine, and pelvic, (2) with intact clinical data during in hospital and follow-up. The exclusion criteria were as follows: (1) patients with GCT in soft tissue, (2) incomplete medical and surgical records during in hospital, (3) incomplete information of follow-up.

Statistical analysis

Statistical analysis was conducted using SPSS 19.0 (SPSS Inc., USA). Continuous variables were summarized with means, medians, and ranges; categorical variables were summarized with frequency counts and percentages. A multivariate logistic regression was applied to identify significant independent predictors of pulmonary metastasis for patients with GCT. Model selection methods such as Wald-backward elimination were used to identify significant factors from the explanatory variables. A P value of < 0.05 was considered to indicate statistical significance.

Results

Clinical characteristics

The clinical detailed information is shown in Table 1. The mean follow-up of the present cohort was 45.6 ± 35.3 months (median, 36.6 months; range, 6.1–193.4 months). There were 225 patients receiving initial surgery in our hospital, which were defined as those with a primary giant cell tumour. Meanwhile, eighty-five patients were referred from other hospitals because of local recurrence, who were defined as ones with a recurrent tumour at presentation. Rate of local recurrence for patients receiving our therapy was 16.8% (52/310). The local recurrence rate (52/310) indicated patients who received our therapy developed local recurrence during their follow-up. Among the 85 patients referred from external centres, part of them did not have the local recurrence after our specialized treatment. All recurrent patients received surgical treatment. The average time to local recurrence after initial operation was 25.3 months (median, 18.0 months; range, 1.1–111.7 months). Kaplan-Meier estimated survivorship curve of local recurrence-free survival rates of one, two and five years were respectively 93.1%, 89.2%, and 89.2% (OR, 127.1; 95% CI 116.2–138.0) (Fig. 2b).

Analysis of characteristics for patients with pulmonary metastasis

Eighteen (5.8%, 18/310) of 310 patients developed pulmonary metastasis. Unilateral metastasis occurred in six patients, and bilateral metastatic lesions occurred in twelve cases. Three patients had a single metastatic lesion, and fifteen had multiple ones. The pulmonary metastasis of GCT is shown in Fig. 1. Seven (38.9%, 7/18) of eighteen cases with pulmonary metastasis were detected concurrently at presentation, and eleven (61.1%, 11/18) metastasis were detected during follow-up of 3.1 to 61.4 months. The average interval from surgery of primary tumor to detection of pulmonary metastasis was 15 months (range, 0–61.4 months). Kaplan-Meier estimated survivorship curve of pulmonary metastasis-free survival rates of one, two and five years were, respectively, 97.9%, 96.3%, and 96.3% (OR, 152.5; 95% CI 145.5–159.5) (Fig. 2a). Among eighteen patients with pulmonary metastasis in our cohort,

Table 1 Clinical detailed information of 310 GCT patients

Variables	Number (%)
Gender	
Male	181 (58.4%)
Female	129 (41.6%)
Age (years)	34.0 ± 12.7 years (range, 11–75 years)
Side	
Axial	70 (22.6%)
Left	113 (36.5%)
Right	121 (39.0%)
Multiple GCTs	6 (1.9%)
Campanacci grade	
I	10 (3.2%)
II	75 (24.2%)
III	225 (72.6%)
Location	
Proximal humeral	9 (3.0%)
Distal humeral	4 (1.3%)
Distal radial	21 (6.9%)
Distal ulnar	4 (1.3%)
Hand	
Metacarpal	1 (0.3%)
Phalanx	2 (0.7%)
Proximal femoral	18 (5.9%)
Distal femoral	81 (26.4%)
Proximal tibial	42 (13.8%)
Distal tibial	4 (1.3%)
Proximal fibular	11 (3.6%)
Patella	3 (1.0%)
Foot	
Talus	2 (0.7%)
Navicular	3 (1.0%)
Cuboid	1 (0.3%)
Cuneiform	1 (0.3%)
Mobile spine	27 (8.9%)
Sacrum	44 (14.5%)
Pelvic	26 (8.6%)
Tumor types	
Primary	225 (72.6%)
Recurrent	85 (27.4%)
Surgical methods	
Intralesional curettage	169 (54.5%)
Wide resection	141 (45.5%)
With soft tissue mass (yes/no)	124 (40.0%)/186 (60.0%)
Pathological fracture (yes/no)	19 (6.1%)/291 (93.9%)
Combined with ABC (yes/no)	131 (42.3%)/179 (57.7%)

seven cases received denosumab treatment, and all metastatic lesions had the stable status after denosumab treatment. One of them received tumour resection and three received chemotherapy. One patient received the cyber knife. However, progressive disease occurred in this case. Three cases had the zoldronic acid treatment. The remaining cases received observation. Three patients died of uncontrollable pulmonary metastasis and respiratory failure caused by severe hydrothorax, and one of them received chemotherapy. These three patients could not come to our hospital, and they also had no attempt to receive the invasive procedure to acquire the accurate diagnosis because of the severe hydrothorax. Notably, all of the three patients who died of pulmonary metastasis had primary giant cell tumor at the spine. Their death may be related to the malignancy change of pulmonary metastatic lesions. The typical case receiving denosumab had stable status of metastatic lesions, and the nodule size was becoming smaller during follow-up, and the other patients receiving denosumab treatment showed no change of the pulmonary metastatic nodule size and number. The description of eighteen patients with pulmonary metastasis is shown in Table 4.

Analysis of risk factors for pulmonary metastasis of GCT patients

In univariate analysis of risk factors related to pulmonary metastasis for patients with GCT, risk factors included overall local recurrence ($P < 0.001$), local recurrence after our therapy ($P = 0.018$), recurrent tumor at presentation ($P = 0.002$), and with soft tissue mass ($P = 0.081$) (Table 2). All factors mentioned in univariate analysis P value ≤ 0.20 were considered eligible for further analysis. A multivariate logistic regression analysis showed that overall local recurrence (OR 12.937; 95% CI 1.611–103.917; $P = 0.016$) was the significant risk factor of developing pulmonary metastasis (Tables 3 and 4). Notably, Campanacci grade did not have the significant influence on pulmonary metastasis in the present cohort.

As overall local recurrence was found to be an independent risk factor for pulmonary metastasis, we performed the analysis to determine the local recurrence rate of these eighteen patients and interval time between initial surgery and pulmonary metastasis. Among eighteen patients with pulmonary metastasis, sixteen cases had history of local recurrence (88.9%, 16/18), including eleven (68.8%, 11/16) with LR at presentation before receiving our therapy and seven (43.8%, 7/16) with LR after receiving treatment at our hospital. Time to local recurrence differed between patients with and without pulmonary metastasis, and patients with pulmonary metastasis were prone to recur earlier (Table 2).

Stratification analysis of pulmonary metastasis-free survival for patients with GCT

We performed the stratification analysis of patients with GCT in our cohort and revealed the influence of overall LR (local recurrence), recurrent tumour at presentation, LR after our therapy, combined with ABC, with soft tissue mass,

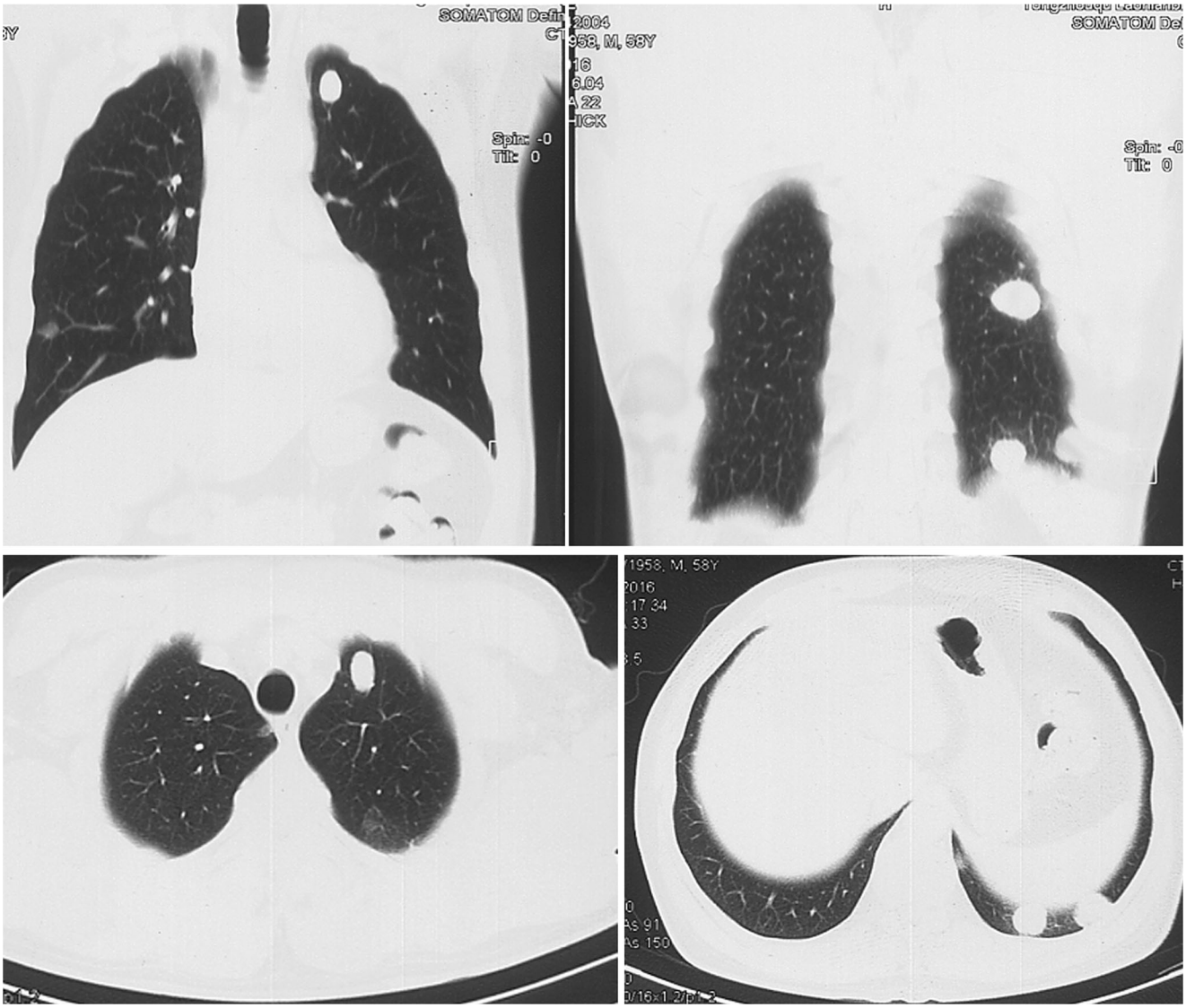

Fig. 1 Case-1, a typical patient with multiple metastatic nodules which was shown at coronal and axial CT scans

pathological fracture, Campanacci grade, multiple GCT, and surgery methods on the pulmonary metastasis-free survival rates. Kaplan-Meier estimated survivorship curves of patients with overall LR, LR after our therapy, and recurrent tumour at presentation showed statistical differences in the pulmonary metastasis-free survival rates. Afterward, Kaplan-Meier estimated survivorship curves of patients with and without soft tissue mass also revealed significant difference between two groups in the pulmonary metastasis-free survival rates (Fig. 3).

Discussion

It has been reported that the rate of lung metastasis of giant cell tumour is very low, and only 2.1–4.0% of all affected patients suffer from pulmonary metastasis in the literature [6, 13–17]. The vast majority of GCT metastasis progress more slowly. Due to possibility of pulmonary metastasis, it is necessary to perform CT scan at the time of first presentation and during follow-up investigations [3, 14–16].

The duration from initial presentation to appearance of pulmonary metastasis was reported to be 0 to 6.7 years, and some cases presented with pulmonary metastasis at first presentation [5–7]. In our present study, seven (38.9%) of eighteen metastasis cases were detected concurrently at presentation, and eleven (61.1%) metastatic lesions were detected during follow-up of 3.1 to 61.4 months. All of eighteen patients were confirmed by CT scan, and in some cases, X-ray may not detect the existence of metastatic lesion, which was concordant with the result of previous study in the literature [3]. Thus, we recommend that CT scan is necessary when firstly at presentation and during follow-up. It has been reported that pulmonary metastasis was detected at 207 months from

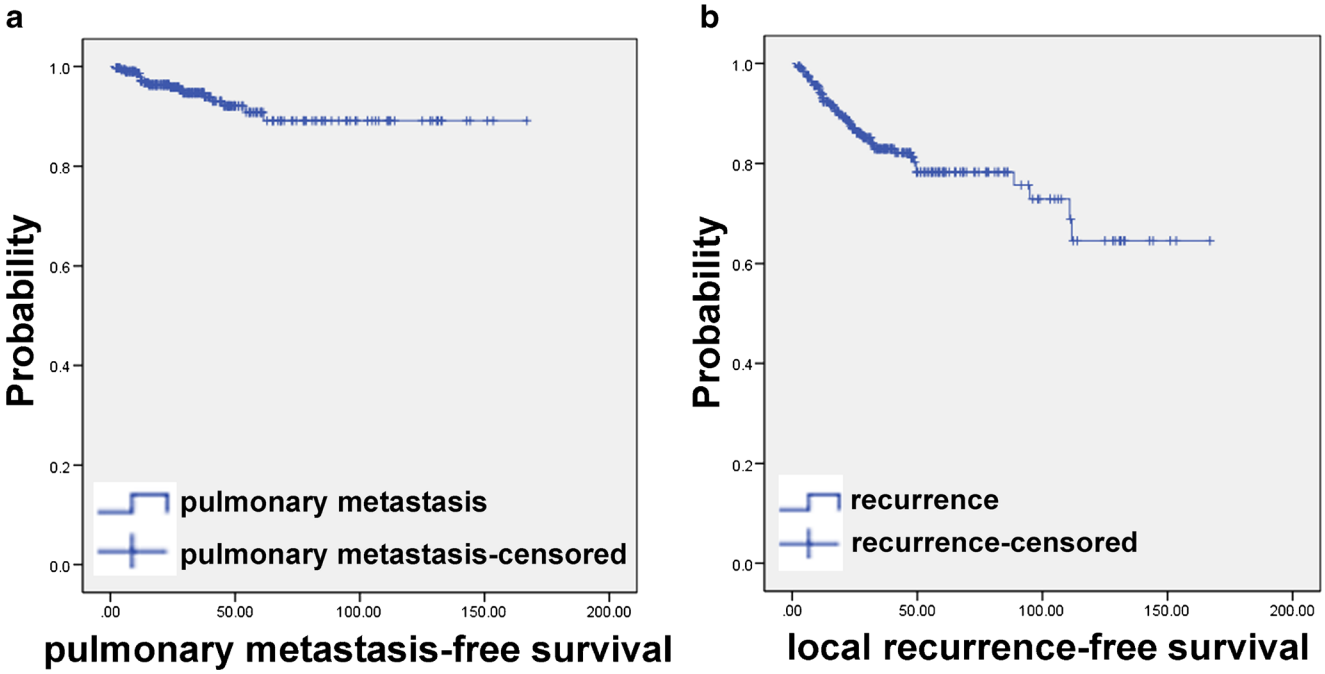

Fig. 2 Kaplan-Meier estimated survivorship curve of local recurrence-free survival rates of 1, 2, and 5 years were respectively 93.1%, 89.2%, and 89.2%

diagnosis of primary tumour, and median metastasis time of lesion at the axial skeleton was shorter than that at the lower and upper limbs [4]. In our cohort, we found all of three patients who died of pulmonary metastasis had the primary giant cell tumour at the axial skeleton. These findings illustrate the giant cell tumour at the axial skeleton may have more aggressive nature and need more attention for their pulmonary metastasis. Several cases in other studies were also diagnosed after five years from the primary diagnosis, and these studies revealed that giant cell tumour patients needed longer follow-up to inhibit the missed diagnosis [1–3, 5]. Meanwhile, our results showed that average interval from surgery of primary tumour to detection of pulmonary metastasis was 15 months (range, 0–61.4 months). It illustrated that pulmonary metastasis of giant cell tumour was weird although it did not occur at the early stage.

More studies reported local recurrence had a close relationship with the pulmonary metastasis [1, 3, 5, 7]. Our finding revealed that overall local recurrence, including those with local recurrence after receiving our therapy and those who referred from other hospitals because of local recurrence, was the only independent risk factor of developing pulmonary metastasis. Meanwhile, time to local recurrence differed between patients with and without pulmonary metastasis, and patients with pulmonary metastasis were prone to recur earlier. In the literature review, several studies reported Campanacci grade III had a close relationship with pulmonary metastasis, and soft tissue extension could increase the rate of local recurrence due to the contamination of surrounding tissue and poor surgical margin. Thus, en bloc resection should be recommended in the case of soft tissue extension when structural integrity cannot be regained after reconstruction [18]. Our analysis showed that Campanacci grade could not influence the occurrence of pulmonary metastasis whereas GCT with soft tissue mass had a lower rate in the analysis of pulmonary metastasis-free survival rate, and this finding illustrated soft tissue mass extension really exerts worse influence on the GCT prognosis. In fact, Campanacci grade III has two aspects which are tumors protruding cortical bone with and without soft tissue mass. Our results demonstrated Campanacci grade III increasing the risk of pulmonary metastasis may be associated with the existing soft tissue mass.

In the literature review, fourteen articles have been published on pulmonary metastasis of giant cell tumours [1, 3–7, 9, 11, 12, 19–23]. The rate of local recurrence of these patients with pulmonary metastasis was obviously higher, which had mean rate of 66.5%. Just in the study of Ng et al., the local recurrence occurred in only one among four patients with pulmonary metastasis. From the perspective of literature review, we can also draw a conclusion that GCT patients with local recurrence were prone to develop the pulmonary metastasis. Based on the analysis of studies in the literature, mortality rate for patients with pulmonary metastasis was 10.3% [1, 4–7, 9, 12, 19–23] and 0.5% (11/2342) for patients with giant cell tumor [1, 5–7, 9, 12, 19–23]. Generally, giant cell tumour patients with the pulmonary metastasis have a better prognosis, which is concordant with our opinion.

The probability of pulmonary metastasis increases when local recurrence of primary giant cell tumour occurs. Meanwhile, local recurrence has a closed relationship with more factors, and it has been reported that overall local recurrence rates ranged from 14.3 to 36% [16, 24, 25]. Several

Table 2 Univariate analysis of risk factors of pulmonary metastasis

	With metastasis ($n = 18$)	Without metastasis ($n = 292$)	P value
Gender			
Male ($n = 181$)	10 (5.5%)	171 (94.5%)	0.810
Female ($n = 129$)	8 (6.2%)	121 (93.8%)	
Age (years)	32.3 ± 13.0	34.1 ± 12.7	0.557
Side			
Axial ($n = 70$)	6 (8.6%)	64 (91.4%)	0.627
Left ($n = 113$)	5 (4.4%)	108 (95.6%)	
Right ($n = 121$)	7 (5.8%)	114 (94.2%)	
Multiple GCTs ($n = 6$)	0 (0)	6 (100.0%)	
Location*			
Upper extremity ($n = 41$)	1 (2.4%)	40 (97.6%)	0.552
Lower extremity ($n = 166$)	10 (6.0%)	156 (94.0%)	
Axial and pelvic ($n = 97$)	7 (7.2%)	90 (92.8%)	
Overall LR			
Yes ($n = 123$)	16 (13.0%)	107 (87.0%)	< 0.001
No ($n = 187$)	2 (1.1%)	185 (98.9%)	
LR after our therapy			
Yes ($n = 52$)	7 (13.5%)	45 (86.5%)	0.018
No ($n = 258$)	11 (4.3%)	247 (95.7%)	
Recurrent tumor at presentation			
Recurrent ($n = 85$)	11 (12.9%)	74 (87.1%)	0.002
Primary ($n = 225$)	7 (3.1%)	218 (96.9%)	
Time to tumor recurrence after our therapy (month)	11.0 ± 8.8	27.5 ± 25.8	0.003
Combined with ABC			
Yes ($n = 131$)	8 (6.1%)	123 (93.9%)	1.000
No ($n = 179$)	10 (5.6%)	169 (94.4%)	
With soft tissue mass			
Yes ($n = 124$)	11 (8.9%)	113 (91.1%)	0.081
No ($n = 186$)	7 (3.8%)	179 (96.2%)	
Pathological fracture			
Yes ($n = 19$)	1 (5.3%)	18 (94.7%)	1.000
No ($n = 291$)	17 (5.8%)	274 (94.2%)	
Campanacci grade			
I ($n = 10$)	0 (0)	10 (100.0%)	0.505
II ($n = 75$)	3 (4.0%)	72 (96.0%)	
III ($n = 225$)	15 (6.7%)	210 (93.3%)	
Multiple GCT			
Yes ($n = 6$)	0 (0)	6 (100.0%)	1.000
No ($n = 304$)	18 (5.9%)	286 (94.1%)	
Surgical methods			
Intralesional curettage ($n = 169$)	11 (6.5%)	158 (93.5%)	0.632
Wide resection ($n = 141$)	7 (5.0%)	134 (95.0%)	

LR local recurrence, *ABC* aneurysmal bone cyst

*Six multiple GCTs were not assessed

studies demonstrated that local recurrence may differ at distinct anatomic locations [13–17]. GCTs of small bones at the

Table 3 Multivariate logistic regression analysis of risk factors of pulmonary metastasis for GCT patients

	Adjusted odds ratio (95% confidence interval)	P value
Overall LR	12.937 (1.611–103.917)	0.016
LR after our therapy	1.061 (0.269–4.186)	0.933
Recurrent tumor at presentation	1.026 (0.236–4.471)	0.972
With soft tissue mass	2.113 (0.663–6.739)	0.206

LR local recurrence

foot and hand are believed to behave more aggressively than of long bones. Meanwhile, higher local recurrence seems to be related to anatomical sites, occurring more frequently in the proximal femur and distal radius, and local recurrence rates have been described for different surgery types. Intralesional curettage was considered to have a higher local recurrence compared with wide resection [16, 18, 24–27]. In the literature, it has been reported that GCTs combined with pathologic fracture had a higher local recurrence rate for patients who received intralesional curettage compared with ones who received segmental resection [18]. However, in our cohort, anatomic sites and surgery types had no significant correlation with the pulmonary metastasis of GCT. Several studies recommended wide excision for Campanacci grade III GCTs [18, 24, 25]. Otherwise, some experts suggested intralesional curettage for Campanacci grade III of GCT can also obtain excellent oncological prognosis [26, 27]. Some researchers reported the choice of surgical treatment may influence the postoperative limb function. Thus, they recommended that extensive curettage should be selected as the first choice to treat giant cell tumours at the extremity [27].

The pulmonary metastasis has been reported to be related to its vascular invasive nature [1, 6, 11]. While some researchers had the opinion that intralesional curettage can dislodge the tumour into blood vessel [1, 11, 19, 28]. However, in our cohort, several patients had the metastatic lesion in the lung at the presentation, who did not receive any surgery at that time. We reckon that pulmonary metastasis of GCT is mainly caused by the ability of vascular invasive nature because they do not receive any surgical procedure at the presentation. In the literature, one study demonstrated the tumour biological feature had an important influence on the disease progression. They reported the histochemistry characteristics of GCT had a close relationship with pulmonary metastasis, and co-overexpression of NFIB, RANK, and RANKL significantly increased the risk of metastasis. Thus, this study also illustrated the metastatic feature of GCT had a close relationship with its biological and histological nature [28]. However, our univariate analysis illustrated that there was no obvious difference between intralesional excision and wide resection on the pulmonary metastasis. Thus, it is recommended that it

Table 4 Clinical detailed information for 18 GCT patients with pulmonary metastasis

No.	A	G	Primary site	G	TPS	RTAP	OLR	LRAOT	ABC	STM	FU (month)	ITTDM (month)	NOM	LOM	TPM	P	DS
1	55	M	Right proximal femur	III	IC	Yes	Yes	Yes	No	Yes	48.9	18.5	8	Bilateral lung	Observation	AWD	SD
2	23	M	Right proximal femur	II	WR	Yes	Yes	Yes	Yes	No	54.3	28.7	8	Bilateral lung	Denosumab	AWD	SD
3	16	M	Left proximal femur	III	WR	No	No	No	No	Yes	40.8	6.3	2	Bilateral lung	Denosumab	AWD	SD
4	17	F	Right distal femur	III	IC	No	Yes	No	Yes	No	18.7	9.8	1	Unilateral lung	Observation	AWD	SD
5	31	M	Left distal femur	III	IC	Yes	Yes	Yes	No	No	24.0	0[a]	> 10	Bilateral lung	Deno + chemo	AWD	SD
6	58	M	Left distal femur	III	WR	Yes	Yes	Yes	No	No	61.4	61.4	1	Unilateral lung	Observation	AWD	SD
7	29	F	Left distal femur	III	WR	No	No	No	No	No	12.6	11.6	6	Bilateral lung	Observation	AWD	SD
8	48	M	Left distal femur	III	WR	Yes	Yes	Yes	No	Yes	50.2	0[a]	5	Bilateral lung	Observation	AWD	SD
9	15	F	Right proximal tibia	II	IC	No	Yes	No	No	No	51.8	48.2	> 10	Bilateral lung	Denosumab	AWD	SD
10	22	M	Right distal tibia	II	IC	Yes	Yes	Yes	Yes	No	12.1	12.1	2	Unilateral lung	Denosumab	AWD	SD
11	33	M	Right distal humerus	III	WR	Yes	Yes	Yes	Yes	Yes	12.2	0[a]	> 10	Bilateral lung	Deno + chemo	AWD	SD
12	23	F	Sacrum	III	IC	No	Yes	No	Yes	Yes	68.8	47.5	1	Unilateral lung	Denosumab	AWD	SD
13	25	F	Sacrum	III	IC	Yes	Yes	Yes	Yes	Yes	37.6	0[a]	4	Bilateral lung	Cyber knife	AWD	PR
14	31	F	Sacrum	III	IC	No	Yes	No	Yes	Yes	22.4	22.4	> 10	Bilateral lung	Zoldronic acid	DOD	–
15	38	F	Sacrum	III	IC	Yes	Yes	Yes	No	Yes	44.9	0[a]	7	Bilateral lung	Zoldronic acid	AWD	SD
16	30	M	Thoracic spine	III	IC	No	Yes	No	No	Yes	24.9	3.1	3	Unilateral lung	Observation	AWD	SD
17	45	F	Lumbar spine	III	IC	Yes	Yes	Yes	No	Yes	11.7	0[a]	2	Unilateral lung	Resection + chemo	DOD	–
18	42	M	Sacrum	III	WR	Yes	Yes	Yes	Yes	Yes	29.2	0[a]	4	Bilateral lung	Zoldronic acid	DOD	–

A age, *G* gender, *G* Campanacci grade, *TPS* treatment of primary site, *RTAP* recurrent tumor at presentation, *OLR* overall local recurrence, *LRAOT* local recurrence after our therapy, *ABC* combined with ABC, *STM* with soft tissue mass, *FU* follow-up, *ITTDM* interval time from treatment of primary lesion to diagnosis of metastasis, *NOM* No. of metastasis, *LOM* location of metastasis, *TPM* treatment of pulmonary metastasis, *IC* intralesional curettage, *WR* wide resection, *P* Prognosis, *DS* disease status

[a] Pulmonary metastasis at presentation

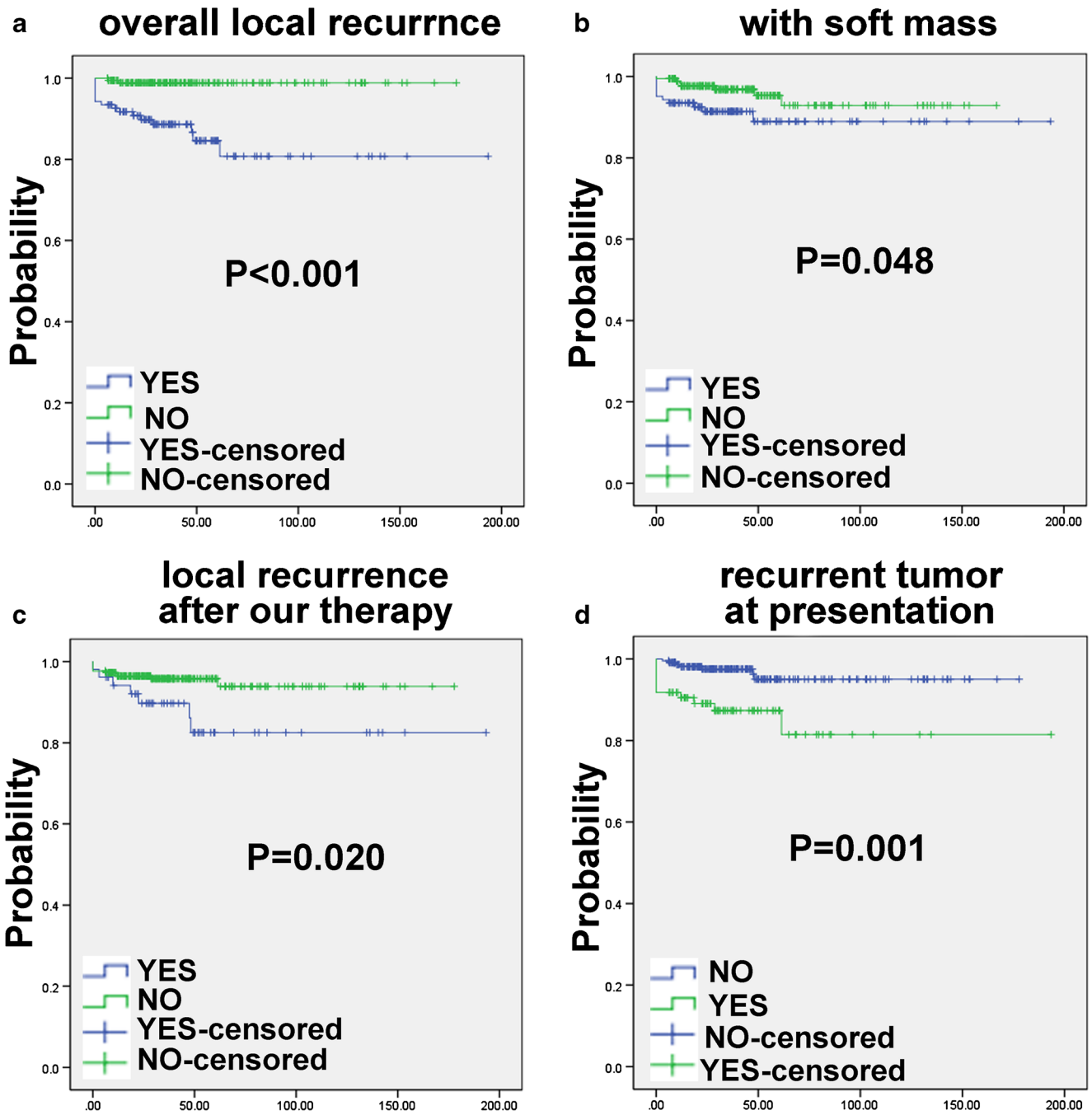

Fig. 3 Kaplan-Meier estimated survivorship curves of patients with overall LR, LR after our therapy, recurrent tumour at presentation and with soft tissue mass showed statistical differences in the pulmonary metastasis-free survival rates

is unnecessary to consider the problem of pulmonary metastasis when we chose surgery methods.

Giant cell tumour is rarely fatal and the mortality rate of reported metastatic cases varies widely from 0 to 23%. Some authors recommended not to take aggressive measures of pulmonary metastasectomy for patients with pulmonary metastatic lesion due to the fact that they often exhibited no change in volume and showed self-limited characteristics [7, 29]. For metastatic lesions, we consider that it is unnecessary to perform pulmonary metastasectomy immediately, and only in some cases when the volume of metastatic nodules increases, we recommend it is more appropriate to perform the metastasectomy. In our present study, among eighteen patients with pulmonary metastasis in our cohort, the conservative treatment of pulmonary metastasis is safe and recommended, including chemotherapy, denosumab, radiation, and observation. Denosumab is a monoclonal antibody to RANK ligand to inhibit RANK-RANKL interaction, which is a key

mediator of osteoclastic activity. It has been proved that denosumab has more positive effect on the therapy of giant cell tumour, and it has gained popularity in recent years to reduce surgical morbidity in cases with unresectable and recurrent disease in some complex anatomic sites [30–34]. However, there is no consensus and guideline regarding the management of pulmonary metastasis treated with denosumab. The value of denosumab treatment of GCT is still unclear, and some studies showed denosumab did not decrease the risk of lung metastases for patients with bone GCT [31]. Furthermore, a systematic review of the influence of denosumab on the local recurrence and results illustrated that the available evidence for the benefit of denosumab in more aggressive giant cell tumours was inconclusive, and denosumab treatment may even be associated with an increase in local recurrence rate for GCT patients. This finding demonstrated that although denosumab could inhibit giant cell tumour proliferation and invasion, the calcification of lesion could lead to the difficulty of complete excision of GCT during the intralesional curettage [34]. The value of denosumab treatment probably needs more randomized studies to be confirmed. In our experience, treatment of pulmonary metastasis in patients with giant cell tumours is recommended when the volume and size of metastasis are increasing during follow-up, and denosumab treatment is considered as an important component of a systematic treatment plan, particularly in patients with progressive pulmonary metastasis. Among eighteen patients with pulmonary metastasis in our cohort, seven cases received denosumab treatment, and all metastatic lesions had the stable status after denosumab treatment. Although the effect of denosumab on pulmonary metastasis is currently not confirmed, further study is needed to elucidate therapeutic effect of denosumab on the metastatic lesions.

Notably, specialized team matters more for a satisfactory prognosis. Some experts analyzed 203 patients with extremities GCT treated with intralesional curettage and concluded that neither the training in orthopaedic oncology nor the years of orthopaedic practice significantly predict local recurrences, function, and complications after curettage as first surgery for GCT. The skilled surgeon and surgical procedure could provide more probability of complete tumour excision and decrease the risk of local recurrence [35]. To date, whether specialized treatment influences the pulmonary metastasis is unclear. Our results showed overall local recurrence was the only independent risk factor to predict pulmonary metastasis. In the present study, patients with overall local recurrence indicated those with local recurrence after receiving our therapy and those who referred from other hospitals because of local recurrence. It illustrated during the follow-up, if the local recurrence occurred, it may significantly increase the risk of pulmonary metastasis. From this perspective, specialized treatment is more important, and it can effectively control the rate of local recurrence for GCT. Furthermore, it can also decrease the risk of developing pulmonary metastasis during the follow-up due to their lower local recurrence rate.

The present study had several limitations. Firstly, this was a retrospective study which may lose several cases or detailed information during follow-up. Secondly, the metastatic lesion was diagnosed just according to CT criteria, and it lacked the histological confirmation. Thirdly, treatment of pulmonary metastasis has more controversy, and the number of cases receiving denosumab was so small that the effect of denosumab on metastatic lesions cannot be elucidated. In further study, we will collect more data to illustrate the effect of denosumab on the pulmonary metastasis.

In conclusion, giant cell tumour patients with soft tissue mass and overall local recurrence are prone to develop the pulmonary metastasis. Although giant cell tumour is a benign tumour, more attention should be paid to the problem of pulmonary metastatic lesions, and chest CT scan should be recommended during follow-up.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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