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

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Original Article

The prognostic factors of recurrent GCT: A cooperative study by the Eastern Asian Musculoskeletal Oncology Group (EAMOG)

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Running title: Prognostic factors of recurrent GCT

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ABSTRACT

BACKGROUND: Giant cell tumor (GCT) of bone is a common primary benign tumor that has a high local recurrence rate and has the potential of 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 (EAMOG). The factors that affected the number of recurrences and distant metastasis were analyzed.

RESULTS: The median interval between initial surgery and 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 repetitive recurrence groups (two and three recurrences) and 28.3 months for the single recurrence group ($p = 0.016$). Campanacci Grade did not correlated with repetitive recurrences ($p = 0.446$). The venue of the initial surgery did not correlate with recurrence but did affect preservation of the adjacent joint (chi-square test; $p = 0.046$). Campanacci Grade II & III also correlated with the sacrifice of 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. Repetitive recurrences were associated with lung metastasis ($p = 0.018$).

CONCLUSIONS: Early local recurrence of giant cell tumor is a risk factor for repetitive recurrences. Repetitive recurrences also correlate 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 exhibits aggressive behavior and sometimes develops 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 methylmethacrylate 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 to 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 the clinical outcome has not been fully ellucidated[17–22]. In this multi-center study by the Eastern Asian Musculoskeletal Oncology Group (EAMOG), we retrospectively investigate 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 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 the local recurrence rate 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 the current 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 repetitive recurrence (more than two recurrences) group. Metastasis-free survival was defined as the time interval 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. Unpaired t-test and the chi-square test were used to determine the factors influencing repetitive recurrence and the preservation of adjacent joint. Statistical significance was defined as $p \leq 0.05$. Data were analyzed with SPSS for Windows (version 11.0; SPSS Inc., Chicago, IL, USA).

Since this was a multicentr retrospective study, there was no random protocol of the surgical procedure for the recurrent GCT. The treatment procedure was decided by the surgeons at each of the participating centers.

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

RESULTS

There were 60 males and 50 females, with a median age of 30.5 years (range 11–75 years) and a median follow-up period of 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 three patients were included in site A, and 7 patients in site B (Table 1). Site A was further divided into 2 groups: 663 patients who had primary treatment at EAMOG institution (Group P) and 37 patients who were initially treated at outside hospitals and referred to an EAMOG institution after developing a 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 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 modalities.

The median interval between the initial surgery and the 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 rate 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 the initial surgery and the first recurrence for patients with repetitive recurrences (14.1 months) was significantly shorter than the mean interval for patients with a single recurrence (28.3 months, p = 0.016). The rate of repetitive recurrence was 10.0% in Grade I and 10.8% in Grade II, and 27.9% in Grade III. Campanacci grade did not correlated with repetitive 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 repetitive recurrence (Table 4).

Surgical recurettage was successful in preserving the adjacent joint in 49 patients. The success rate of preserving the adjacent joint in Group P (61.0%) was significantly higher than that in Group R (39.4%) (chi-square test; p = 0.046, Table 2). The Campanacci grade II & III correlated with the rate of adjacent joint sacrificing compared to 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). There was a significant higher incidence of lung metastasis (p = 0.018) in the repetitive recurrence groups compared to the single recurrence group (Figure 1); however, the Campanacci grade lesion was not correlated with this incidence (Figures 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).

Malignant transformation was detected in only 3 patients (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), respectively. They were initially graded as Campanacci Grade II (Case 2) and III (case 1 and 3). The histological findings of these patients showed that the malignant lesions excisted juxtaposed with typical GCT lesion. All cases were diagnosed as malignant transformations at the time of second recurrence. The durations from initial surgery to malignant transformation were 9, 56 and 60 months, respectively. All patients died of the subsequent lung metastasis in 8, 12, and 2 months after the diagnosis of malignant transformation.

The 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 had stable pulmonary metastasis but were free of 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 still preserved in 48.5% of the patients who had received an initial surgery with curettage. The initial treatment venue (Group R) was a risk factor for sacrificing the adjacent joint. Early recurrence (less than 15 months after the initial surgery) was associated with repetitive recurrences. The incidence of lung metastasis was significantly correlated with repetitive recurrences. The lung metastases was only detected in the patients with Campanacci Grade II in 3 patients and III in 5 patients, although no significant difference was observed in the metastasis-free survival between Campanacci Grade I with Grade II & III.

The treatment of recurrent GCT treatment has been reported in several previous papers. Prosser et al.[17] performed repeat curettage after the local recurrence of GCT in 43 cases with a 100% success

rate in patients who had previously undergone curettage in the author's hospital, and a 79.3% success rate in patients referred from elsewhere. They concluded that in most cases recurrence or the degree of the 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 recurrences 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 the 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 the larger study, Balke et al.[20] and Becker et al.[21] mentioned that the importance of combination treatment of thorough curettage with adjuvant treatments such as high-speed burr, PMMA, or phenolization even when they were recurrent GCT. Balke et al.[20] reported that they could reduce the re-recurrence rate from 58.8% in no adjunct group to 21.7% in all adjuncts (PMMA + burring) group. In this study, second recurrence rate after recurettage with adjuvant treatment was 33.9%, it could stand comparison with other reported rate.

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 a 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 present 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 that the significant correlation with Campanacci Grade II & III and the 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 controls 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 through a careful follow-up before the chance to 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 effect of Campanacci grade upon the recurrence rate for the initial surgery in all GCT patients.

The mechanism for metastasis of GCT is still 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 have remained static for many years, while 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. The incidence of lung metastasis seems to be high compared to the previously reported incidence in a general GCT population

(approximately 3%)[17, 18]. However, the cohort of patients in this study includes only those patients with recurrent GCT, and this may form a selection bias towards patients with a higher risk of metastasis. Moreover, repetitive 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 are still alive at last follow-up (3 patients NED, 5 patients AWD but free of disease at the primary site) after a median follow-up period of 28 months (16–240 months).

Malignant transformation of GCT was reported that most cases occurred after radiation treatment and high-grade malignant transformation without prior irradiation were very rare.[27] Bertoni F et al.[28] reported 6 cases of post surgical secondary malignant GCT without prior irradiation. They also mentioned that the average interval between benign GCT and sarcoma diagnosis of these patients was 18 years, much longer than the average interval observed in patients who received previous radiotherapy (9 years). In this study, all of three cases of malignant transformation occurred postsurgically without prior irradiation. The intervals were 9, 56 and 60 months, respectively. The interval for Case 1 in particular (9 months) was quite short compared to 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 (56Gy) 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 remains 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 this study was a multicenter retrospective study and had no randomization protocol of surgical procedures. Thus, the indication of the surgery (recurettage or *en bloc* excision) was not same in each center. The final decision of the type of surgery was made by the surgeon of each institution.

In conclusion, time to recurrence (less than 15 months) was associated with multiple local recurrences. Multiple local recurrences also correlated with lung metastasis. Recurettage could preserve the adjacent joints, however, it still has 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, a continuous careful follow-up is mandatory.

The authors indicate no potential conflicts of interest.

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FIGURE LEGENDS

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

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

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骨巨細胞腫再発例の臨床成績に影響を及ぼす予後因子の解析：東アジア骨軟部肉腫治療研究会多施設共同研究（**Eastern Asian Musculoskeletal Oncology Group: EAMOG**）

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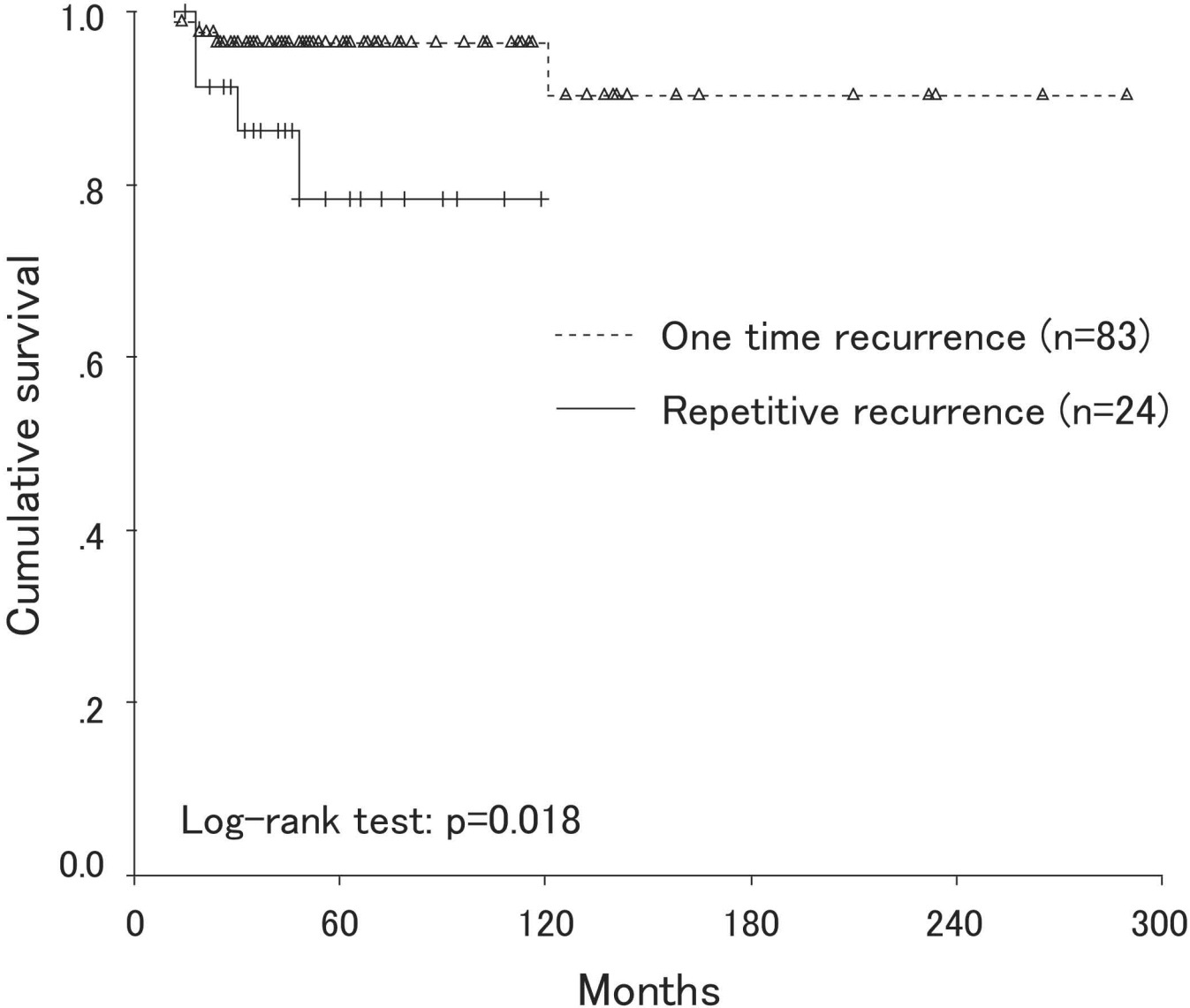
【目的】骨巨細胞腫（以下、GCT）は骨端部に好発する良性腫瘍であるが、再発率が高くまた転移や悪性転化をきたすことがある。関節近傍に発生するため初回治療は関節を温存することを目的に、徹底的な掻爬とフェノールや液体窒素などの補助療法を併用した手術が行われことが多い。しかし、再発した GCT の臨床経過、治療方針、また臨床経過に影響を及ぼす因子の解析は十分になされていない。本研究の目的は、四肢に発生し再発した GCT の臨床成績とそれに影響を及ぼす因子を検討することである。
【対象と方法】東アジア骨軟部肉腫治療研究会（Eastern Asian Musculoskeletal Oncology Group: EAMOG ）に所属する施設で治療された 110 例の四肢の GCT 再発例を対象とし、再発の回数、隣接関節の温存率、遠隔転移、そして悪性転化の発生率とそれらに影響を及ぼした因子の解析を行った。
【結果】初回治療から再発までの平均期間は 16 ヶ月（2-18 ヶ月）であった。全例が再発に対して追加の手術を施行されたが、25 例は 2 回目の再発をきたし、さらに 6 例は 3 回目の再発をきたした。初回の再発までの期間が、再発回数が 1 回であった群（28.3 ヶ月）と多数回の再発（2 回以上）の群（14.1 ヶ月）で有意な差をみとめた（p=0.016）。Campanacci 分類は、再発の回数と相関しなかった

（p = 0. 446）。初回治療が行われた施設（腫瘍専門施設かそれ以外の施設）は、再発の回数に影響を及ぼさなかったが、隣接関節の温存率は、初回治療が腫瘍専門施設で行われた群において有意に高かった（p=0.046）。さらに、Campanacci 分類の Grade II と III は、隣接関節の温存率が Grade I よりも有意に低かった（p = 0.020）。肺転移は、悪性転化を除く 107 例中 8 例（7.5%）にみとめ、悪性転化は、110 例中 3 例（2.7%）にみとめた。多数回の再発（2 回以上）は、肺転移と有意に相関していた（p = 0.018）。

【結語】GCT の初回術後早期の再発（14 ヶ月以内）は、多数回の再発の危険因子である。また、多数回の再発は、肺転移の危険因子でもある。再発病巣に対する種々の補助療法を併用した再掻爬術と隣接関節の温存は、妥当な術式であるが、さらなる慎重な経過観察がなされるべきである。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0.0
Cumulative survival
One time recurrence (n=83)
Repetitive recurrence (n=24)
Log-rank test: p=0.018
0
60
120
180
240
300
Months

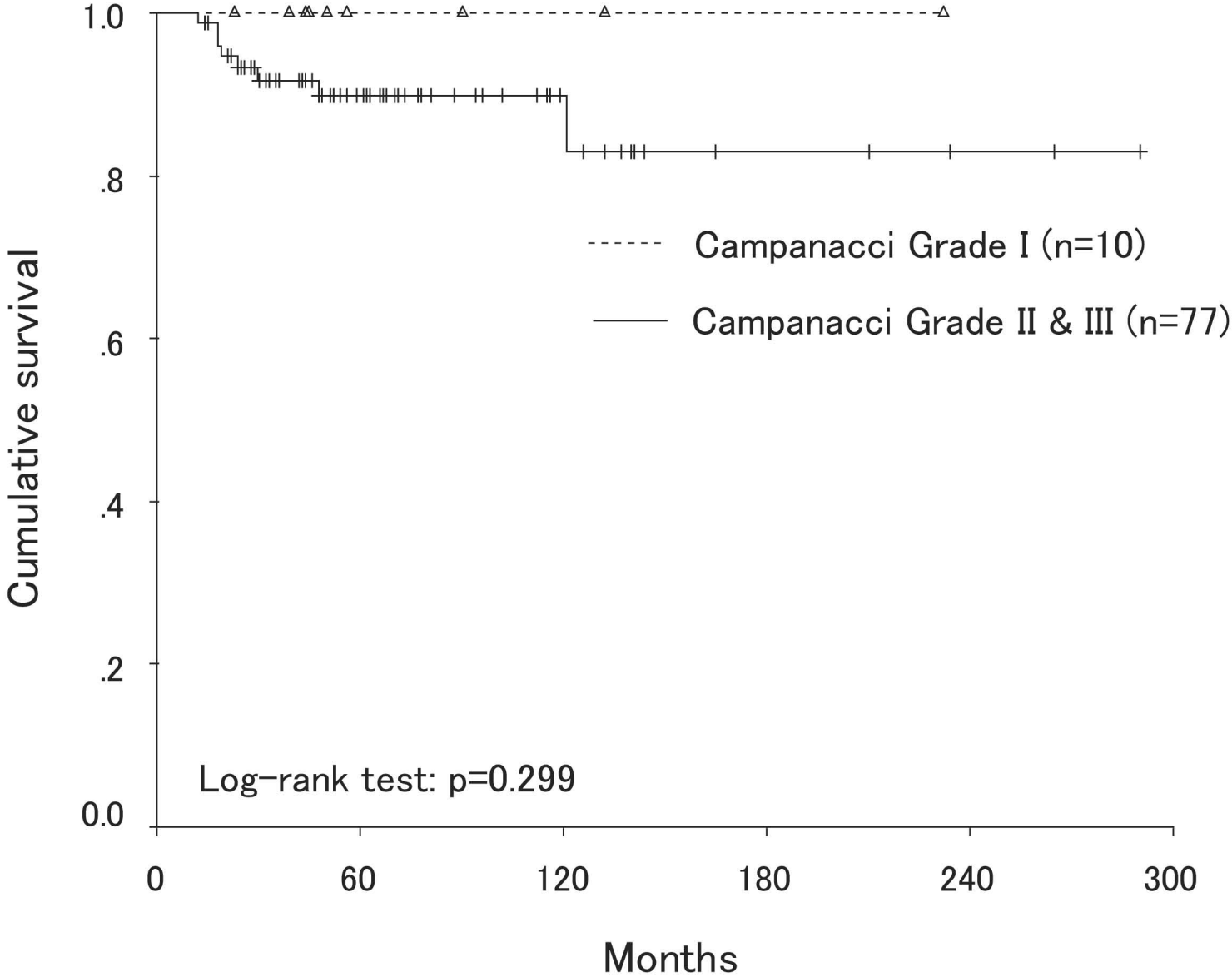
1.0
.8
.6
.4
.2
0.0
Cumulative survival
Campanacci Grade I (n=10)
Campanacci Grade II & III (n=77)
Log-rank test: p=0.299
0
60
120
180
240
300
Months

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	

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		
		Cure-ttage	En-bloc	Cure-ttage	En-bloc	Amp	STR	Cure-ttage	En-bloc	Amp	STR	Cure-ttage	En-bloc	STR	Yes	No	
A	Group P	56	10	42	20	3	1	14	1	2	2	1	3	1	36	23	
	Group R	33	4	14	22	1	0	2	0	2	2	0	1	0	13	20	p=0.046
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	
One time recurrence	9	33	31	Grade I VS Grade II & III P=0.446
Repetitive recurrence	1	4	12	
Preservation of adjacent joint				
yes	8	15	17	Grade I VS Grade II & III P=0.020
no	1	16	19	

Table 4. Correlation between factors and number of recurrences

Factor	One time recurrence	Repetitive 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	
Hydroxiapatite	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: Polymethylmethacrylate