

Recurrent Giant Cell Tumor of Long Bones

Analysis of Surgical Management

Frank M. Klenke MD, PhD, Doris E. Wenger MD,
Carrie Y. Inwards MD, Peter S. Rose MD,
Franklin H. Sim MD

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Abstract

Background Treatment of giant cell tumor of bone (GCT) often is complicated by local recurrence. Intralesional curettage is the standard of care for primary GCTs. However, there is controversy whether intralesional curettage should be preferred over wide resection in recurrent GCTs.

Questions/purposes We investigated the rerecurrence-free survival after surgical treatment of recurrent GCTs to determine the influence of the surgical approach, adjuvant treatment, local tumor presentation, and demographic factors on the risk of further recurrence.

Patients and Methods We retrospectively reviewed the medical records of 46 patients with recurrent GCTs of long bones treated with wide resection or intralesional curettage and compared these cohorts. Recurrence rates, risk factors for recurrence, and the development of pulmonary metastases were determined. The minimum followup was 37 months (mean, 134 months; range, 37–337 months).

Results The rate of rerecurrence after wide resection was 6%. Intralesional curettage showed an overall rerecurrence rate of 32%. Implantation of polymethylmethacrylate (PMMA) instead of bone grafting was associated with a lower risk of subsequent recurrence in intralesional procedures (14% versus 50%). Extracompartmental disease did not increase the risk of rerecurrence. Pulmonary metastases occurred in seven patients and appeared independent of the surgical treatment modality chosen.

Conclusions Intralesional curettage with methylmethacrylate for recurrent GCT provided equivalent tumor control compared with resection in this retrospective study. If joint salvage is possible, we advocate this treatment over resection in recurrent GCTs to preserve the native joint articulation.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research.

F. M. Klenke, P. S. Rose, F. H. Sim (✉)
Department of Orthopedic Surgery, Mayo Clinic,
200 First Street SW, Rochester, MN 55905, USA
e-mail: sim.franklin@mayo.edu

D. E. Wenger
Department of Radiology, Mayo Clinic, Rochester, MN, USA

C. Y. Inwards
Department of Anatomical Pathology, Mayo Clinic, Rochester, MN, USA

Introduction

GCT of bone is a rare benign primary bone tumor accounting for approximately 5% of all primary bone tumors [9, 43]. Tumors arise in the metaepiphyseal region of long bones, predominantly in the distal femur and the proximal tibia, but they can occur in the entire skeleton [7]. Histologically, these tumors are classified as a benign neoplastic lesion consisting of three cell types: mononuclear histiocytic cells, multinucleated giant cells that resemble osteoclasts, and neoplastic stromal cells [2, 19, 46, 48].

The clinical behavior of GCTs ranges from latent, non-active tumors to locally aggressive tumors with destruction of the cortex and soft tissue extension. The clinical course of a GCT often is complicated by the tumor's tendency

toward local recurrence. Depending on the type of treatment and the local presentation of the tumor, recurrence rates of a primary GCT range from 0% to 65% [1, 4, 6, 7, 18, 21, 22, 25, 29, 32, 33, 35, 37, 42]. Despite their generally benign nature, GCTs are able to seed lung metastases. The frequency of lung metastases ranges from 2% to 5% and the risk for development of lung metastases seems to be associated with local recurrence [4, 5, 8, 10, 18, 28, 34, 36, 38, 41]. In rare occasions, patients can have lung metastases with fatal progression.

Our preferred treatment of primary GCTs is intralesional curettage followed by high-speed burring of the tumor cavity to improve the thoroughness of tumor removal. It is the least invasive surgical option and usually provides the possibility to save the joint adjacent to the tumor. Intralesional curettage may be combined with the use of local adjuncts, such as PMMA void filling [1, 3, 4, 15, 20, 33, 37, 42, 45], hydrogen peroxide [3, 4], phenol [15, 37, 39, 40, 42], and cryotherapy [24, 26, 27] with the intention to further reduce the risk of local recurrence.

In contrast to primary GCTs, the value of intralesional curettage in recurrent tumors is more controversial. Studies have analyzed subpopulations of recurrent tumors within the scope of studies focusing on the recurrence of primary GCTs (Table 1) [1, 35, 42]. These studies indicate the highest probability to avoid multiple recurrences is achieved with wide resection of the recurrent lesions. Thus, wide resection may be a reasonable choice to minimize the risk of multiple recurrences and decrease the risk of pulmonary metastases. However, intralesional curettage results in superior function and offers the option of repeated curettage to address

multiple local recurrences. Studies specifically focusing on the treatment of recurrent GCTs are rare [3, 45]. These two studies indicated that repeat intralesional curettage of recurrent GCTs can be performed without sacrificing local tumor control and suggested application of PMMA void filling to minimize the risk of further recurrences. However, these studies contain a heterogeneous population of patients (eg, axial and appendicular lesions for which prognosis and surgical options vary) and do not analyze the impact of disease-related factors on recurrence.

For this reason, we sought to review the experience with recurrent GCTs of long bones at our institution. We specifically sought (1) to determine the rerecurrence rates of recurrent GCTs after wide resection and intralesional surgery; (2) to analyze whether PMMA void filling decreased the risk of local recurrence after intralesional curettage as compared with bone grafting; (3) to evaluate whether disease-related factors such as tumor extension, pathologic fractures, and tumor localization or patient-related factors such as gender and age contributed to the risk of local rerecurrence; and (4) to evaluate the association of surgical treatment of recurrent disease and the development of pulmonary metastases.

Patients and Methods

From the Mayo Clinic files we identified 66 patients with histologically confirmed recurrent GCTs treated surgically from January 1983 through July 2005. Of these, we excluded 20 patients with recurrent disease affecting the

Table 1. Comparison of studies investigating recurrent GCT

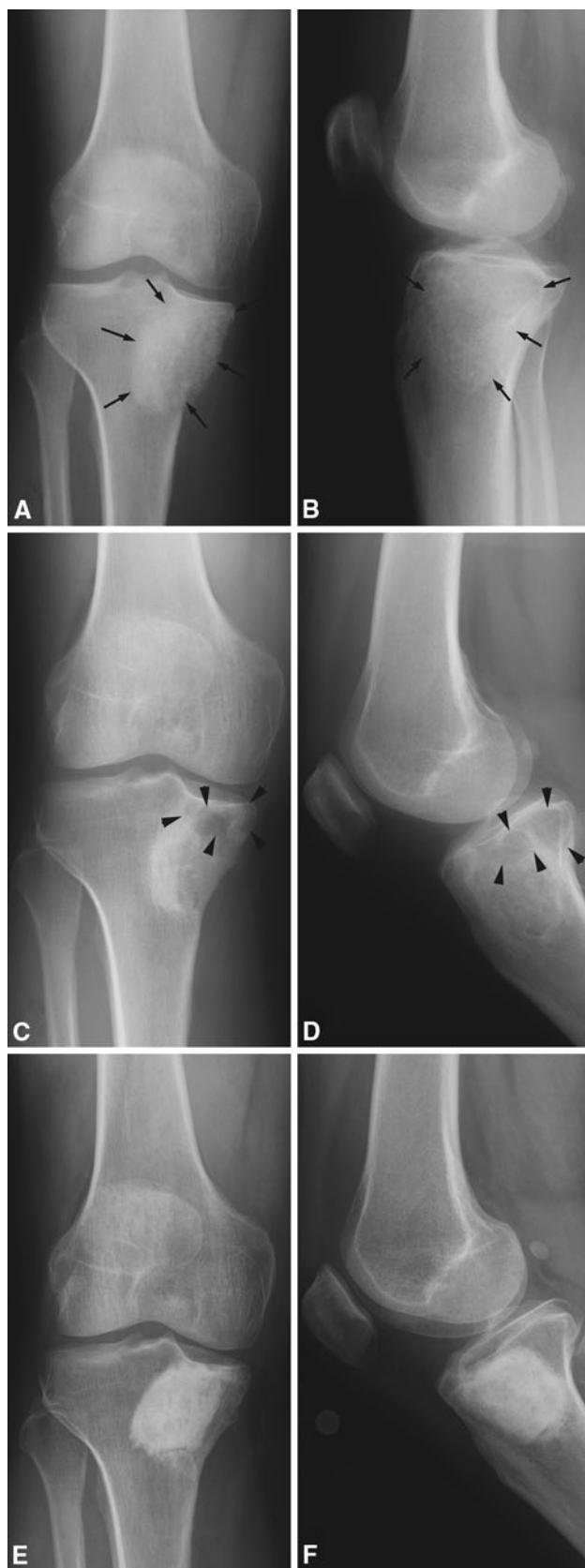
Study	Year	Followup	Patients	Surgical treatment	Rerecurrences	Factors influencing rerecurrence rate
Arbeitsgemeinschaft Knochentumoren et al. [1]	2008	63 months (0–421)	19	Wide resection Curettage +/- PMMA +/- phenol	6% 36%	Surgical margin
Balke et al. [3]	2009	77 months (13–267)	66	Wide resection Curettage Curettage + PMMA Curettage + burr + PMMA	0% 67% 36% 22%	Burr + PMMA
Prosser et al. [35]	2005	70 months (24–214)	26	Wide resection Curettage + burring	0% 21%	Extraosseous extension
Turcotte et al. [42]	2002	60 months (24–192)	23	Curettage +/- burr +/- PMMA +/- phenol	35%	None
Vult van Steyern et al. [45]	2006	53 months (3–128)	19	Curettage + PMMA	26%	nr
Current study	2010	134 months (37–337)	46	Wide resection Curettage + burr + phenol Curettage + burr + PMMA + phenol	6% 50% 14%	Surgical margin PMMA

nr = not reported.

Fig. 1A–F A 31-year-old woman was diagnosed with a GCT of the right proximal tibia. (A) AP and (B) lateral radiographs show the radiographic situation after curettage and bone grafting of the primary tumor (former tumor cavity filled with bone graft is marked by arrows). (C) AP and (D) lateral radiographs taken 26 months after the index surgery show regions of osteolysis of the proximal tibia that indicate local recurrence (osteolytic lesions marked by arrowheads). (E) AP and (F) lateral radiographs show the tibia after treatment of the recurrence with intralesional curettage, PMMA void filling, and local phenol application. No additional recurrences were observed at final followup.

spine, sacrum, pelvis, scapula, hand, or foot to evaluate a consistent group of patients with comparable treatment regimes. These exclusions left 46 with recurrent GCTs of the humerus, radius, femur, tibia, or fibula who were included in the study. Thirty of the 46 patients had received their primary treatment at an outside hospital and were referred to our institution for surgery of the recurrent lesion. The choice for wide resection versus intralesional therapy was individualized. Our groups' treating philosophy was to preserve the native articulation whenever possible by performing intralesional curettage. Extracompartmental tumor growth per se was not a criterion for wide resection; patients were equally likely to undergo wide resection as intralesional treatment for T1 versus T2 tumors. Wide resection was indicated when the tumor extension rendered joint preservation impossible or when the tumor affected dispensable bones such as the fibular head. The minimum followup was 37 months (mean, 134 months; range, 37–337 months). No patients were lost to followup. No patients were recalled specifically for this study; all data were obtained from medical records and radiographs.

Intralesional curettage was performed in 28 of 46 patients (Fig. 1). In all of these patients, additional tumor abrasion using a high-speed burr was performed and phenol was used as a local adjunct. Bone defects were filled either with autologous and/or allogenic bone grafts ($n = 14$) or PMMA ($n = 14$). Wide resections were performed in 18 patients. Reconstructive procedures included arthroplasties ($n = 4$), osteoarticular allografts ($n = 3$), allograft prosthesis composite ($n = 1$), structural allografts ($n = 1$), and arthrodeses of the wrist with interposition of structural bone grafts ($n = 3$). Three wide resections of soft tissue recurrences and one wide resection of the head of the fibula were performed without skeletal reconstructions. Amputations were performed in two patients. One of these patients had extensive recurrent disease of the distal humerus with involvement of the neurovascular structures of the antecubital fossa. The other patient had undergone wide resection of a recurrent lesion of the proximal tibia and implantation of a hinged TKA. Although this



procedure provided successful oncologic control, the patient ultimately had knee dysfunction develop with worsening pain and stiffness and was treated with an above-knee amputation.

Routine followups were performed 3 and/or 6 months after surgery. Subsequently, followups were performed in 6-month intervals until 5 years after surgery. Afterward, checkups were not routinely scheduled. Routine followups included clinical examination and conventional radiographs in two planes and chest radiography. If there was suspicion for local recurrence, additional imaging including MRI and/or CT was performed. All patients returned for the 3-month or 6-month followup. Forty-one patients returned for the 1-year followup and 24 patients returned for followups after 5 years and beyond. A physician in the patient's home community examined patients not able to return for followups and the radiographs were sent to our institution for evaluation. Radiographic followup studies were available for all 46 patients.

Radiographs were reviewed (FMK, DEW; not by the treating surgeons) for pathologic fractures. Intracompartmental or extracompartmental tumor growth was identified on the basis of preoperative imaging studies, including CT and MRI, and intraoperative findings. The compartmental extension of primary and recurrent GCTs was graded T1 or T2 according to the system of Enneking et al. [12–14] and Wolf and Enneking [47]. Data to evaluate the compartmental growth of the recurrent tumors were available for all 46 cases. All 46 surgical specimens originally had been reviewed by a certified pathologist (CYI, KKU) and histologically classified as benign GCTs.

Differences in the rerecurrence-free survival between the surgical procedures were calculated with the Kaplan-Meier survival; the log rank test of equality of survivor function was applied to compare treatment groups (A = wide resection; B1 = intralesional curettage, PMMA + phenol; B2 = intralesional curettage, bone grafting + phenol). Patients who did not experience rerecurrence were censored at the time of the last followup. Multivariate Cox regression was used to analyze the risk factors of local tumor recurrence. Statistical analysis was performed using SPSS® Version 16 for Mac (SPSS Inc, Chicago, IL, USA).

Results

Local rerecurrence occurred in 10 of 46 patients with a mean interval of 24.7 ± 12.0 months after the surgery of the recurrent lesion. In nine of 10 patients, rerecurrences occurred within 36 months after the surgery for recurrent GCTs. One of 18 patients treated with wide resection had two local soft tissue rerecurrences and finally was cured with repeated wide resection. Nine local rerecurrences

were observed in patients treated with intralesional surgery (bone grafting + phenol = six skeletal, one soft tissue; PMMA + phenol = two soft tissue). Repeated surgical intervention achieved no evidence of disease at followup in all patients. Of the six patients with bony rerecurrence, three finally needed a wide resection to achieve local control of the disease whereas three patients were cured with repeated intralesional surgery.

Survival analysis (Fig. 2) showed patients treated with wide resection had a higher ($p = 0.043$) rerecurrence-free survival as compared with patients treated with intralesional curettage. Wide resection resulted in a rerecurrence-free survival of 94%. Overall, intralesional curettage achieved rerecurrence-free survivals in 68%. Intralesional curettage together with PMMA void filling resulted in a higher ($p = 0.046$) percentage of rerecurrence-free survivals as compared with intralesional curettage and subsequent bone grafting (86% versus 50%). We observed no difference ($p = 0.685$) in rerecurrence-free survival between patients receiving wide resection or intralesional curettage with PMMA void filling.

None of the disease-related factors and demographic factors including tumor location, pathologic fractures, extracompartmental tumor extension, age, and gender had an impact on the risk of local rerecurrence (Table 2).

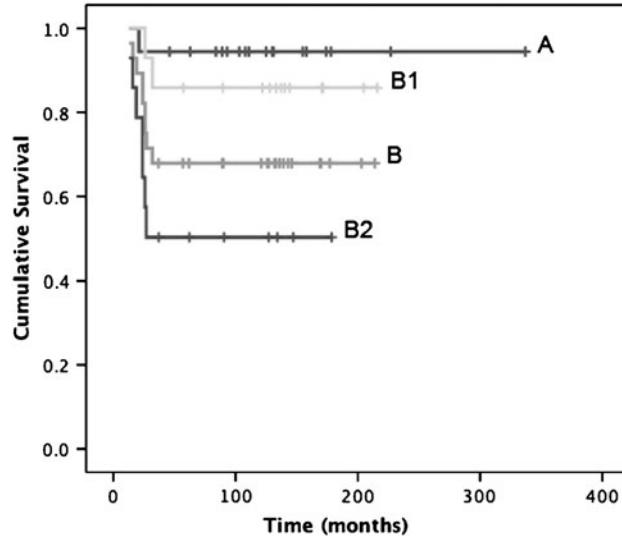


Fig. 2A–B Rerecurrence-free survival is shown for recurrent GCTs treated with wide resection (A) and intralesional surgery (B). Subgroups of patients were treated with intralesional surgery and PMMA and phenol (B1) and bone grafting and phenol (B2). The rate of rerecurrence was lower in patients treated with wide resection versus intralesional curettage ($p = 0.043$). Use of PMMA decreased the rate of rerecurrence in patients treated with intralesional curettage ($p = 0.046$). The estimated cumulative rerecurrence free survival (95% confidence interval) for Group A was 0.947 (0.838–0.999), for Group B, 0.677 (0.503–0.851), Group B1, 0.857 (0.722–0.992), and Group B2, 0.490 (0.223–0.756).

Table 2. Treatment data and risk of recurrence in association with potential risk factors

Variable	Value	Risk	95% CI for risk		p Value
			Lower	Upper	
Patient age at diagnosis (years)*	31.1 (12.8)	0.95	0.89	1.03	0.20
Gender					
Male	21	0.98	0.25	3.88	0.98
Female	25		1.00		
Location					
Femur, proximal	5	2.62	0.56	123.26	0.62
Femur, distal	11	2.05	0.21	20.51	0.54
Tibia, proximal	9	0.87	0.72	10.53	0.91
Tibia, distal	5	1.79	0.98	33.06	0.69
Fibula, proximal	2	7.09	0.39	128.21	0.19
Humerus, proximal	5	0.81	0.04	15.39	0.89
Humerus, distal	2	0.00	0.00	-	0.99
Distal radius	7	1.00			
Tumor extension					
T1	24	0.33	0.08	1.30	0.11
T2	22	1.00			
Pathologic fractures					
No	42	2.26	0.07	74.71	0.65
Yes	4	1.00			
Treatment					
Wide resection	18	0.12	0.01	0.92	0.04
Intralesional curettage	28	1.00			
Adjuvants					
PMMA + phenol	14	0.11	0.14	0.91	0.04
Bone grafting + phenol	14	1.00			

* Values are expressed as mean, with standard deviation in parentheses; PMMA = polymethylmethacrylate.

The risk of rerecurrence was influenced only by the type of surgery. Wide resection had a lower ($p = 0.021$) risk of local rerecurrence than intralesional curettage. Among patients undergoing intralesional procedures, those treated with PMMA and local phenol application had a smaller ($p = 0.033$) risk of having local rerecurrence than patients treated with bone grafting and local phenol application.

Pulmonary metastases occurred in seven patients. In four of these cases, pulmonary metastases were associated with the first recurrence. Three patients were diagnosed with pulmonary metastases during routine checkups after the first recurrence without evidence of a second local recurrence. Treatment of pulmonary metastases consisted of a multidisciplinary approach, including wedge resection, chemotherapy, and radiotherapy. At followup, three

patients were alive without evidence of metastatic disease and three patients were alive with stable metastatic disease but no evidence of local disease. One patient had died owing to progressive metastatic disease without evidence of local disease at the time of death. The development of pulmonary metastases was not influenced by whether wide resection or intralesional curettage was performed in primary tumors (hazard ratio, 2.35; $p = 0.36$) and in recurrent lesions (hazard ratio, 1.42; $p = 0.67$).

Discussion

It is still controversial whether recurrent GCTs should be treated with intralesional surgery or wide resection. Wide resection decreases the risk of multiple recurrences as compared with intralesional curettage but often necessitates complex skeletal reconstructions associated with higher rates of surgical complications and decreased function [17, 22, 32]. Intralesional curettage offers the possibility of joint preservation and previous studies suggest better limb function after intralesional curettage than after wide resection [32, 42]. However, the benefit in function should not come at the price of unacceptably high rerecurrence rates and increased frequencies of pulmonary metastases. We investigated the risk of rerecurrence after wide resection and intralesional curettage of recurrent GCTs, the factors contributing to the risk of rerecurrence, and the association of surgical treatment and the development of pulmonary metastases.

Our study is subject to several limitations. First, data were gathered from clinical files, and patients were not contacted to assess ultimate function or rerecurrences subsequent to last followup. Thus, we may have underestimated the rerecurrence rate. Second, the total sample size is relatively small limiting the number of patients in each treatment group and our ability to draw conclusions. However, recurrent GCTs are very rare; only two studies have been published specifically focusing on the treatment of recurrent GCTs [3, 45]. Third, we have treated bony and soft tissue recurrences as equivalent outcomes events. However, tumor recurrence mandates treatment in either location, making this an appropriate outcome parameter. As such, acknowledging these limitations, our study adds new information regarding surgical management of recurrent GCTs.

Consistent with previous studies [1, 3, 16, 20, 35], we found wide resection had a lower rerecurrence rate as compared with the rate for the entire collective of patients treated with intralesional curettage. Wide resections required complex reconstructions of the adjacent joints including arthroplasties, allograft prostheses composites, and osteoarticular allografts in eight patients. We did not measure function in the scope of the current study.

However, it is reasonable to assume that wide resections were associated with greater functional impairment than joint-preserving intralesional surgery.

When intralesional curettage is performed, local adjuvants such as PMMA, phenol, cryotherapy, and hydrogen peroxide have been reported to reduce the risk of local recurrence [1, 4, 11, 20, 23]. We found use of PMMA instead of bone grafting was associated with a decreased risk of tumor rerecurrence. Similar observations were reported for a series of 66 patients with recurrent GCTs of the axial skeleton and the extremities [3]. Balke et al. reported high-speed burring plus use of PMMA decreased the rerecurrence rate compared with that of intralesional curettage without any additive therapy. PMMA void filling without high-speed burring showed a tendency toward decreased rerecurrence rates. In a smaller series of 19 patients, Vult von Steyern et al. [45] reported 14 patients treated with repeat curettage and PMMA void filling had no evidence of disease at followup. The impact of PMMA has been attributed to the substance's thermal and toxic effects on tumor cells [30, 31]. Additionally, PMMA may allow for more aggressive tumor removal owing to its favorable mechanical properties decreasing the risk of collapse of the tumor cavity. Considering the critical importance of thorough tumor removal, this capacity may outweigh the effects of heat-mediated tumor cell death. This suggestion also was made by Ghert et al. [16].

Demographic factors and disease-related factors (in particular soft tissue extension) did not influence the risk of further recurrence in this study. In analyzing primary GCTs, other groups have similarly reported that location, pathologic fractures, age, and gender do not influence the risk of tumor recurrence [1, 4, 37, 42]. However, the prognostic relevance of soft tissue extension is controversial. Some authors have reported increased recurrence rates in primary tumors with soft tissue extension [1, 4], whereas others have not seen such an effect [20, 35]. However, the aggressiveness of the treatment of lesions with and without soft tissue extension must be considered to interpret the correlation of soft tissue extension and local recurrence correctly. In this study, an equal number of patients in the wide resection and intralesional curettage groups had soft tissue extension (39% in each group). These results show recurrent GCTs can be treated with intralesional curettage without sacrificing local tumor control independent of the presence of soft tissue extension.

The overall frequency of lung metastases in patients with GCTs ranges from 2% to 5%, and the risk of having lung metastases develop seems to be associated with local recurrence [4, 8, 10, 18, 28, 36, 41]. Studies analyzing subpopulations of recurrent GCTs found lung metastases in as much as 10% [3, 45]. With seven of 46 patients, the frequency of pulmonary metastases was higher in our study

than previously reported for primary and recurrent tumors [3, 4, 8, 10, 18, 28, 36, 41, 45]. The development of pulmonary metastases was independent of the type of surgery chosen for recurrent disease. With the limited numbers available, we did not find a difference in the risk of metastasis based on treatment with resection versus intralesional curettage. Even with metastatic disease, GCTs usually take a benign clinical course. Several studies reported a survival of 100% for patients with metastatic GCTs [8, 35, 44, 45]. However, one patient in our study died from progressive metastatic disease. Similar results were reported by Balke et al. [3], showing that GCTs, in particular recurrent GCTs, have the potential to progress, although rare, to a life-threatening disease.

Intralesional curettage is a valuable option to treat recurrent GCTs and preserve native joint articulation. We consider intralesional curettage with PMMA void filling the preferred treatment for most recurrent GCTs of long bones independent of whether soft tissue extension is present. We reserve wide resection for cases of extensive bone destruction where joint preservation is impossible or when expendable sites (eg, fibular head) are affected. As lung metastases developed independent of the type of surgery, our group makes the decision for either intralesional surgery or wide resection based on the local extent of the tumor and not on the potential risk of pulmonary metastases.

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