

Factors of Local Recurrence of Giant Cell Tumor of Long Bone after Treatment: Plain Radiographs, Pathology and Surgical Procedures

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Background: To evaluate the relationship between local recurrence of giant cell tumor (GCT) after surgical treatments and plain radiography, pathology grade and surgical procedures.

Material and Method: Patients with pathologically proven primary giant cell tumor of long bones, who underwent surgical treatment in Siriraj Hospital between 1995 and 2007, were retrospectively reviewed. Plain radiographic findings were reviewed by an experienced musculoskeletal radiologist without knowledge of the clinical history or pathologic results. Specific attention on plain radiographic evaluations included site of tumor in long bone, total tumor volume, expansion of cortex, breaking of cortex, and presence of pathological fracture. Patients with grade III tumor were excluded due to malignant histology. Patients received treatments with amputation were also excluded due to no possibility of tumor recurrence. Only patients who received surgical treatments with wide excision or curettage with cement were included in the present study. Univariate analysis and Cox proportional hazard ratio was used to evaluate the influence of plain radiographic findings and histology grade on risk of tumor recurrence.

Results: Seventy-four patients participated in this study and included 32 males (43%) and 42 (57%) females with a mean age of 35 years (range 17 to 84). The median follow-up time was 3.2 years. Forty-eight patients (65%) underwent curettage with cement or bone graft and 26 patients (35%) underwent wide excision. Sixty-three patients (85%) did not develop tumor recurrence while 11 patients (15%) developed local recurrent tumor. Those occurred only in patients who underwent curettage with cement or bone graft. None of the patients who underwent wide excision developed local recurrence. Median of time after operation to recurrence was 3.5 years (range, 0.5 to 10.3 years). Local recurrence occurred in the distal femur in five patients (45%), in the proximal tibia in five patients (45%), and in distal radius in one patient (9%). Risk of local recurrence of GCT was not statistically different in patients with any abnormal features of plain radiography as well as histology grade.

Conclusion: No radiographic findings and histological grade of GCT can predict tumor recurrence after curettage procedure. Compared with wide excision, risk of local recurrence in patients that received treatment with curettage was significantly higher. However, the choice of treatment should be balanced between preserving maximal joint function and risks of tumor recurrence.

Keywords: Giant cell tumor; Long bone; Local recurrence; Plain film; Radiography

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Giant cell tumor (GCT) is one of the commonest benign bone tumors, which are composed of undifferentiated cells containing multinucleated giant cells that were formed from the fusion of mononuclear cells. The reported incidence of GCT in

Southeast Asia is higher than that in the West, about 20% of primary bone tumor compared to 4-5% in the West^(1,2). They are a slightly more common in females with a peak incidence at age group of 20-40 years old⁽³⁾. In general, GCT is a usually solitary and locally aggressive tumor that occurs predominantly in long bones. A common presentation involves pain in the area of the lesion as well as associated swelling and tenderness to palpation. On radiography, lesions appear mostly lytic, lucent and eccentrically located

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within the epiphysis. In sixty percent of cases, the lesion was localized in the long bone around the knee^(4,7). In a very rare instance, it can present with pulmonary metastasis or malignant transformation such as osteosarcoma or fibrosarcoma⁽⁸⁻¹¹⁾.

The main treatment method for GCT is surgery, which includes curettage with cement or bone graft, wide excision and amputation. For treatment with amputation and wide excision, total tumor removal is usually adequate with a low rate of tumor recurrence. However, after wide resection or amputation, quality of life of patients is unfavorable because the joint function cannot return to normal activity. In contrast, curettage can preserve normal organ and function; however, tumor control rate may not be favorable. The previous studies described the treatment of GCT of the long bones with curettage and cement packing and specific attention of histology grade, which has been largely discounted as having any relationship to local recurrence of GCT⁽⁴⁾. Currently, there are limited data that correlated risk of local tumor recurrence with plain radiographic findings, histology grade and surgical procedures. The present study aimed to evaluate whether any abnormal plain radiographs, pathological grade of GCT and surgical procedures can predict the risk of local tumor recurrence.

Material and Method

Patients

All patients with pathologically proven primary giant cell tumor of long bones, who underwent surgical treatment in Siriraj Hospital between 1995 and 2007, were retrospectively reviewed. In each patient, the definite diagnosis was made on the basis of pathological results after surgery. Tumors were graded into three grades as grade I, grade II, and grade III by using pathological grade described by Jaffe et al (Table 1). Surgical treatments were classified into three groups; 1) curettage with cement or bone graft, 2) wide excision, and 3) amputation. All of the operations had been performed by three surgeons who

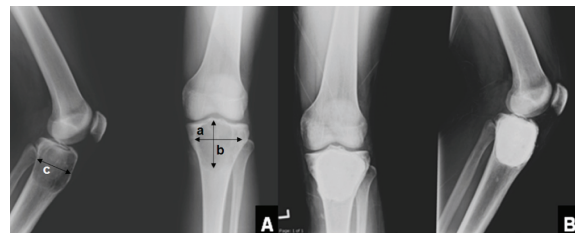


Fig. 1 A) Tumor volume was calculated by the volume of an ellipsoid formula ($4/3 abc/8$), where a, b, and c are the maximal three diameters. B) Plain radiography after surgery

had the experience of surgery for 25 years, 14 years and 5 years respectively. All patients with available clinical data, plain radiographs, histological results and at least 24 months follow-up data after surgical treatment were enrolled in the present study. Exclusion criteria included patients who have the malignant nature of the tumor established by pathological grade (grade III) or newly developed other metastases at clinical follow-up. Only patients who received surgical treatments with wide excision or curettage with cement were included. The patients who underwent amputation were excluded due to no possibility for tumor recurrence.

Imaging and imaging interpretation

All imaging studies in each patient were grouped together at the time of analysis. Plain radiographs were interpreted in a retrospective fashion by an experienced musculoskeletal radiologist without knowledge of the clinical history or pathologic results. The reviewer evaluated the presence or absence of individual imaging criteria. The following presentations in plain radiographs were evaluated with particular attention to site of tumor in long bone (proximal or distal), extension to metaphysis, total tumor volume, expansion of cortex, breaking of cortex and presence of pathological fracture. The tumor volume was calculated by the volume of an ellipsoid formula ($4/3 abc/8$), where a, b and c are the maximal three diameters (Fig. 1).

Table 1. Pathological grade of giant cell tumor by Jaffe et al

Tumor grade	Characteristics
Grade-I	has spindle-shaped stromal cells and few or no mitoses
Grade-II	constitutes a somewhat varied group, ranging from tumors in which the stromal cells show only slight atypism to those in which they are strikingly atypical.
Grade-III	has a large number of closely compacted anaplastic stromal cell presenting an irregular whorled arrangement, and tend to recur and metastasize

Statistical analysis

Categorical and ordinal data were described by frequencies. The age of the patients and the follow-up times were expressed as median and standard deviation with the minimum and maximum. The hazard ratio with 95% confidence interval (95% CI) for a recurrence was analyzed by univariate Cox regression, for various factors of plain radiograph presentation. The significance level was set at $p < 0.05$.

Results

Patients' characteristics, plain radiographic findings, and type of surgery are shown in Table 2. Of 74 patients, there were 32 males (43%) and 42 (57%) females with a mean age of 31 years (range 17 to 84 years). Forty-eight patients (65%) underwent curettage with cement or bone graft and 26 patients (35%) underwent wide excision. There were no differences in baseline characteristics and radiographic findings in both treatment groups, except cortical expansion, which was found higher in patients who received

wide excision. The median follow-up time was 3.2 years (range 0.5 to 10.3 years). Overall, 11 patients (15%) developed recurrent tumor. There were 63 patients (85%) in the group without recurrence (Fig. 2). The mean age was 36.4 years (range, 17 to 84 years) in those without tumor recurrence and 26.9 years (range, 17 to 52 years) in those with tumor recurrence.

Characteristics of individual patients with local tumor recurrence are shown in Table 3. There were three men and eight women with median age of 23 years. Of 48 patients who underwent curettage with cement or bone graft, 22.9% (11/48) of patients developed local tumor recurrence. None of the patients who underwent wide excision developed local tumor recurrence. Site of local recurrence occurred in the distal femur in five patients (45%), in the proximal tibia in five patients (45%), and in distal radius in one patient (9%) (Fig. 3, 4). In six of 11 (54%) patients, local recurrence occurred within two years after operation. Two patients (cases 2 and 4 in Table 3) developed second local recurrence after

Table 2. Patients' characteristics, plain radiographs and type of surgical treatment

	Curettage (n = 48)	Wide excision (n = 26)	Total (n = 74)
Gender - M:F	21:27	11:15	32:42
Age (years) [median (SD, range)]	34 (14.9,17-84)	31.5 (11.8,19-69)	31 (14,17-84)
Tumor location			
Femur - proximal	1 (2%)	2 (8%)	3 (4%)
- distal	28 (58%)	2 (8%)	30 (40%)
Fibular - proximal	0	3 (12%)	3 (4%)
Humerus - proximal	0	6 (23%)	6 (8%)
Phalange - proximal	0	1 (4%)	1 (1%)
Radius - distal	2 (4%)	8 (31%)	10 (14%)
Tibia - proximal	16 (33%)	2 (8%)	18 (24%)
- distal	1 (2%)	0	1 (1%)
Ulnar - distal	0	2 (8%)	2 (3%)
Pathological fracture			
No	30 (63%)	15 (58%)	45 (61%)
Yes	18 (37%)	11 (42%)	29 (39%)
Cortical expansion			
No	15 (31%)	2 (8%)	17 (23%)
Yes	33 (69%)	24 (92%)	57 (77%)
Cortical breaking			
No	29 (60%)	9 (35%)	38 (51%)
Yes	19 (40%)	17 (65%)	36 (49%)
Volume (mL) [median (SD, range)]	143 (219.2, 8.3-1503.9)	81.3 (249.1, 12.8-1162.2)	115.2 (244.4, 8.3-1503.9)
Pathology grade			
Grade I	26 (54%)	15 (58%)	41 (55%)
Grade II	22 (46%)	11 (42%)	33 (45%)
Median follow-up time to recurrence (years)	3.5	2.3	3.2

Table 3. Characteristics of individual patients with local tumor recurrence*

No.	Sex	Age (yrs)	Bone	Site	Patho. fracture	Cortical expansion	Cortical breaking	Tumor vol. (mL)	Patho grade	Time to recurrence (yrs)
1	F	19	Femur	Distal	No	Yes	Yes	237.6	1	1.0
2	M	31	Femur	Distal	No	Yes	No	89.7	1	4.1
3	F	34	Femur	Distal	No	Yes	No	147.1	1	5.3
4	F	21	Femur	Distal	No	Yes	No	258.1	2	10.3
5	F	52	Femur	Distal	Yes	Yes	No	182.2	2	1.2
6	M	23	Tibia	Prox.	No	No	No	38.4	1	3.5
7	F	20	Tibia	Prox.	No	No	No	47.6	2	1.0
8	F	17	Tibia	Prox.	No	Yes	No	191.1	2	1.2
9	F	25	Tibia	Prox.	No	Yes	Yes	139.0	1	3.6
10	F	20	Tibia	Prox.	Yes	No	Yes	115.9	1	4.6
11	M	34	Radius	Distal	No	Yes	No	14.4	1	0.5

* All these 11 patients were received surgical treatment with curettage and cement

Patho. fracture = pathological fracture; Patho. grade = pathological grade; Tumor vol. = tumor volume



Fig. 2 Anteroposterior and lateral radiographs of a 42-year-old man who had a giant cell tumor of the right distal femur (pathological grade II) received treatment with curettage and cement with plate and screw fixation. A) Image before surgery showed geographic osteolytic lesion at meta-epiphysis with cortical expansion, no cortical breaking, no pathological fracture and total volume of the lesion of 193.6 mL. B) Follow-up image after surgery 2 years showed no evidence of recurrence

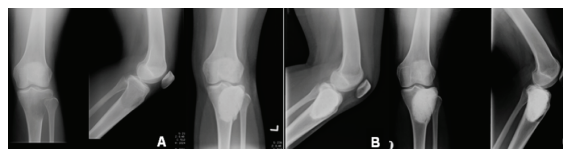


Fig. 3 Anteroposterior and lateral radiographs of a 20-year-old woman who had a giant cell tumor of the left proximal tibia (pathological grade II) received treatment with curettage with cement. A) Image before surgery showed geographic osteolytic lesion at lateral aspect of meta-epiphysis without cortical expansion, no cortical breaking, no pathological fracture, and total volume of the lesion of 47.6 mL. B) Follow-up image 1 month after surgery C) Follow-up image at 1 year after surgery showed lytic lesion at anteroinferior aspect of cement, with pathologically proven of recurrent bone tumor

first treatments at 0.83 and 2.3 years and were treated with wide excision.

Comparison of characteristics of patients with and without recurrence tumor who received surgical treatment with curettage and with cement is shown in Table 4. Median of time to recurrence after operation was 3.5 years (range, 0.5 to 10.3 years). Of 48 patients who underwent curettage with cement, pathological fractures were presented in 18 patients, of which local recurrence developed in two patients (11%). In 30 patients without pathological fracture, 30% (9/30) of patients developed local recurrence ($p = 0.17$). Local tumor recurrences in the patients with and

without cortical breaking were 15.8% (3/19) and 28% (8/29), respectively ($p = 0.40$). Local tumor recurrences in the patients with and without cortical expansion were 24.2% (8/33) and 20% (3/15), respectively ($p = 0.74$). Tumor volume in the non-recurrent group and in recurrent group was not significantly different (147.5 mL vs. 138.9 mL, $p = 0.22$). Local tumor recurrences in the patients with pathological grade I and grade II were 27% (7/26) and 18.2% (4/22) respectively ($p = 0.38$). Table 5 shows the univariate analysis with the Cox proportional hazard ratio to determine the influence of individually radiological features and pathological grade for risk of recurrence



Fig. 4 Anteroposterior and lateral radiographs of a 23-year-old man who had a giant cell tumor of the left proximal tibia (pathological grade I) received treatment with curettage with cement. A) Image before surgery showed geographic osteolytic lesion at lateral aspect of meta-epiphysis of left proximal tibia without cortical expansion, no cortical breaking, and no pathological fracture with total volume of the lesion of 38.4 mL. B) Follow-up image at 3.5 year after surgery showed geographic osteolytic lesion at medial aspect of tibial plateau with pathologically proven of recurrent bone tumor

tumor. In the patients who had cortical breaking on radiographs, pathological fracture, and pathological grade II, the hazard ratio for risk of recurrent tumor occurrence were 0.56 ($p = 0.40$), 0.34 ($p = 0.17$), 0.55 ($p = 0.38$), respectively. The authors found that there were no plain radiographic findings or pathology grade that can predict the local recurrence of tumor.

Discussion

Giant cell tumor of long bone is a benign bone tumors but it can be locally aggressive causing significant bony destruction, which commonly occurs at distal femur and proximal tibia^(4,7). It is slightly predominant in female patients with age range between 20-50 years old and rarely begins before the age of 15 or after 60⁽⁴⁾. GCT is likely to recur from its histological characteristics^(1,5,6). Tumor recurrence rate have been reported to vary 22-54%^(1,3,5,7,12-16) and the majority of recurrence usually occurs within the first two years. Local recurrence is higher in patients who received

Table 4. Comparison of characteristics of patients with and without recurrence tumor who received surgical treated with curettage and cement

	No recurrence (n = 37)	Recurrence (n = 11)	Total (n = 48)
Male:Female	18:19 (49%:51%)	3:8 (27%:73%)	21:27
Age (years) [median, mean (SD, range)]	34, 36.4 (14.9, 17-84)	23, 26.9 (10.3, 17-52)	34, 34.2 (17.9, 17-84)
Location			
Femur - proximal	1 (3%)	0	1
Femur - distal	23 (62%)	5 (45%)	28
Fibular - proximal	0	0	0
Humerus - proximal	0	0	0
Phalanx - proximal	0	0	0
Radius - distal	1 (3%)	1 (9%)	2
Tibia - proximal	11 (30%)	5 (45%)	16
Tibia - distal	1 (3%)	0	1
Ulnar - distal	0	0	0
Pathological fracture			
No	21 (57%)	9 (82%)	30
Yes	16 (43%)	2 (18%)	18
Cortical expansion			
No	12 (32%)	3 (27%)	15
Yes	25 (68%)	8 (73%)	33
Cortical breaking			
No	21 (57%)	8 (73%)	29
Yes	16 (43%)	3 (27%)	19
Volume (mL) [median (SD, range)]	147.5 (244.4, 8.3-1503.9)	138.9 (80.7, 14.4-258.1)	143.0 (219.2, 8.3-1503.9)
Pathology grade			
Grade I	19 (51%)	7 (64%)	26
Grade II	18 (49%)	4 (36%)	22
Median follow-up time to recurrence (years)	4.2	3.5	3.5

Table 5. Univariate analysis using the Cox proportional hazard ratio for the predictors of recurrence tumor

Parameters	HR (hazard ratio)	95% CI	p-value
Presence of cortical breaking	0.56	0.14-2.16	0.40
Presence of pathological fracture	0.34	0.07-1.61	0.17
Pathological grade II*	0.55	0.14-2.11	0.38

* Reference group = pathological grade I

only curettage, current treatment with extensive curettage and cementing results in a decrease in local recurrence rate to 15-25%. In the present study, the authors found the concordant results of demographics distribution of the GCT as previous studies^(1,4,5,7,12-16) and found that tumors at distal femur and proximal tibia had the higher rate of recurrence than the other site of long bone⁽⁷⁾. The overall incidence of local recurrence after the procedures of 15% in the present study was not different from those reported in larger series^(1,4,5,7). The present study demonstrated that tumor recurrence appeared to correlate with the surgical margin that was obtained. In patients who received treatment with intralesional curettage had tumor recurrence rate of 23% (11 of 48), while patients who received treatment with wide excision had no tumor recurrence. A difference in the recurrence rate after curettage and wide resection had also been reported in previous studies^(1,6,13), and it was regarded as a reflection of the adequacy of treatment.

The main treatment modality of GCT is surgery including curettage alone, curettage combined with adjuvant therapy (cryosurgery and bone cement or bone graft), wide section, and amputation. Wide excision has been recommended for tumors that have extended through the cortex into the soft tissue. However, wide resection of a tumor near a joint, results in relatively severe functional impairment compared to curettage⁽³⁾. It is only indicated in the lesion at proximal radius and fibula and distal ulna. The advantage of curettage with cement is better for preservation of the limb function than wide excision. Compared with curettage alone, curettage with cementing has some advantages including tumoricidal effect of the cement, extend the boundary of tumor kill by thermal effect (hyperthermia), immediate structural support allows for intensive curettage even of large tumors, and easier radiographic detection of tumor recurrence. For these reasons, curettage with cementing is more extensively used now than before, using both mechanical curettage and mechanical burr. Adequate

removal of tumor seems to be a more important predictive factor for the tumor recurrence than the use of adjuvant. The choice of surgical treatment should be balanced between reducing the incidence of local recurrence while preserving maximal function and quality of life.

Murphy et al⁽¹¹⁾ reported that recurrence of the tumor did not correlate with the tumor size and size of the giant cells but did have correlation with the number of mitoses and degree of nuclear irregularity. In the present study, the authors excluded patients with the malignant nature of the tumor established by pathological grade III or newly developed other metastases at clinical follow-up. The authors found that the local tumor recurrence did not correlate with histology grade and plain radiographic features including cortical breaking, pathological fracture, and total tumor volume. The present study emphasized that no plain radiographic findings and histology grade can predict local tumor recurrence as previous studies^(1,11-16). Though the median time to tumor recurrence was 3.5 years, a late recurrence up to 10 years was found. Therefore, long-term surveillance is needed in these patients. The present study does have some limitations, there was a small sample size, and the surgical procedures were performed by three surgeons who have different surgical experience.

Conclusion

In the present study, the authors found that no plain radiographic findings and histology grade of GCT that can predict tumor recurrence after curettage procedure. Compared with wide excision, risk of local recurrence in patients who received treatment with curettage was about 23%, which was significantly higher. Curettage with cement should be used in the aim of preserving maximal joint function with awareness of risks of tumor recurrence.

Potential conflicts of interest

None.

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ปัจจัยที่มีผลต่อการกลับเป็นซ้ำของ giant cell tumor ของกระดูกยาวๆ โดยใช้ลักษณะภาพถ่ายทางรังสี ผลพยาธิวิทยาและวิธีการผ่าตัด

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วัตถุประสงค์: เพื่อประเมินการกลับเป็นซ้ำของ giant cell tumor ของกระดูกยาวๆ หลังผ่าตัดโดยใช้ลักษณะภาพถ่ายทางรังสี ผลพยาธิวิทยาและวิธีการผ่าตัด

วิธีการวิจัย: เป็นการศึกษาย้อนหลังภาพถ่ายทางรังสีในผู้ป่วย giant cell tumor ของกระดูกยาวๆ ที่ได้รับการยืนยันการวินิจฉัยจากผลตรวจทางพยาธิวิทยา และได้รับการผ่าตัดที่โรงพยาบาลศิริราชระหว่างปี พ.ศ. 2528-2550 โดยรังสีแพทย์ที่เชี่ยวชาญด้านกระดูกและข้อต่อที่ประเมินจะไม่ทราบประวัติผู้ป่วยและผลตรวจทางพยาธิวิทยาของชิ้นเนื้อ โดยประเมินลักษณะภาพถ่ายรังสีต่อไปนี้ ตำแหน่งของเนื้องอกบนกระดูก ปริมาตรของเนื้องอก การขยายตัวของกระดูก การแตกหักและการหักจากพยาธิสภาพ เพื่อดูว่ามีปัจจัยใดหรือไม่ที่ช่วยทำนายการกลับเป็นซ้ำ ผู้ป่วยที่มีผลการตรวจทางพยาธิวิทยาเป็นเนื้องอก grade III และที่ได้รับการรักษาด้วยการตัดกระดูกยาวๆ จะถูกคัดออกจากการศึกษา การวิเคราะห์ทางสถิติใช้ Univariate และ Cox hazard ratio

ผลการศึกษา: ผู้ป่วยทั้งหมด 74 ราย อายุเฉลี่ย 35 ปีเป็นชาย 32 ราย หญิง 42 ราย ระยะเวลาติดตามเฉลี่ย 3.2 ปี มีผู้ป่วย 48 ราย (ร้อยละ 65) ได้รับการรักษาด้วยวิธี curettage with cement หรือ bone graft และผู้ป่วย 26 ราย (ร้อยละ 35) ได้รับการรักษาด้วยวิธี wide excision ในผู้ป่วยที่พบการกลับเป็นซ้ำ 11 ราย (ร้อยละ 15) ทั้งหมดได้รับการรักษาด้วยวิธี curettage with cement ส่วนในกลุ่มที่ได้รับการรักษาด้วยวิธี wide excision ไม่พบการกลับเป็นซ้ำเลย ระยะเวลาเฉลี่ยตั้งแต่หลังผ่าตัดจนถึงพบการกลับเป็นซ้ำประมาณ 3.5 ปี ส่วนใหญ่มักพบที่ตำแหน่ง distal femur (ร้อยละ 45) และ proximal tibia (ร้อยละ 45) ส่วน distal radius พบร้อยละ 9 การศึกษานี้ไม่พบความสัมพันธ์ของการกลับเป็นซ้ำของเนื้องอก และลักษณะภาพถ่ายทางรังสีหรือผลพยาธิวิทยา

สรุป: การศึกษานี้พบว่าไม่มีลักษณะภาพถ่ายทางรังสีและผลทางพยาธิวิทยาที่สามารถทำนายการกลับเป็นซ้ำของ giant cell tumor ของกระดูกยาวๆ การรักษาโดยวิธี curettage with cement โอกาสกลับเป็นซ้ำสูงกว่าวิธี wide excision อย่างไรก็ตามการเลือกวิธีการรักษาที่เหมาะสมต้องคำนึงถึงการสแกนการทำงานของรยางค์ให้มากที่สุดและโอกาสการกลับเป็นซ้ำ
