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ORIGINAL ARTICLE

The prognostic factors of recurrent GCT: a cooperative study by the Eastern Asian Musculoskeletal Oncology Group

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Abstract
Background Giant-cell tumor (GCT) of bone is a common primary benign tumor with high local recurrence and potential distant metastasis or malignant transformation. We have investigated the clinical behavior of recurrent GCT of bone in the extremities.
Methods We retrospectively reviewed 110 patients with recurrent GCTs of bone in the extremities treated by the Eastern Asian Musculoskeletal Oncology Group. The factors that affected the number of recurrences and distant metastasis were analyzed.
Results The median interval between initial surgery and the first recurrence of GCT was 16 months (2–180 months). All patients received additional surgery for first recurrence. Twenty-five patients had a second recurrence and 6 patients had a third recurrence. The mean interval between the initial surgery and the first recurrence correlated with the eventual number of recurrences—14.1 months for the repeated recurrence groups (two and three recurrences) and 28.3 months for the single recurrence group ($p = 0.016$). Campanacci grade did not correlate with repeated recurrence ($p = 0.446$). The venue of the initial surgery did not correlate with recurrence but did affect preservation of the adjacent joint (chi-squared test; $p = 0.046$). Campanacci grade II and III also correlated with sacrifice of the adjacent joint ($p = 0.020$). The incidence of lung metastasis and malignant transformation were 7.5% (8 out of 107 patients) and 2.7% (3 out of 110 patients), respectively. Repeat recurrence was associated with lung metastasis ($p = 0.018$).

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Conclusions Early local recurrence of GCT is a risk factor for repeat recurrence. Repeat recurrence also correlates with lung metastasis. Recurettage with meticulous adjuvant treatment to completely preclude recurrent lesions is a reasonable method for preserving the adjacent joint. However, a continuous careful follow-up is mandatory.

Introduction

Giant cell tumor (GCT) of bone is a common primary benign tumor; however, it has aggressive behavior and sometimes leads to pulmonary metastasis [1, 2]. GCT generally arises from the epiphyseal region. To reduce local recurrence and preserve the adjacent joint, a variety of adjuvant treatments using phenol, liquid nitrogen, high-speed burr, or methyl methacrylate cement have been advocated by various authors [3–12]. These reports have shown that adjuvant treatment may contribute to the prevention of local recurrence (0–34%) [3–12] compared with treatment without adjuvants (12–52%) [6, 7, 13, 14]. The incidence of local recurrence, lung metastasis after treatment of primary GCT, and malignant transformation have been described [1, 2, 6, 7, 13–16]. However, the clinical behavior of recurrent GCT, treatment strategy, and the factors affecting clinical outcome have not been fully elucidated [17–22]. In this multi-center study by the Eastern Asian Musculoskeletal Oncology Group (EAMOG), we retrospectively investigated the prognosis for 110 patients with recurrent GCT of bone in the extremities, and we examine the potential factors affecting the clinical outcome of these patients.

Patients and methods

Data were collected from the 9 cancer centers and university hospitals that participate in the EAMOG. A total of 562 patients with GCT of bone in the extremities were treated from April 1996 to December 2004, and 119 patients were identified with recurrent GCT. Forty-one of 119 patients were initially treated outside hospitals and referred to an EAMOG institution after developing a recurrence of GCT, so local recurrence after initial treatment at an EAMOG institution was 15.0% (78 of 521 patients). Two patients were excluded because the follow-up period was less than 12 months, and 7 patients were excluded because they lacked histological confirmation of recurrent GCT. This left 110 patients to form the cohort for this study.

The inclusion criterion was histologically proven recurrent GCT of bone in the extremities. Data regarding age, gender, location, Campanacci grade [21], initial treatment, venue of initial treatment, time to local recurrence, treatment of recurrence, number of recurrences, distant metastasis, malignant transformation, term of follow-up, and outcome were collected by questionnaire.

We divided the patients into 2 groups depending on the anatomical site of disease: Site A included the distal radius, proximal humerus, proximal femur, distal femur, proximal tibia, and distal tibia; Site B included the ulna, fibula, and talus (Table 1). Site A is adjacent to major joints, including the wrist, shoulder, hip, knee, and ankle: Site B includes all other joints.

Median interval from initial surgery to first recurrence was compared between the single recurrence group and the repeat recurrence group (more than two recurrences). Metastasis-free survival was defined as the time from initial diagnosis to metastasis, analyzed using the Kaplan–Meier method, and the log-rank test was used to compare the survival curves for univariate analysis. The unpaired *t* test and the chi-squared test were used to determine the factors affecting repeat recurrence and preservation of the adjacent joint. Statistical significance was defined as $p \leq 0.05$. Data were analyzed with SPSS for Windows (version 11.0; SPSS, Chicago, IL, USA).

Because this was a multicenter retrospective study, there was no randomization of the surgical procedure for recurrent GCT. The treatment procedure was decided by the surgeons at each of the participating centers.

Complete informed consent was obtained from each patient or appropriate family member. Institutional review board approval was obtained from the centers of the primary investigators.

Results

There were 60 males and 50 females; the median age was 30.5 years (range 11–75 years) and the median follow-up

Table 1 Distribution of anatomical site

	No. of cases	Percentage
Site A		
Humerus/proximal	5	4.5
Radius/distal	16	14.5
Femur/proximal	6	5.5
Femur/distal	36	32.7
Tibia/proximal	37	33.6
Tibia/distal	3	2.7
Site B		
Ulna/distal	2	1.8
Fibula/proximal	3	2.7
Tarus	2	1.8
Total	110	

period 56 months (range 14–290 months). The anatomical locations were the upper extremity in 23 patients and the lower extremity in 87 patients (Table 1). One-hundred and three patients were included in the Site A group, 7 in the Site B group (Table 1). Site A was further divided into 2 groups: 66 patients who had primary treatment at an EAMOG institution (Group P) and 37 patients who were initially treated at outside hospitals and referred to an EAMOG institution after developing recurrence of GCT (Group R). At the time of diagnosis of the primary lesion, 90 patients were graded according to the Campanacci grading system (76 patients from Site A and 14 patients from Site B) [21]: Grade I in 10 patients, Grade II in 37 patients, and Grade III in 43 patients. Surgical curettage with adjuvant treatment was performed initially in 96 patients and en-bloc resection was performed in 14 patients. Of the patients in the latter group, the adjacent joint was sacrificed in 11 patients. The type of adjuvant treatment included liquid nitrogen, high-speed burr, bone cement, phenol, or a combination of these.

The median interval between initial surgery and first recurrence was 16.0 months (range 2–180 months). For Group P, the treatment of the second surgery was recurettage in 42 patients, en-bloc excision in 20 patients, amputation in 3 patients, and excision of soft tissue recurrence in 1 patient. For Group R, the treatment consisted of en-bloc excision in 22 patients, curettage in 14 patients, and amputation in 1 patient. The 7 patients with Site B disease were treated as follows: en-bloc excision in 5 patients, and amputation in 2 patients.

Twenty five patients (23.4%) developed a second recurrence and the other 3 patients developed malignant transformation. The success rate of the second surgery was 76.6% (82 of 107 patients). However, the incidence of second recurrence after recurettage with adjuvant treatment was 33.9% (19 of 56 patients). The treatment (third surgery) for the second recurrence was recurettage in 16 patients, en-bloc excision in 1 patient, amputation in 4 patients, and excision of soft tissue recurrence in 4 patients. Six patients developed a third recurrence, and the success rate of the third surgery was 76.0% (19 of 25 patients). The treatment (fourth surgery) for the third recurrence was recurettage in 1 patient, en-bloc excision in 4 patients, and excision of soft tissue recurrence in 1 patient; however, 1 patient experienced incomplete surgical results (Table 2).

The median interval between initial surgery and first recurrence for patients with repeat recurrences (14.1 months) was significantly shorter than the mean interval for patients with single recurrence (28.3 months, $p = 0.016$). The incidence of repeat recurrence was 10.0% in Grade I, 10.8% in Grade II, and 27.9% in Grade III. Campanacci grade did not correlate with repeat recurrence ($p = 0.446$) (Table 3). We also analyzed the correlation between number of recurrences and factors such as age, gender, tumor location, type of adjuvant for first recurrence, and type of grafted materials; however, we identified no other significant factor for repeat recurrence (Table 4).

Surgical recurettage was successful in preserving the adjacent joint in 49 patients. Success in preserving the adjacent joint in Group P (61.0%) was significantly higher than that in Group R (39.4%) (chi-squared test; $p = 0.046$, Table 2). Campanacci grades II and III correlated with rate of adjacent joint sacrifice compared with Grade I (Table 3).

During the follow-up period, lung metastasis was detected in 8 patients (7.5%) by chest computed tomography (CT); its overall incidence was 5.6% (31 of 550 patients). The incidence of lung metastasis ($p = 0.018$) was significantly higher in the repeat recurrence groups than in the single recurrence group (Fig. 1); however, the Campanacci grade of the lesion was not correlated with this incidence (Fig. 2). Lung metastases were treated by metastasectomy in 3 patients and metastatic GCT was histologically confirmed. The remaining 5 patients were managed by observation. All patients were alive at the time of last-follow-up (median 28 months, range 16–240).

Table 2 Treatment of local recurrence

Anatomic site	Initial surgery		Second surgery for first recurrence ($n = 110$)				Third surgery for second recurrence ($n = 25$)				Forth surgery for third recurrence ($n = 6$)			Joint preservation		
	Curettage	En-bloc	Curettage	En-bloc	Amp	STR	Curettage	En-bloc	Amp	STR	Curettage	En-bloc	STR	Yes	No	
A																
Group P	56	10	42	20	3	1	14	1	2	2	1	3	1	36	23	$p = 0.046$
Group R	33	4	14	22	1	0	2	0	2	2	0	1	0	13	20	
B	5	2	0	5	2	0	0	0	0	0	0	0	0			

Site A: humerus, radius, femur, tibia, Site B: ulna, fibula, talus

Group P: patients who had primary treatment at our group's institution

Group R: patients who were referred to our group's institution with a recurrence of GCT after undergoing treatment elsewhere

En-bloc, en bloc excision; Amp, amputation; STR, resection of soft tissue recurrence; Malig, malignant transformation

Table 3 Correlation between Campanacci grade and clinical outcome

	Campanacci grade			
	Grade I	Grade II	Grade III	
Single recurrence	9	33	31	Grade I vs. Grade II and III
Repeat recurrence	1	4	12	$p = 0.446$
Preservation of adjacent joint				
Yes	8	15	17	Grade I vs. Grade II and III
No	1	16	19	$p = 0.020$

Table 4 Correlation between factors and number of recurrences

Factor	Single recurrence	Repeat recurrence	Significance
Mean age	33.8	32.7	$p = 0.738$
Gender			
Male	44	14	
Female	39	10	$p = 0.645$
Tumor location			
Humerus/proximal	4	1	
Radius/distal	10	6	
Femur/proximal	6	0	
Femur/distal	28	7	
Tibia/proximal	27	10	
Tibia/distal	3	0	
Ulna/distal	2	0	
Fibula/proximal	3	0	
Tarus	2	0	$p = 0.496$
Second surgery for first recurrence			
Curettage	38	18	
Adjuvant			
Burr	16	7	
Burr + phenol	3	1	
Burr + PMMA	10	2	
Burr + phenol + PMMA	3	2	
PMMA	6	6	$p = 0.503$
Grafted materials			
Allograft or autograft	3	5	
Hydroxyapatite	11	7	
PMMA	23	6	
None	1	0	$p = 0.113$
En-bloc excision	39	6	
Amputation	5	1	
Soft tissue resection	1	0	

PMMA poly(methyl methacrylate)

Malignant transformation was detected in 3 patients only (2.7%); its overall incidence was 2.1% (12 of 562 patients). The diagnoses were low-grade osteosarcoma (Case 1), malignant fibrous histiocytoma (MFH, Case 2), and undifferentiated high-grade sarcoma (Case 3). They were initially graded as Campanacci grades II (Case 2) and III (Case 1 and 3). The histological findings of these patients showed that the malignant lesions excised juxtaposed with typical GCT lesion. All cases were diagnosed as malignant transformations at the time of second recurrence. The time from initial surgery to malignant transformation was 9, 56, and 60 months, respectively. All patients died of the subsequent lung metastasis 8, 12, and 2 months, respectively, after the diagnosis of malignant transformation.

Final status was as follows: NED (no evidence of disease), 98 patients; AWD (alive with disease), 6 patients; DOD (died of disease), 3 patients; DOC (died of other causes), 3 patients. Five of the 6 patients who were AWD

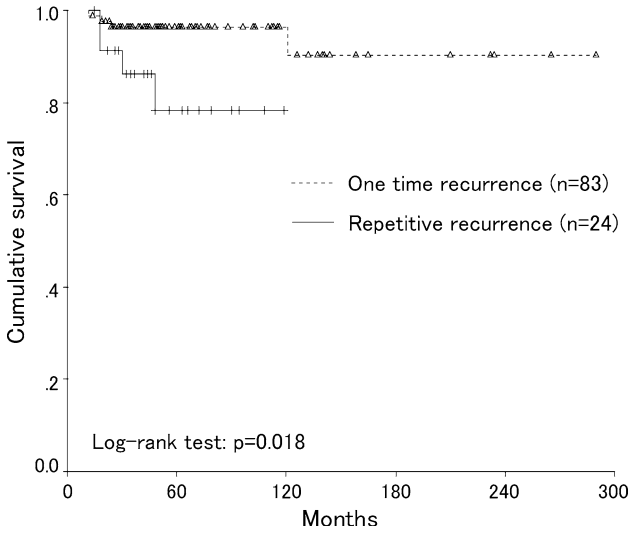

Fig. 1 Metastasis-free survival was significantly worse for patients who presented with repeat recurrence. Survival at 5 years was 96.3% for patients who presented with a single recurrence and 78.4% for patients who presented with repeat recurrences ($p = 0.018$)

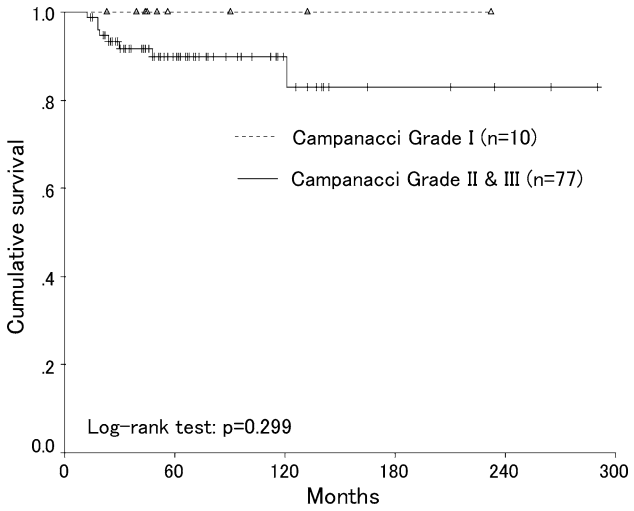

Fig. 2 Campanacci grade did not significantly affect metastasis-free survival. Metastasis-free survival at 5 years was 100% for patients with Campanacci grade I lesions and 89.9% for patients with Campanacci grade II and III lesions ($p = 0.299$)

had stable pulmonary metastasis but were free from disease at the primary site.

Discussion

In this study, we found that 98 of the 110 patients (89.1%) with recurrent GCT of bone were successfully rendered NED by further treatment. The adjacent joint (wrist, shoulder, hip, knee, ankle) was preserved in 48.5% of the patients who had received initial surgery with curettage. The initial treatment venue (Group R) was a risk factor for sacrifice of the adjacent joint. Early recurrence (less than 15 months after the initial surgery) was associated with repeat recurrence. The incidence of lung metastasis was significantly correlated with repeat recurrence. Lung metastasis was only detected in patients with Campanacci grade II in 3 patients and III in 5 patients, although no significant difference was observed in metastasis-free survival between Campanacci grade I and Campanacci grades II and III.

Treatment of recurrent GCT has been reported in several papers. Prosser et al. [17] performed repeat curettage after local recurrence of GCT in 43 cases, with 100% success in patients who had previously undergone curettage in the author's hospital, and 79.3% success in patients referred from elsewhere. They concluded that in most cases, except when the degree of soft tissue involvement precludes it, recurrence could be treated with curettage with a reasonable chance of success. They also stated that locally aggressive disease and multiple recurrence may be risk factors for the development of pulmonary metastasis.

Vult von Steyern et al. [19] reported that 13 patients with a total of 15 local recurrences were successfully treated by further curettage and cementation. Two of the patients with a second local recurrence were, consequently, treated twice. They concluded that local recurrence of GCT after curettage and cementation in the long bones can generally be successfully treated by further curettage and cementation, with only a minor risk of increased morbidity.

In larger studies, Balke et al. [20] and Becker et al. [21] mentioned the importance of combining thorough curettage with adjuvant treatment, for example high-speed burr, PMMA, or phenolization, even for recurrent GCT. Balke et al. [20] reported they reduced re-recurrence from 58.8% in a no adjunct group to 21.7% in an all-adjuncts (PMMA + burring) group. In this study, second recurrence after recurettage with adjuvant treatment was 33.9%; this could stand comparison with other reported results.

McGough et al. [22] treated 45 cases of recurrent GCT. They divided the patients into 2 groups: those who had their first surgery at the author's institution (23 patients), and those who had been referred from other institutions after the development of local recurrence (22 patients). The former group was salvaged by a repeat curettage ($n = 12$) or en-bloc osteoarticular resection ($n = 10$) for bone recurrence and wide local excision for soft tissue recurrence ($n = 1$). The latter group was salvaged by repeat curettage ($n = 7$) or en-bloc osteoarticular resection ($n = 15$) for bone recurrence. They concluded that incomplete initial surgery, a delay of more than 6 months in the diagnosis of recurrence, and subchondral recurrence of the tumor were factors that contributed to the failure to preserve the joint.

In our study, 43 of 110 patients eventually required amputation, prosthetic replacement, or arthrodesis.

Although the indications of these procedures were not unified in each center, the venue of the initial treatment (Group R) was a risk factor for adjacent joint sacrifice. We also found a significant correlation between Campanacci grades II and III and adjacent joint sacrifice. Balke et al. [20] reported that 70% of local recurrence occurred within the first 2 years after initial treatment, and they recommended short-term monitoring by X-ray or MRI. In this study, median interval from initial surgery to first recurrence was 16.0 months and 69% of recurrence occurred within 24 months. We consider it important to detect recurrence earlier, by careful follow-up, before the chance of recurettage is lost.

The Campanacci classification was used to grade these tumors radiologically as Grades I, II, and III [23]. Proccer et al. [17], O'Donnell et al. [8], and Rock [24] reported a correlation of recurrence with Grade III tumors. In this study, we focused only on recurrent GCT patients. Therefore, we could not assess the correlation of Campanacci grade with recurrence for the initial surgery on all GCT patients.

The mechanism of metastasis of GCT is unknown. Some authors have hypothesized that permeation of GCT cells locally into vessels may cause some emboli to escape and be lodged in the pulmonary parenchyma and, thus, remain viable [25]. Other authors have found no correlation between vascular invasion and dissemination of benign GCT of bone [15, 26]. The natural history of metastatic lesions is unpredictable. Some patients have relentlessly progressive pulmonary disease while others have a more indolent course. In some cases the metastasis has remained static for many years whereas in a few rare cases complete spontaneous regression of disease has been observed [13, 15, 16].

In this study, 8 patients (7.5%) developed lung metastasis. This incidence of lung metastasis seems high compared with previously reported incidence in a general GCT population (approximately 3%) [17, 18]. However, the cohort of patients in this study includes only those with recurrent GCT, and this may form a selection bias toward patients with a higher risk of metastasis. Moreover, repeat recurrence significantly correlated with subsequent lung metastasis ($p = 0.018$) and it might be a risk factor of subsequent lung metastasis. Three patients received metastasectomy, and 5 patients were controlled conservatively. All were still alive at last follow-up (3 patients NED, 5 patients AWD but free from disease at the primary site) after a median follow-up period of 28 months (16–240 months).

It has been reported that most cases of malignant transformation of GCT occurred after radiation treatment, and that high-grade malignant transformation without previous irradiation is very rare [27]. Bertoni et al. [28] reported 6 cases of post-surgical secondary malignant GCT without previous irradiation. They also mentioned that the average time between benign GCT and sarcoma diagnosis for these patients was 18 years, much longer than the average time for patients who received previous radiotherapy (9 years). In this study, all three cases of malignant transformation occurred postsurgically without previous irradiation. The intervals were 9, 56 and 60 months, respectively. The interval for Case 1 in particular (9 months) was quite short compared with previously reported cases [28]. The 42-year-old woman with low-grade osteosarcoma in the distal radius had a recurrence 6 months after the initial surgical curettage at a non-EAMOG affiliated hospital; this was treated by en-bloc excision. Three months after treatment of the recurrence, a second recurrence was detected and treated by wide excision. Histological examination showed low-grade osteosarcoma with typical benign GCT, so postoperative radiotherapy (56 Gy) was performed. Although the initial pathologic slides were carefully reexamined, no malignant cells were detected. The patient died with subsequent lung and bone metastases 8 months after the final surgery. The etiology of malignant transformation of GCT is unknown. Sakkers et al. [29] proposed a noteworthy theory regarding the malignant transformation of GCT treated by curettage and bone grafting. In this study, all cases of malignant transformation were initially treated by curettage and bone grafting.

The limitation of this study is that it was a multicenter retrospective study and there was no randomization of surgical procedures. Thus, the surgery (recurettage or en bloc excision) was not the same in each center. The final decision of the type of surgery was made by the surgeon at each institution.

In conclusion, time to recurrence (less than 15 months) was associated with multiple local recurrence. Multiple local recurrence also correlated with lung metastasis. Recurettage could preserve the adjacent joints, but with a risk of further recurrence. Recurrence can still occur after en-bloc excision, even if there is a lower chance than after an intralesional procedure. This suggests that recurettage with meticulous adjuvant treatment to completely preclude recurrent lesions is a reasonable method for preserving the adjacent joint. However, continuous careful follow-up is mandatory.

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Conflict of interest The authors indicate no potential conflicts of interest.

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