Eur J Orthop Surg Traumatol (2017) 27:813–819
DOI 10.1007/s00590-017-1983-z

ORIGINAL ARTICLE • TUMORS - LOWER LIMB

Higher local recurrence rates after intralesional surgery for giant cell tumor of the proximal femur compared to other sites

Costantino Errani[1,4] · Shinji Tsukamoto[2] · Giulio Leone[1] · Manabu Akahane[3] · Luca Cevolani[1] · Piergiuseppe Tanzi[1] · Akira Kido[2] · Kanya Honoki[2] · Yasuhito Tanaka[2] · Davide Maria Donati[1]

Received: 13 April 2017 / Accepted: 19 May 2017 / Published online: 6 June 2017

Abstract
Purpose The treatment of giant cell tumor (GCT) of bone remains controversial. Intralesional surgery (curettage) results in a higher rate of local recurrence, but better functional results compared to resection. The aim of this study was to assess whether the use of curettage was successful in the treatment of GCT of long bones. We evaluated the influence of adjuvant treatment, local tumor presentation, and demographic factors on the risk of recurrence.
Methods We retrospectively reviewed the records of patients treated for GCT of long bones between 1990 and 2013, using curettage. No patient had any treatment other than surgery. After detailed curettage, the bone cavity was filled with bone allografts and/or cement. Recurrence rates, risk factors for recurrence and the development of pulmonary metastases were determined. The minimum follow-up was 24 months.
Results We enrolled 210 patients with GCT of long bones treated by curettage. The rate of local recurrence was 16.2% (34/210 patients). The median follow-up was 89.2 months. In the multivariate analysis, no significant statistical effect on the local recurrence rate could be identified for gender, patient's age, Campanacci's grading, or cement versus bone allografts. The only independent risk factor related to the local recurrence was the site, with a statistically significant higher risk for patients with GCT of the proximal femur.
Conclusions Our observation on the correlation of tumor location and risk of local recurrence is new. We suggest that patients with GCT of bone in the proximal femur should be followed closely soon after surgery to identify any possible recurrence.

Keywords Benign bone tumor · Giant cell tumor · Surgery · Curettage

✉ Costantino Errani
costantino.errani@ior.it

[1] Department of Orthopaedic Surgery, Rizzoli Institute, Bologna, Italy

[2] Department of Orthopaedic Surgery, Nara Medical University, Nara, Japan

[3] Department of Public Health, Health Management and Policy, Nara Medical University, Nara, Japan

[4] Musculoskeletal Oncology Department, Istituto Ortopedico Rizzoli, via Pupilli n1, 40136 Bologna, Italy

Introduction

Giant cell tumor (GCT) of bone is a rare primary benign bone tumor accounting for approximately 5% of all primary bone tumors [1]. GCT is composed of mononucleated cells and osteoclast-like multinucleated giant cells, presenting itself as a locally aggressive lesion with unpredictable behavior [2]. GCTs arise in the metaepiphyseal region of long bones, predominantly in the distal femur and the proximal tibia, but they can occur in the entire skeleton [3].

The ideal treatment for GCT remains controversial [2, 3]. Surgical treatment options include curettage (intralesional surgery) or segmental resection. Curettage has a higher recurrence rate but does preserve adjacent joint function [4]. Wide resection results in low rates of local recurrence but is associated with morbidity and loss of function. Resection is usually reserved when bone destruction is extensive with large soft tissue mass and it is no possible to preserve the joint, or when sacrifice of bone

would provide better tumor control and minimal functional impairment such as for tumors located in the proximal fibula and distal ulna [1]. After curettage, filling the bone cavity with bone grafts or cement is common in order to provide structural support and prevent collapse [5, 6]. Recent studies indicated cement and other adjuvants decrease the risk of local recurrence [3, 7]. However, other authors reported similar recurrence rates without the use of cement or other adjuvants [8].

The aim of this study was to assess whether the use of curettage was successful in the treatment of GCT of long bones. We evaluated the influence of adjuvant treatment, local tumor presentation, and demographic factors on the risk of recurrence.

Materials and methods

This study was approved by our hospital's institutional ethics board and registered with ClinicalTrials.gov, identifier NCT02996734. We retrospectively reviewed the medical charts of patients diagnosed with GCTs of the long

Table 1 Descriptive characteristics

Variable ($n = 210$)	No. of patients	Without local recurrence ($n = 176$)	With local recurrence ($n = 34$)
Age (years)			
<30	118 (56.2%)	96 (54.5%)	22 (64.7%)
30≤	92 (43.8%)	80 (45.5%)	12 (35.3%)
Gender			
Male	92 (43.8%)	77 (43.8%)	15 (44.1%)
Female	118 (56.2%)	99 (56.3%)	19 (55.9%)
Site			
Distal femur	84 (40.0%)	73 (41.5%)	11 (32.4%)
Proximal tibia	75 (35.7%)	62 (35.2%)	13 (38.2%)
Distal tibia	13 (6.2%)	12 (6.8%)	1 (2.9%)
Proximal femur	12 (5.7%)	6 (3.4%)	6 (17.6%)
Distal radius	8 (3.8%)	8 (4.5%)	0 (0%)
Proximal humerus	7 (3.3%)	6 (3.4%)	1 (2.9%)
Distal ulna	5 (2.4%)	5 (2.8%)	0 (0%)
Distal humerus	4 (1.9%)	2 (1.1%)	2 (5.9%)
Proximal radius	1 (0.5%)	1 (0.6%)	0 (0%)
Proximal ulna	1 (0.5%)	1 (0.6%)	0 (0%)
Campanacci classification			
Stage I	5 (2.4%)	5 (2.8%)	0 (0%)
Stage II	165 (78.6%)	141 (80.1%)	24 (70.6%)
Stage III	40 (19.0%)	30 (17.0%)	10 (29.4%)
Previous surgery			
None	189 (90.0%)	159 (90.3%)	30 (88.2%)
1	21 (10.0%)	17 (9.7%)	4 (11.8%)
Surgery			
Curettage without cement			
Curettage only	4 (1.9%)	3 (1.7%)	1 (2.9%)
Curettage and bone allografts	43 (20.5%)	30 (17.0%)	13 (38.2%)
Curettage, subchondral bone chip allografts and cement	46 (21.9%)	39 (22.2%)	7 (20.6%)
Curettage with cement			
Curettage and cement	92 (43.8%)	82 (46.6%)	10 (29.4%)
Curettage, cortical bone allografts and cement	25 (11.9%)	22 (12.5%)	3 (8.8%)
Phenol adjuvant			
Yes	196 (93.3%)	166 (94.3%)	30 (88.2%)
No	14 (6.7%)	10 (5.7%)	4 (11.8%)

bones between January 1990 and December 2013. Patients were eligible for the study if the histologic diagnosis of GCT was confirmed, the definitive surgery was done in our Institute, and there was a minimum follow-up of two years after treatment. GCTs were graded radiographically by the Campanacci classification system [9]. All tumors were treated by curettage. No patient had any treatment other than surgery. The bone defect was reconstructed with nothing, bone allografts, cement alone, or cement with bone allografts. Reconstruction by cement with bone allografts was performed in two different procedures. One procedure was to fill the cavity with cement after using bone chip allografts in a subchondral area in order to protect the articular surface from the thermal effect of cement. The other procedure was to fill the cavity with cement and cortical bone allografts in order to support mechanically the articular surface. Cases reconstructed with cement and subchondral bone chip allografts were included in the group of "curettage without cement" as we were unable to differentiate areas subjected to the thermal effects of cement. Therefore, the cases reconstructed with nothing, bone allografts, or cement with subchondral bone chip allografts were classified as the group of "curettage without cement," while the cases reconstructed with cement alone or cement with cortical bone allografts were classified as the group of "curettage with cement". The Musculoskeletal Tumor Society Score developed by Enneking was used to assess functional results [10].

We defined recurrence-free survival as the interval between the first curettage and manifestation of a local recurrence by imaging during follow-up. All the recurrent tumors were treated surgically by another curettage or resection, and the recurrence of the tumors was confirmed pathologically.

The Fisher's exact test was used to evaluate the association between two variables. Recurrence-free survival was estimated by the Kaplan–Meier method. The log-rank test was used to evaluate the differences between survival curves. Cox proportional hazards regression analysis was conducted to estimate the HRs for positive risk factor for

Table 2 Univariate analysis for recurrence-free survival

Variable	No. of patients	5-year recurrence-free survival (%)	*p* value
Age (years)			
<30	118	81.2	0.162
30≤	92	87.4	
Gender			
Male	92	83.6	0.829
Female	118	84.1	
Site			
Distal femur	84	87.5	
Proximal tibia	75	81.6	
Distal tibia	13	92.3	
Proximal femur	12	58.3	0.002*,[a]
Others	26	88.5	
Campanacci classification			
Stage I	5	100	
Stage II	165	85.1	
Stage III	40	77.0	0.060
Previous surgery			
None	189	83.9	0.692
1	21	83.5	
Surgery			
Curettage without cement	93	78.6	0.050
Curettage with cement	117	88.2	
Phenol adjuvant			
Yes	196	78.6	0.529
No	14	84.2	

* Statistically significant

[a] Comparison of proximal femur and the others (distal femur, proximal and distal tibia, and others)

recurrence. Data were statistically analyzed using the Mann–Whitney *U* test used for nonparametric analyses. Statistical significance was defined as $p < 0.05$. All analyses were performed with IBM SPSS version 21.0 (IBM Co., Armonk, NY, USA).

Results

A total of 210 patients met our inclusion criteria. Table 1 summarizes characteristics of patients. The median age of patients was 28.4 years old (IQR 22.8–37.6). No patient had lung metastasis at presentation. The median follow-up was 89.2 months (IQR 59.5–123.4). Oncological outcome showed 172 patients continuously disease-free, 34 patients with non-evidence of disease after treatment of local recurrence, one patient with non-evidence of disease after treatment of lung metastasis, and two patients alive with lung metastases. One patient died of other disease. Local recurrence rate was 16.2% (34 patients), and the median interval between the first surgical treatment and local recurrence was 15.0 months (IQR 9.0–40.8). In 34 patients who developed local recurrence, 61.8% (21 out of 34) of those underwent additional curettage with cement or bone allografts, 32.3% (11 out of 34) of those received resection with prosthesis or allograft-prosthetic composite, and 5.9% (2 out of 34) of those underwent excision of the local recurrence in the soft tissue. Lung metastasis rate was 1.4% (three patients), and the median interval between the time of the primary disease and lung metastasis was 68.4 months (IQR 49.7–74.6).

Univariate analysis revealed that the proximal femur site showed a significant association with unfavorable recurrence-free survival compared to the other sites ($p = 0.002$, Table 2; Fig. 1). A multivariate analysis was conducted with all the clinical variables. The multivariate analysis revealed that the proximal femur site was the only independent poor prognostic factor for recurrence-free survival ($p = 0.049$, Table 3). In the multivariate analysis, no significant statistical effect on local recurrence rate could be identified for gender, patient's age, Campanacci's stage, presence or absence of previous surgery, cement, and phenol. Local recurrence occurred only in stage II or III tumors without any statistical significance. Local recurrence was lower in patients treated by curettage and cement compared to patients treated by curettage without cement, without any statistical significance.

Median MSTS score in the 210 patients was 96.7 (IQR 93.3–100). In comparing patients who received cement with patients receiving bone allografts after curettage, there

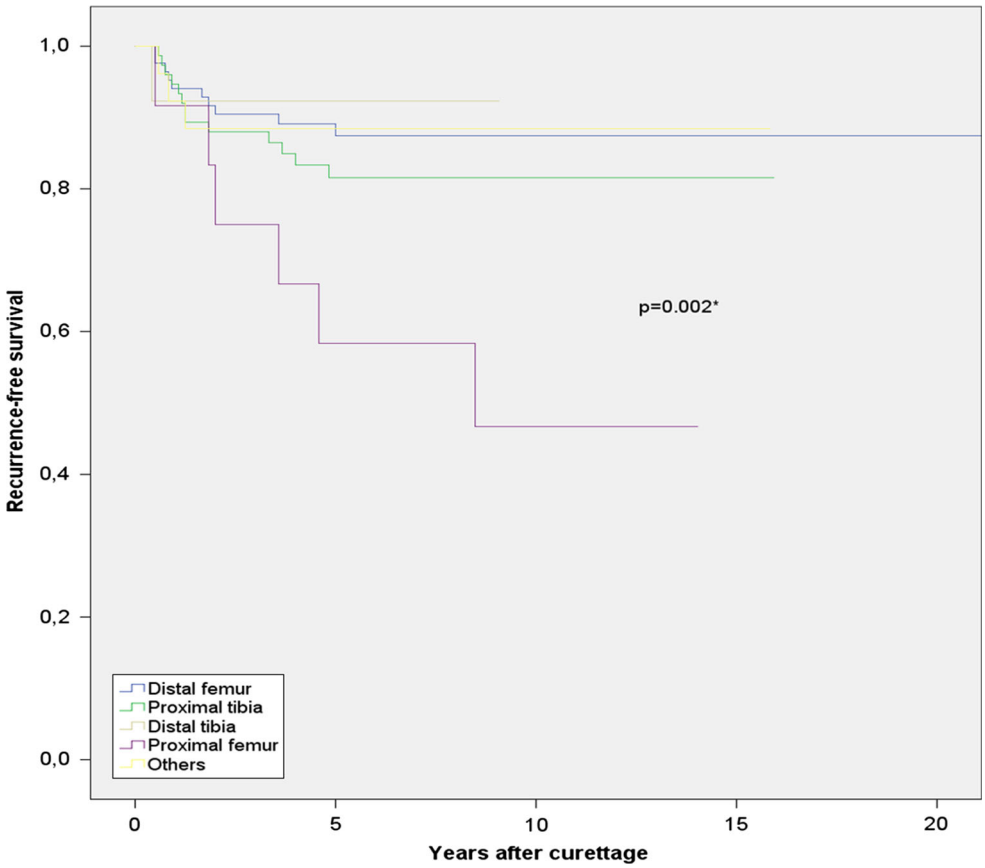

Fig. 1 Recurrence-free survival by site of tumor in 210 GCTB of the long bones. *Proximal femur versus other sites (distal femur, proximal and distal tibia, and others)

Table 3 Multivariate Cox regression analysis of recurrence-free survival

Variable	HR (95% CI)	*p* value
Age (years)		
<30	1	
30≤	0.64 (0.30–1.37)	0.251
Gender		
Male	0.95 (0.47–1.95)	
Female	1	0.896
Site		
Distal femur	1	
Proximal tibia	1.19 (0.50–2.81)	0.695
Distal tibia	0.48 (0.06–3.88)	0.494
Proximal femur	3.07 (1.00–9.39)	0.049*
Others	0.79 (0.21–2.97)	0.727
Campanacci classification		
Stage I, II	1	
Stage III	1.86 (0.86–4.02)	0.113
Previous surgery		
None	1	
1	0.87 (0.28–2.76)	0.819
Surgery		
Curettage without cement	1	
Curettage with cement	0.59 (0.28–1.22)	0.153
Phenol adjuvant		
Yes	0.81 (0.23–2.85)	
No	1	0.743

* Statistically significant

was no significant difference in the mean MSTS functional rating score. Significantly worse functional results were observed in patients with recurrence compared to patients without recurrence ($p = 0.005$, Fig. 2). The median MSTS score in patients with recurrence was 95.0 (IQR 85.8–100.0), while without recurrence was 100.0 (IQR 93.3–100.0).

Discussion

The correlation of tumor location in the proximal femur and risk of local recurrence is a new observation. Special attention must be given to GCTs in the proximal femur. This can be demonstrated by the findings reported by other authors where primary benign bone tumors in the proximal femur are difficult to treat due to the risk of secondary osteonecrosis of the femoral head or pathologic fracture [11]. The actual incidence of these events is unknown, and this is also associated with difficulties in choosing surgical techniques [12, 13]. We found that GCTs located in the proximal femur emerged as the only independent risk factor for local recurrence.

The classic treatment for GCT is curettage [14]. The use of different adjuvant therapies is still being debated, without a clear solution being found [15]. At present, there are no randomized clinical studies that justify the use of any adjuvant [14]. Some authors recommend the use of local adjuvants combined with curettage to reduce the risk

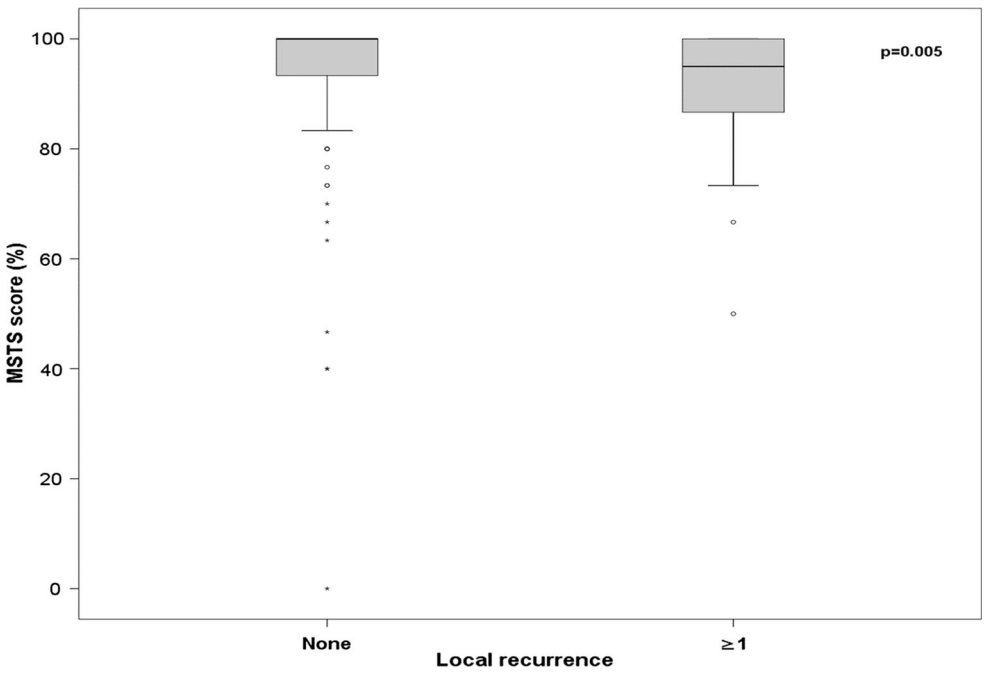

Fig. 2 Mann–Whitney *U* test shows significant difference in the MSTS score between presence and absence of local recurrence ($p = 0.005$)

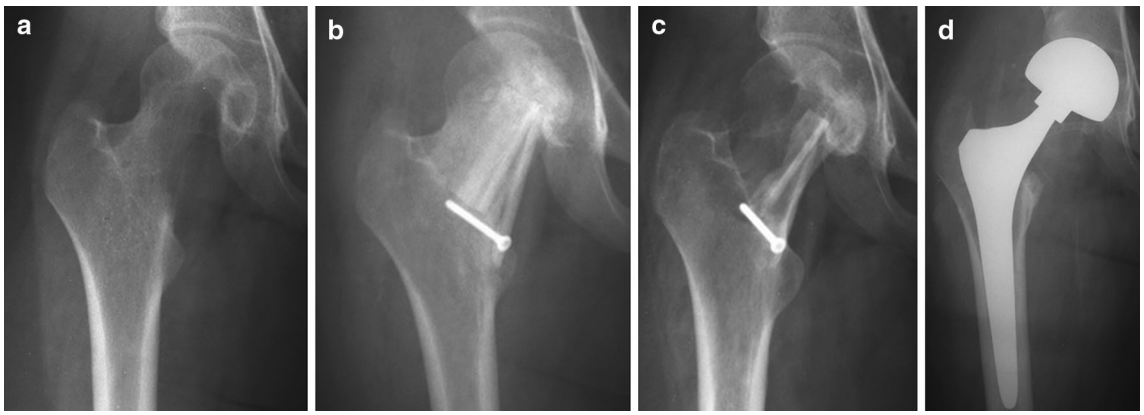

Fig. 3 GCT of the right proximal femur on a 17-year-old girl: **a** anteroposterior preoperative radiograph shows lytic lesion involving the right proximal femur. **b** Anteroposterior radiograph showing the result after curettage and filling the bone defect with bone allografts. **c** anteroposterior radiograph shows a local recurrence. **d** Anteroposterior radiograph shows the result after resection of the proximal femur and reconstruction with bipolar hip arthroplasty

of local recurrence, while according to others this is unnecessary [16]. In the Scandinavian Sarcoma Group multicentric study by Kivioja et al. [7] involving 294 patients, filling the cavity with cement was shown to be a positive prognostic factor. On the contrary, in the Canadian multicentric study by Turcotte et al. [8] involving 186 patients, the adjuvant method or filling material was not associated with the risk of recurrence. Our observations on the influence of cement or adjuvants were not statistically significant. Considering the importance of thorough tumor removal, this capacity may overshadow the effects of adjuvant therapies, a suggestion also made by others [14, 17].

Some authors reported that the recurrence rate was higher in stage III GCTs [5], but Campanacci et al. [9] showed that the risk of recurrence was unrelated to the stage of the lesion. Recurrences seem to reflect the inadequacy of treatment, and appropriate removal of the tumor seems to be the most important predictive factor. The recurrence rate found in the present study was not statistically correlated with the tumor stage, although it only occurred in stages II or III. We found that local recurrences can be treated successfully with repeat curettage as reported in the literature [16].

Anatomic location has been suggested to be associated with local recurrence. O'Donnell et al. highlight a higher risk of recurrence when the tumor is located in the distal radius rather than other sites [18]. On the basis of our study, GCT of the proximal femur has a greater tendency to local recurrence. Other demographic variables had no influence on local recurrence in our patients. GCT of the proximal femur seems to be difficult to treat because of a risk of iatrogenic fracture. Most authors agree that adequate exposure and high-speed burring of the edge of the cavity is mandatory in the treatment of GCT, but in some locations—particularly when the bone is thin—this can lead to an increased risk of fracture [14, 19]. This is particularly true in the proximal femur, where the risk of fracture is very high. GCT of proximal femur has one of the highest rates of pathological fracture of any site [14].

Sakayama et al. [11] reviewed the records of nine patients with GCT of the proximal femur with a mean age of 27.5 years old who were treated with resection and prosthesis versus curettage with or without cement. Four patients were treated with resection and total hip arthroplasty (THA) or bipolar hip arthroplasty (BHA). All these patients had no local recurrence, and the functional result was 93%. Five patients underwent curettage with or without cement. Two of them had a local recurrence, and these patients were treated with subsequent resection using a BHA and THA, respectively. The functional evaluation in this group was 93.3%. Although the functional outcome of THA or BHA was good, the authors emphasized that patients are very young and need to be followed for a very long period.

Wijsbek et al. [14] treated 24 patients with GCT of the proximal femur. Their mean age at diagnosis was 31.5 years old. A pathological fracture was present at the time of diagnosis in 11 of 24 patients (46%). Of the 11 patients with a pathological fracture, seven underwent THA and four had proximal femur endoprosthetic replacement (EPR). Of the 13 without a fracture, one had EPR, two THA, and the other ten underwent curettage. Local recurrence occurred in 5 out of 24 patients (21%). In two of the nine patients treated by THA (22%) and in three of the ten patients treated by curettage (30%). None of the five patients treated by EPR had a local recurrence. Of the local recurrences, two patients initially treated by THA were revised to EPR and three patients initially treated by curettage both had a THA.

We acknowledge the limitations of our study. Firstly, it is a retrospective study with data gathered from clinical files. Secondly, although the total sample size is relatively large, the number of each site or phenol adjuvant and events of local recurrence become relatively small for multivariate logistic regression analysis. Finally, we limited patients to those treated at a single institution.

We present the epidemiological characteristics and results of treatment of GCT of long bones in a large series of patients. In our series, tumor location significantly affected prognosis. The rate of local recurrence in GCT of the proximal femur is higher compared to the other sites, and this could have clinical implications. In fact, there remains the difficult management decision as to whether to minimize local recurrence by resection of the lesion, or to try to save the joint using curettage [14]. Resection usually results in a poorer functional outcome and has a greater risk of complications [2]. Numerous methods of reconstructions of the proximal femur have been reported [11–13]. Among these, THA or BHA should be avoided when possible as more cases of GCT are observed in young patients. Therefore, we do not suggest the alternative surgical approach of resection instead of curettage for GCT of the proximal femur as it is much more difficult to treat than in other sites. But the best treatment remains to save the joint with a higher risk of local recurrence, knowing that the sacrifice of hip articulation in case of recurrence is always possible with THA or BHA (Fig. 3). We suggest following the patients with GCT in the proximal femur soon after surgery to identify any possible recurrence.

Compliance with ethical standards

Conflict of interest All authors declare to have no conflict of interest.

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