



Giant cell tumour of bone in the appendicular skeleton *An analysis of 276 cases*

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This retrospective study analyzed 276 cases of giant cell tumour of bone in the appendicular skeleton of patients first diagnosed and treated at the Orthopaedic Department of the West China Hospital in Sichuan University between 1988 and 2007. Fifty-eight percent of the tumours involved the knee region. The most common primary treatment was curettage (162 patients) combined with adjuvant local therapy. The effects of bone cement (PMMA), high-speed burring, electro-cauterization, liquid nitrogen, and phenol on the recurrence rate were also analyzed. The differences in local recurrence rates were analyzed between giant-cell tumours confined to bone (Campanacci grades I and II) and giant-cell tumours with extraosseous extension (Campanacci grade III) treated with intralesional curettage. The recurrence rate of patients who received the first treatment at our institution was 11.2%. Recurrence was observed in 31 cases and multiple recurrences were observed in 5 cases. Treatment included intralesional curettage (17.3%), marginal excision (14.3%), wide excision (1.9%), or radical resection (0%). Metastases, which mainly involved the lung, occurred in 6 cases (2.2%). There was a significantly lower recurrence rate ($p = 0.004$) following intralesional curettage combined with high-speed burring ($n = 102$) as compared with intralesional curettage without high-speed burring ($n = 60$). Although the efficacy of liquid nitrogen and electrocauterization did not reach significance, they seem to have a similar effect to high-speed burring. Therefore, we recommend high-speed burring as a necessary adjuvant therapy. The combination of all adjuvants (burring, liquid nitrogen, and electro-cau-

terization) is recommended as a standard treatment. Cement filling of the cavity after curettage was not widely used in this series, but its merits have been reported in several studies; we therefore recommend that cement filling should be added to the adjuvants to be used after burring, liquid nitrogen and/or electrocauterization.

Keywords : Giant cell tumor of bone ; local recurrence ; *en bloc* resection ; curettage.

INTRODUCTION

Although giant cell tumour of bone (GCTB) is generally considered a benign tumour, it is well known for its locally aggressive behaviour and its

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potential for recurrence after intralesional curettage or incomplete resection. In addition there is a risk of metastatic spread. The recurrence rate after intralesional curettage without adjuvant therapy has been reported to be 12-60% (1,4,14). Local recurrence is accompanied by an increased risk of so called “benign” pulmonary metastases (4,7,14,18,19), which has resulted in application of adjuvant therapies to minimize residual microscopic tumorous tissue, and prevent local recurrence after curettage, such as high speed burring, liquid nitrogen, phenol, alcohol, hydrogen peroxide, locally delivered chemotherapy, acrylic cement, radiation therapy, or embolization of the feeding vessels. The local recurrence rates have been reported to be controlled within 6-25% in GCTB patients treated with the various methods listed above (1,3,12,15,16,20,23,25).

This study reviewed the treatments and outcomes of patients first diagnosed and treated at the West China Hospital of Sichuan University, China from 1988 to 2008, for GCTB in the appendicular skeleton. Treatment consisted in intralesional curettage combined with adjuvant therapies, or en bloc resection. The efficiency of various adjuvant therapies regarding local recurrence was also evaluated.

PATIENTS AND METHODS

We analyzed 276 cases of GCTB in the extremities of patients first diagnosed and treated at the Orthopedics Department of the West China Hospital in Sichuan University (China) between 1988 and 2008. The diagnostics before treatment included plain radiographs of the involved region, local magnetic resonance imaging (MRI), nuclear scintigraphy, chest radiograph, and/or chest computed tomography (CT). The inclusion criteria included histologically confirmed giant cell tumour involving the extremities and a minimum of 25 months of follow-up for each patient. The term “multifocal” was used if two or more bones were involved at different anatomical locations. The surgical treatments for patients were divided into two categories: intralesional curettage and resection. Intralesional curettage was usually associated with local adjuvant therapy, including bone cement filling, high-speed burring, liquid nitrogen, alcohol, and electrocauterization. Resection surgery included marginal excision, wide excision, or radical resection. The patients were divided into two groups based on whether the GCTBs were confined to bone (Campanacci grades I and II) or

Table I. — Demographics of the patients

Age (years)	Male	Female	Total
0-10	2	0	2
10-18	8	11	19
18-20	5	8	13
21-30	64	48	112
31-40	44	27	71
41-50	14	19	33
51-60	10	7	17
61-70	4	4	8
71-90	1	0	1
Total	152	124	276

had an extraosseous extension (Campanacci grade III). The difference in recurrence rate between these two groups was analyzed. In addition, a comparison of the recurrence rate was performed based on different surgical treatments. Statistical analysis was performed with SPSS v15.0 (IBM, Inc., NY, USA). $p < 0.05$ was considered statistically significant which was determined using the chi-squared test of a four-fold table.

RESULTS

There were 152 male and 124 female patients in the study at a ratio of 1.23:1 (Table I). The mean age of the patients at the time that they received the treatment was 32.3 years (range: 9-80 years), and the mean follow-up was 64.2 months (range: 25-80 months). A total of 159 cases of GCTBs were located in the knee joint (57.6%, 159/276), and 116 of these cases were treated with intralesional curettage associated with local adjuvant therapy (Table II). There were 20 cases of GCTB that recurred, and the recurrence rate was 12.6% (20/159). These cases were treated with intralesional curettage associated with local adjuvant therapy.

Of the 276 cases analyzed, 162 patients were treated with intralesional curettage associated with local adjuvant therapy, and the other 114 patients were managed with resection. The overall recurrence rate was 11.2% (31/276), with multiple recurrences occurring in five cases. The recurrence rate for the treatment of intralesional curettage was 17.3% (28/162), which was significantly higher than that for patients treated with resection [intralesional

Table II. — Recurrence rates of giant cell tumour of bone related to tumour site

GCT Localization	Intralesional curettage		En bloc excision		Total		
	N-Rec. n	Rec. n	N-Rec. n	Rec. n	N-Rec. n	Rec. n	Total
Proximal Humerus	2	0	21	0	23	0	23
Distal Humerus	1	0	0	0	1	0	1
Proximal Radius	1	0	0	0	1	0	1
Distal Radius	2	2	15	1	17	3	20
Proximal Ulna	2	0	0	0	2	0	2
Distal Ulna	1	0	0	0	1	0	1
Carpus	0	1	0	1	0	2	2
Proximal Femur	15	4	17	1	32	5	37
Distal Femur	53	8	25	0	78	8	86
Proximal Tibia	43	12	18	0	61	12	73
Distal Tibia	1	1	3	0	4	1	5
Proximal fibula	0	0	12	0	12	0	12
Patella	4	0	0	0	4	0	4
Calcaneus	7	0	0	0	7	0	7
Talus	2	0	0	0	2	0	2
Total	134	28	111	3	245	31	276

Rec. n = number of patients with recurrence; N-Rec. n = number of patients without recurrence.

sional curettage : 2.6% (3/114) ; marginal excision : 14.3% (1/7) ; wide excision : 1.9% (2/105) ; and radical resection : 0] ($p < 0.05$).

A total of 51 cases with pathological bone fracture were surgically treated, which accounted for 18.5% (51/276) of all patients. Of these 51 cases, the location of fracture was as follows : knee joint, 41 cases, 80.4% ; proximal humerus, 4 cases, 7.8% ; proximal femur, 3 cases, 5.9% ; distal radius, 2 cases, 3.9% ; fibular head, 1 case, 2.0%. In addition, 18 cases (12 cases were fracture of the knee joint) were treated with intralesional curettage, and the recurrence rate was 11.1% (2/18). The other cases were treated with resection, and the recurrence rate was 18.1% (26/144). There was no significant difference between the two groups ($p > 0.05$). There were 5 cases of postoperative pathological bone fracture, and 3 of them had recurrence of GCTB.

Of the 276 cases, there were 6 with Campanacci grade I (all treated with intralesional curettage, recurrence : 1 case), 124 with Campanacci grade II (intralesional curettage treatment : 83, recurrence : 12 cases ; resection : 41, recurrence : 1 case), 131

with Campanacci grade III (intralesional curettage treatment : 64, recurrence : 14 cases ; resection : 67, recurrence : 2 cases), and 15 cases with unknown grade (intralesional curettage treatment : 9, recurrence : 1 case ; resection : 6, no recurrence). Accordingly, the recurrence rate was 10.8% (14/130) for the cases confined to bone (Campanacci grades I and II), and 12.2% (16/131) for the cases with extraosseous extension (Campanacci grade III). There were no significant differences in recurrence between these two groups ($p > 0.05$). In addition, the recurrence rate for the cases confined to bone (Campanacci grades I and II) treated with intralesional curettage was 14.6% (13/89), and for the cases with extraosseous extension (Campanacci grade III) treated with intralesional curettage, the recurrence rate was 21.9% (14/64). There were no significant differences in recurrence between these two groups ($p > 0.05$).

The recurrence rate for the treatment of intralesional curettage associated with high-speed burring, liquid nitrogen, and bone cement filling was significantly lower than that associated with

Table III. — Factors related to recurrence in patients treated by intralesional curettage

Criteria		Number cases	Local Recurrence		p Value
			N	%	
Campanacci grade	I and II	89	13	14.6	0.245
	III	64	14	21.9	
Fracture	Yes	18	2	11.1	0.686
	No	144	26	18.1	
Cement	Yes	13	3	23.1	0.847
	No	149	25	16.8	
High-speed burr	Yes	102	11	10.8	0.004
	No	60	17	28.3	
Liquid nitrogen	Yes	66	7	10.6	0.062
	No	96	21	21.9	
Cauterization	Yes	48	4	8.3	0.051
	No	114	24	21.1	
Without adjuvants	Yes	41	13	31.7	0.005
	No	121	15	12.4	

other local adjuvant therapies [12.4% (15/121) vs. 31.7% (13/41), respectively ; $P < 0.05$; Table III]. The recurrence rate for the treatment of intralesional curettage associated with high-speed burring was significantly lower than that without high-speed burring [10.8% (11/102) vs. 28.3% (17/60) ; $p < 0.05$]. However, significant reduction in recurrence rate was not observed for other treatments combined with intralesional curettage, including liquid nitrogen, bone cement filling, and electrocautery cauterization ($p > 0.05$).

There were a total of 6 cases of pulmonary metastasis (male, 3 cases ; female : 3 cases), with 2 cases occurring in the proximal tibia and 4 cases occurring in the distal femur, which accounted for 2.2% (6/276) of all patients. Of these 6 cases, 3 were associated with recurrence of GCTB (9.7%, 3/31) and the other 3 cases were not associated with recurrence (1.2%, 3/245). Two patients died within 5 years following occurrence of pulmonary metastasis.

DISCUSSION

GCTB had a slight male predominance ($n = 152$; 55.1%) in this study, which has also been observed

in other studies on Eastern populations (20,21). This is in contrast to the female predominance which has been reported in studies of Western populations (3,13,14,24), except for one study which showed a similar incidence in both genders (11). The reason for this disparity is currently unknown. A study by Gupta *et al* found a female preponderance in the second decade of life, which may be ascribed to the earlier skeletal maturation in women compared to men (9). In our study, the age distribution and localization of GCTB are in accordance with previous studies (3,13,14,20,24). We found that the most frequent site of GCTB was around the knee joint ($n = 159$, or 57.6%), and preferentially the lower end of the femur ($n = 86$, or 31.2%). The other common sites of GCTB were the proximal femur ($n = 37$, or 13.4%), proximal humerus ($n = 23$, or 8.3%), and distal radius ($n = 20$, or 7.2%).

Tumour location

We found that the recurrence rate after intralesional curettage significantly varied depending on the tumour location, which was in agreement with previous studies (2,3,21,25). However, recurrence rates at various tumour sites have not been consis-

tent in previous studies (2,3,21). The disparity may not be due to the location of the tumour, but rather to the success of complete excision. In addition, McDonald *et al* found no correlation between the recurrence rate and the location of the tumours (13).

Campanacci grading

This staging system was regarded as being able to accurately evaluate the relationship between outcome and surgical margin as well as predict post-operative outcome. However, some studies have reported that there is no correlation between the risk of recurrence and metastasis and the radiographic grading of the tumour (15). Our study also found no correlation. In addition, Campanacci grade III lesions are generally treated by wide resection due to the higher risk of local recurrence and metastasis. However, several recent studies have shown that grade III lesions can be successfully treated using intralesional curettage (10,16,17,25), which results in a 0-25% local recurrence rate. Our study made similar findings.

Pathological fracture

The incidence of pathologic fracture was reported to range from 2% to 22.4% of patients with GCTB between the first diagnosis and treatment (4,8,14,23). In our series, 18.5% of patients with GCTB in the extremities presented with pathologic fracture. Although some authors regard pathologic fracture as a risk factor of local recurrence (4,6,21) and for systemic spread (6), such correlations were not found in other studies (8,23). No correlation was observed either in our series, and all fractures were successfully treated without nonunion or infection. Therefore, it appears that GCTB coincident with pathologic fracture can be successfully treated with curettage without an increase in complications (8). However, GCTB is typically located in the metaphyseal region of long bones and very close to the articular surface (3,9,14,23), which increases the susceptibility of an intraarticular fracture in patients with GCTB of long bone. Once an intraarticular fracture occurs in patients with GCTB of long bone, resection and arthroplasty is needed because of the

higher incidence of traumatic osteoarthritis when treated with intralesional curettage (6,8,13,19,21). Therefore, it is important to try to minimize the occurrence of pathological fractures in GCTB patients, and especially intraarticular fracture.

Adjuvant therapy

Local recurrence was greater in our patients who had intralesional excision (17.3%) compared to patients who had wide local or radical excision (1.9%), similar to other studies (21). This suggests that incomplete tumour removal may be the major cause for local recurrence. Therefore, we suggest that adjuvant measures should become standard procedures when using the curettage technique, because complete eradication of the tumour is difficult by curettage alone (23). Topical adjuvant therapies include physical adjuvants, such as high-speed burring, cryotherapy, and hyperthermia (4,12,23), chemical substances with cytotoxic effects, such as phenol, alcohol, or hydrogen peroxide (4,12,16,23), and bone cement with thermonecrosis and cytotoxic effects (4). In our study, bone cement, high-speed burring, liquid nitrogen, and electrocauterization were used alone or in combination after curettage. We found that high-speed burring significantly reduced the rate of recurrence, which is most likely due to a thermal effect and the additional millimeter of resection. Therefore, we recommend high-speed burring as a necessary adjuvant therapy. Although liquid nitrogen and electrocauterization did not reach significance, they seem to have a similar effect to high-speed burring in reducing recurrence rate. Electrocauterization is the preferred method in combination with high-speed burring due to its low cost, ease of use, and controllability. The positive effect of cement reported in other studies was not observed in our series, which may have been due to an inadequate cementing technique and the small number of patients receiving the adjuvant therapy. As compared to bone grafting, bone cement is generally considered to have several advantages: it provides immediate weight-bearing stability (12,16) and it allows for early detection of recurrence (24); it also avoids donor site morbidity and it preserves bone graft material in case there is a need to treat

recurrence. Nevertheless, cement and grafting procedures have similar risks of recurrence (3). Therefore, while meticulous and extensive curettage is a prerequisite for reducing local recurrence, the use of adjuvant agents further eliminates small amounts of residual tumour and further minimizes the chance of recurrence. However, adjuvant agents will not be optimally effective if the tumour is not adequately removed during curettage.

Campanacci grade III GTCBs : en bloc excision or intralesional curettage ?

It is well accepted that en bloc resection is the method of choice for Campanacci grade III GTCBs in the proximal fibula and the distal end of the ulna, because it is not necessary to consider reconstruction for these regions. However, the use of en bloc resection as standard treatment for grade III lesions located at other sites remains controversial. Wide resections have been traditionally regarded as the primary method of treatment for these lesions, because they are thought to be related to a higher risk of local recurrence and metastasis (21). Both Lackman *et al* (10) and Saiz *et al* (17) found no statistically significant relation between local recurrence and the Campanacci grade of tumour in GTCB patients treated with intralesional curettage. Rooney *et al* (16) reported that grade III GTCB can be successfully treated with a modified intralesional excision if the articular surfaces and part of the metaphysis are intact. In this study, there was no statistical difference in the local recurrence rates of grades I/II or III lesions treated with intralesional curettage. Therefore, we recommend preserving the joint using intralesional procedures for patients with Grade III lesions if the lesion does not invade the joint surface and the underlying subchondral bone and if intraarticular pathologic fracture is not involved.

Pulmonary metastasis

The incidence of pulmonary metastasis was 2.2% in our series, similar to an incidence of 1.1-9.1% in other studies (3,4,18,19). In our study, a significantly greater number of pulmonary metastasis cases were

observed among patients with local recurrence compared to those without local recurrence (9.7% vs. 1.2%, respectively). These results indicate that local recurrence is a risk factor for lung metastasis, which is underscored by the higher rate (50-82.6%) of local recurrence in cases with pulmonary metastasis (5,18,19). GCTB in the distal radius has been reported to have a higher incidence of metastases to the lung (5,19); however, other studies have not reached the same conclusion, and our study also did not identify a higher incidence (3,7). These results could be due to the lower recurrence rate of the distal radius, as most of the patients received en bloc resection of this region. Therefore, we do not consider this primary tumour site as a risk factor for metastasis, and currently only recurrence of GCTB has been identified as a risk factor of metastasis (19).

Although it has been reported that pulmonary metastases of GCTB have good long-term prognosis and an excellent survival rate, the individual course remains unpredictable. Moreover, some centers simply observe metastases without any treatment, while others treat the condition with bisphosphonates, chemotherapy, radiotherapy, or surgery (14,19,22). To date there is no consensus on the most appropriate and effective treatment strategy for pulmonary metastasis (3,18). In our study, only 2 patients with pulmonary metastasis underwent additional surgical resection. Three (50%) patients with metastasis died within the 5 year follow-up period, but no significant association between treatment of metastases and outcome was observed. Nevertheless, patients with local recurrence should be regularly examined with a chest CT in order to detect metastasis early on in the course of the disease.

Based on these findings, we recommend preserving the joint using intralesional procedures for patients with Grade III lesions if the lesion does not invade the joint surface and the underlying subchondral bone, if intraarticular pathologic fracture is not involved, and high-speed burring is an essential adjuvant when intralesional curettage is used. Therefore, the combination of several adjuvants (burring, liquid nitrogen, and electrocauterization) is recommended as a standard treatment. The positive effect of PMMA cement reported in other studies

was not observed in our series, presumably due to a suboptimal cementing technique and to the small number of patients receiving this adjuvant therapy. As its merits have been verified in many recent studies (1,26), we believe it should also be used routinely in combination with other adjuvants.

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