



## TUMOUR REVIEW

## Giant cell tumor of the extremity: A review of 349 cases from a single institution

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## SUMMARY

Giant cell tumor is still one of the most controversial and discussed bone tumors. Surgical treatment options include intralesional excision or segmental resection. Curettage has a higher recurrence rate but does preserve adjacent joint function. After curettage, the use of adjuvant therapies is still controversial. Three hundred forty-nine patients with giant cell tumors of the extremity, treated in a single institution, were analyzed in a retrospective study. Two hundred patients underwent curettage of the lesion and in 64 of these cases, three local adjuvants, such as phenol, alcohol and cement, were employed. The hypothesis is that an “aggressive curettage” with phenol, alcohol and cement provides better local control and functional results. The correlation between tumor in the proximal femur and higher recurrence rate has not been recorded before. The results of the present study suggest that an “aggressive curettage” reduces the recurrence rate in a disease whose aggressiveness is not easy to predict. Special attention must be given to giant cell tumors not only in the distal radius, but also in the proximal femur, where the treatment is more difficult and associated with a higher rate of local recurrence.

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## Introduction

Giant cell tumor (GCT) is a primary intramedullary bone tumor, with a specific predilection for age and site, composed of mononuclear and giant mononuclear cells similar to osteoclasts, with a variable and unpredictable growth potential.<sup>1,2</sup>

Surgical treatment options include intralesional excision or segmental resection. Curettage has a higher recurrence rate, but preserves adjacent joint function. After curettage, filling the cavity with bone grafts or cement is common in order to provide structural support and prevent collapse. Use of local adjuvants, such as liquid nitrogen, phenol or cement, to decrease recurrence rate, is still controversial. Although resection with wide margins minimizes tumor recurrence, it is associated with worse functional results, and usually with some possible complications in reconstruction.<sup>3,4</sup>

The purpose of our study was to report the results of patients with GCT of limbs treated in a single institution. The hypothesis is that intralesional excision with local adjuvants provides better local control and functional outcome.

## Material and methods

We retrospectively reviewed the records of 349 patients with GCT of the limbs treated at Musculoskeletal Oncology Department of our institution between 1990 and 2006, confirmed histologically and recorded in the Bone Tumor Registry. Patients were eligible for the study on these criteria: if the histologic diagnosis of GCT was confirmed, the definitive surgery was done in our Department, and there was a minimum follow-up of 3 years after treatment. Preoperative evaluation of the lesion consisted of plain radiographs, computed tomography or magnetic resonance imaging scans. The GCT was graded radiologically according to Campanacci et al.<sup>1</sup>

We reviewed 270 cases located in the lower limb and 79 of the upper limb.

This series includes 177 females and 172 males, with a mean age of 32 SD 13 years (ranging from 5 to 77 years). The most common location was the knee (distal femur 112, proximal tibia 87, patella 1), followed by the distal radius (37 cases), proximal femur (26 cases), proximal humerus (19 cases), fibula (18 cases), distal tibia (13 cases), and some very rare sites such as the talus (7 cases),

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distal ulna (7 cases), metacarpal bones (6 cases), distal humerus (6 cases), calcaneus (3 cases), metatarsus (2 cases), proximal radius (2 cases), and finally one case each in the cuboid bone, in the phalanx of the foot and in the phalanx of the hand.

According to Campanacci's grading system, 200 cases were stage 2, 136 cases stage 3, and 13 cases stage 1.

Treatment was curettage (intralesional surgery) or resection (marginal/wide surgery). Indications for resection rather than curettage included large tumor with soft tissue extension, pathological fractures with joint invasion or unstable fracture pattern, multiple recurrences and expendable bones (head of fibula or distal ulna). Curettage was done through a large cortical window using a series of curettes of different sizes to remove all the visible tumor. The cavity was then burred with a high-speed burr and washed until all pathologic tissue was removed. Lesions were curetted in 200 patients. Considering the limited knowledge about the risk of recurrence related to different types of treatment, different procedures were selected. Choice of reconstruction was at the discretion of the treating surgeon. Three local adjuvants, such as phenol, alcohol and cement, were used in 64 cases ("aggressive curettage"). Whereas only phenol and alcohol, without cement, were given in the remaining, and the residual cavity was filled with allografts or autografts ("standard curettage"). Cases with association of subchondral graft and cement were included in the last group because we were unable to differentiate areas subjected to the thermal effects of cement. One hundred forty-nine cases had a resection and reconstruction treatment with a massive bone graft, modular prosthesis, or allograft-prosthesis composite, with the exception of the tumors located in the fibula and distal ulna (25 cases) that were not reconstructed. In patients treated by resection, margins were wide in 136 cases, marginal in 3, and intralesional in 10.

Patients were checked at 4 month intervals for the first 2 years, every 6 months until the 5th year, and every year until the 10th year. At each check up, plain radiographs of the affected area and a computed tomography of the lung were obtained. The Musculoskeletal tumor society score developed by Enneking<sup>5</sup> was used to assess functional results. The median follow-up was 91 months, ranging from 36 to 204 months.

Continuous variables were expressed in terms of mean and standard deviation of the mean. Categorical variables were expressed in terms of percentage and frequency. Kaplan Maier survival analysis was performed in the univariate analysis. The Breslow test was performed to evaluate the influence of the prognostic variables.

The cox survival regression analysis (with Wald Statistics) was performed as a multivariate analysis to find the best model for predicting a relapse.  $P < 0.05$  was considered significant for all tests.

One Way Anova was used to highlight different functional results between the different type of surgery. Scheffè Post Hoc Test was performed as Pair Wise Test analysis. The chi square analysis was performed to evaluate if there was any relationship between the type of surgery and other prognostic factors.

Statistical Analysis was carried out using the Statistical Package for the Social Sciences (SPSS) software version 14.0 (SPSS Inc., Chicago, USA).

## Results

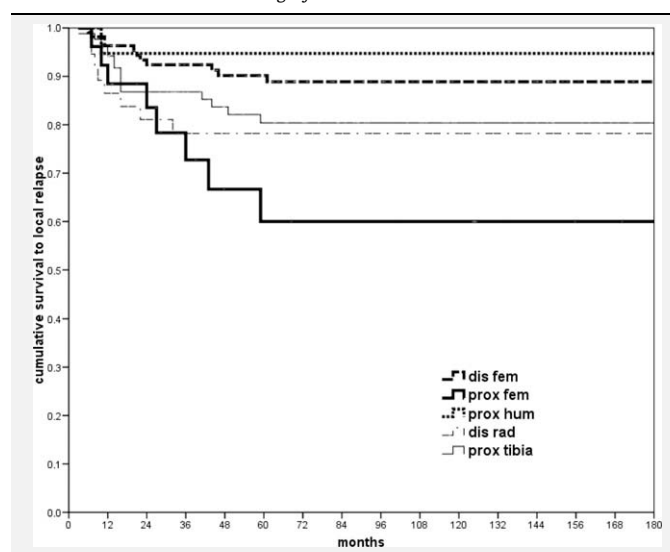
The local recurrence rate was 12% (18 pts) in the 149 resected patients and 16% (32 pts) in the 200 curetted patients. The lung metastases rate was 4% (14 pts).

The local recurrence was 12.5% (8 pts) in patients treated by intralesional surgery and three local adjuvants (64 cases). Conversely, it was higher (24/136 cases) in the second group of patients with

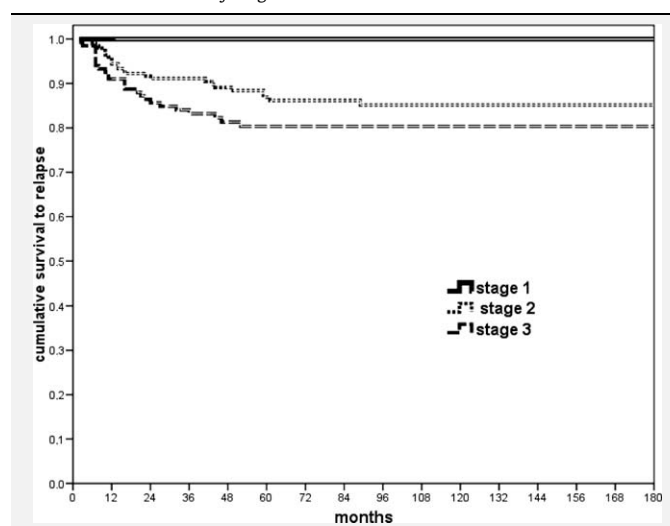
an incidence of 18% of cases. The tumor location was prognostic of local recurrence. In fact, the oncological complications seemed to be related to the site, occurring more frequently in the proximal femur and distal radius (Table 1). Kaplan Meier curves of event free survival show a significant difference between proximal femur (Breslow test  $p = 0.03$ ) and distal radius (Breslow test  $p = 0.04$ ), doing worse than other sites. Local recurrence occurred in stage 2 or 3 tumors (Table 2), without a significant difference between the three stages of the tumor, as shown by Kaplan Meier curves of survival to local recurrence (Breslow test  $p = 0.2$ ). The median interval between the first surgical treatment and local recurrence was 22 months, ranging from 2 to 89 months (Table 3). Thirteen cases of the 32 patients who developed local recurrences after intralesional surgery underwent wide resection.

Metastases to the lungs appeared correlated to the stage of the tumor (Table 4) and the type of the surgery (Table 5), without any relation to the local recurrence (Breslow test  $p = 0.2$ ). A significant correlation between a 3rd stage tumor (Breslow test  $p = 0.01$ ) and

**Table 1**  
Recurrence-free survival after surgery in 349 GCT of the extremities.

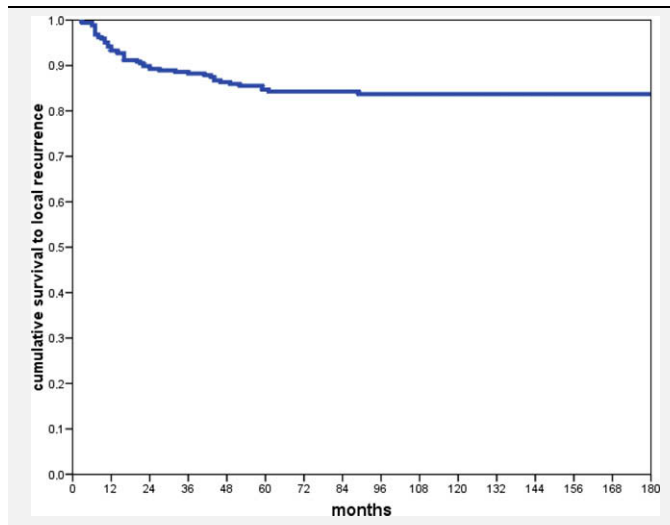


**Table 2**  
Recurrence-free survival by stage of tumor in 349 GCT of the extremities.

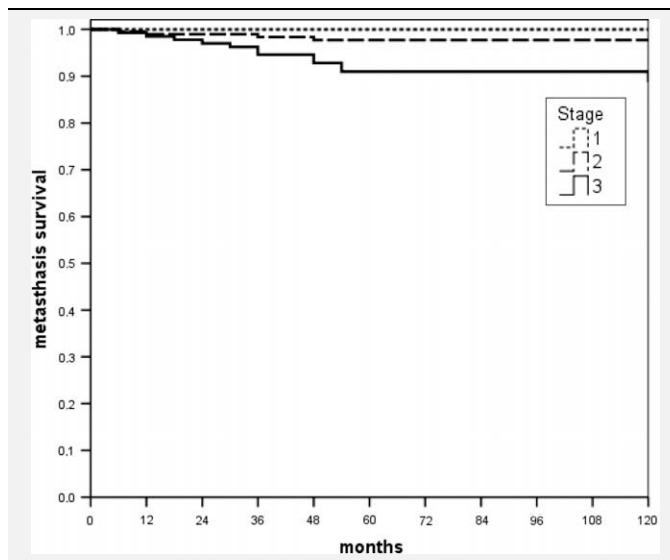


**Table 3**

Kaplan Meier curve of cumulative survival to local recurrence.

**Table 4**

Metastasis survival by stage of tumor in 349 GCT of the extremities.



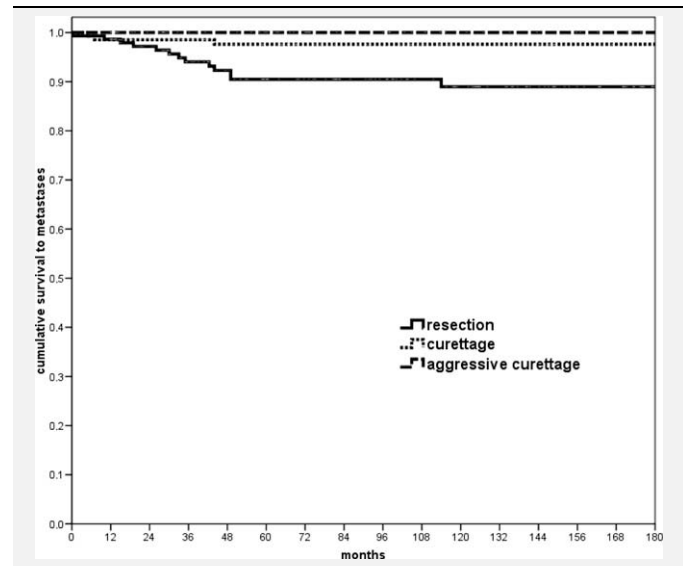
resection (Breslow test  $p = 0.02$ ) as shown by Kaplan Meier curves of survival to lung metastases. Therefore, it seems to be a statistic significance correlation between metastatic presentation and aggressive stage 3 tumors that require a resection. The mean interval between the diagnosis of a primary disease and lung metastasis was 32 SD 27 months, ranging from 0 to 114 months (Table 6). Lung metastasis has the same histological characteristics as the primary tumor with the exception of a case of malignant transformation.

No significant statistical effect on local recurrence rate could be identified for the gender, the patient's age, the Campanacci grading, the surgical margins, and the type of surgery. Multivariate Cox regression analysis with forward Wald method considering margins, type of surgery, tumor stage, and tumor site confirmed that the only variable that influences the survival rate was the site (Table 7).

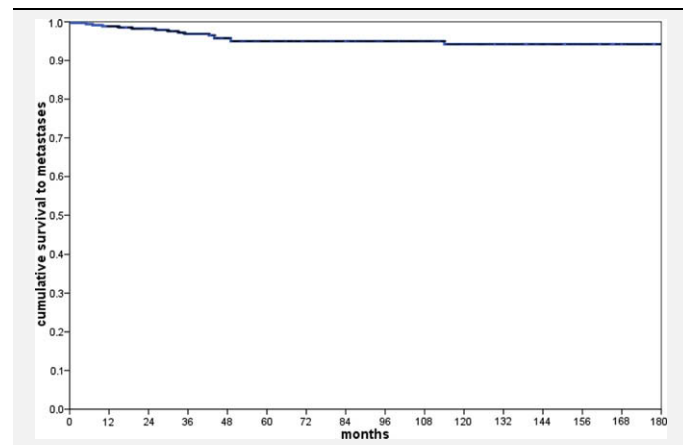
Oncological outcome showed these results: 283 patients alive and continuously disease-free, 47 patients with no evidence of disease after treatment of local recurrence, 3 patients with no evi-

**Table 5**

Metastasis survival after surgery in 349 GCT of the extremities.

**Table 6**

Kaplan Meier curve of cumulative survival to metastases.

**Table 7**

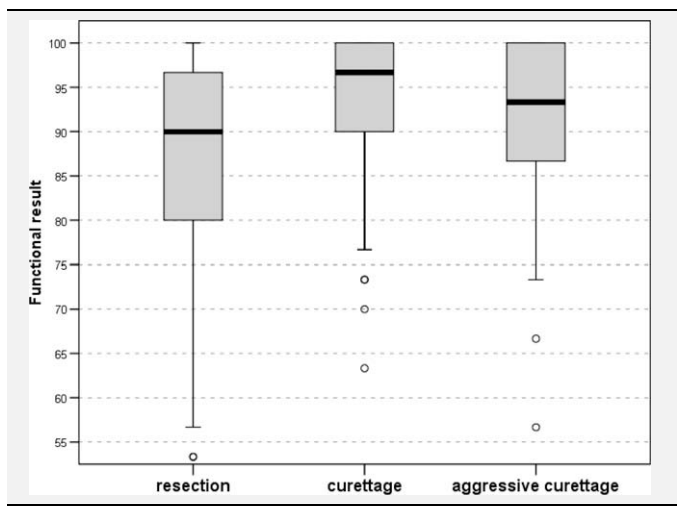
Multivariate Cox regression analysis with forward Wald method considering margins, type of surgery, tumor stage, and tumor site confirmed that the only variable that influences the survival rate was the site: GCT in the proximal femur and in the distal radius does worse than in the other sites.

	OR (95% CI)	Wald statistic
Distal femur	1	
Proximal femur	3.80 (1.5–9.5)	$p = 0.004$
Proximal humerus	0.49 (0.1–3.8)	$p = 0.5$
Distal radius	2.4 (1–5.9)	$p = 0.05$
Proximal tibia	1.9 (0.9–4.0)	$p = 0.12$

dence of disease after treatment of both local recurrences and lung metastases, 11 alive with disease with lung metastases. One patient died with sarcomatous transformation of GCT, while 4 died of unrelated causes.

Worse functional results were observed after resection compared to curettage: the mean score after aggressive curettage was 91.7 SD 9.3, after standard curettage was 93.5 SD 10.6, while

**Table 8**  
One Way Anova Test shows significant difference in the functional results between curettage and resection.



after resection was 86.4 SD 13.4. When comparing patients who received aggressive curettage with patients receiving only standard curettage, there was no significant difference in the Musculoskeletal tumor society scores (Table 8). One Way Anova Test showed a significant difference between the type of surgery and functional outcome ( $p < 0.005$ ). In particular the pair wise post hoc test underlined a significant difference only between resection and intralesional surgery ( $p = 0.01$ ), but not between the two different type of curettage ( $p = 0.6$ ).

### Discussion

GCT is still one of the most controversial and discussed bone tumors.<sup>6–8</sup> Histogenesis of GCT is unknown and a correlation has not been found between histology and clinical course.<sup>9</sup> For this reason many authors<sup>4,6,8,10</sup> consider prognosis unpredictable. Recommendations for treatment are based on results from the retrospective analyses of non-randomized series from single or multiple institutions. The best treatment should insure local control and maintain function, and so most authors<sup>4,8,11–14</sup> advocate intralesional excision as treatment of choice. The recommended curettage technique involves the opening of the bone through a large cortical window that allows visualization of the entire tumor cavity.<sup>4,14,15</sup> After curettage is achieved, the cavity is deepened with the use of high-speed burs.<sup>4,14</sup> Some authors<sup>6,11–13,15,16</sup> recommend the use of local adjuvants combined with curettage to reduce the risk of recurrence, while according to others<sup>4,8</sup> this is unnecessary. Adjuvants presumably remove the tumor cells which remain after curettage because of their thermal (liquid nitrogen, methylmethacrylate) or chemical (phenol, hydrogen-peroxide, alcohol) effects. After tumor evacuation, the cavity can be left unfilled or it can be filled with cement or bone grafting.<sup>4,8,15,17</sup> In the Scandinavian Sarcoma Group multicentric study by Kivioja et al.<sup>6</sup> involving 294 patients, filling the cavity with cement was shown to be a prognostic factor. The recurrence rate was 0.20 for filling with cement and 0.56 for intralesional surgery without cementation ( $p = 0.001$ ). On the contrary, in the Canadian multicentric study by Turcotte et al.<sup>8</sup> involving 186 patients, the adjuvant method or filling material was not statistically significant associated with the risk of recurrence. Our observations on the influence of adjuvants was not statistically significant, but the association of phenol, alcohol and cement produced a decrease of local recurrence.

The rate of local recurrence after intralesional excisions is also very difficult to ascertain. Some authors<sup>18–20</sup> report no cases of relapse, while others rate it from 6–8%<sup>21</sup> to 30–75%<sup>22,23</sup> with an average of 10–20%.<sup>4,11,13,14</sup> The overall risk of local recurrence of all giant cell tumors is 25–35% in older series and 10–20% in recent series. Better results have been reported from single institutions.<sup>6</sup> Blackley et al.<sup>24</sup> had a recurrence rate of 12% in their series of 59 patients that were treated with curettage and bone grafting. Oh et al.<sup>25</sup> reported 9.5% recurrence in a series of 42 patients treated with curettage and adjuvant therapy. In our series the observed recurrence rate was 16% in patients having curettage, but it was lower after a curettage and the association of phenol, alcohol and cement (12.5%).

Resection with wide margins is usually reserved in these cases: aggressive stage 3 tumors, 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.<sup>8,13,21</sup>

For treatment of local recurrences some authors<sup>4,23</sup> recommend resection with wide margins followed by reconstruction using modular prostheses. Others<sup>26,27</sup> show how recurrent GCT can be treated by curettage with an acceptable re-recurrence rate. Steyern et al.<sup>27</sup> found that local recurrence of GCT in long bones after treatment with curettage and cementing is unassociated with a high morbidity or a greater risk of recurrence. Most of their patients with local recurrence were successfully treated with further curettage and cementing with a good outcome. In the series of McGough et al.<sup>28</sup> involving 183 patients diagnosed with GCT and treated with curettage, the recurrence rate was 25%. The incomplete initial surgery, a delay in diagnosis of the recurrence of greater than 6 months, and the subchondral recurrence of the tumor were contributory factors in the failure to salvage the joint.

Some authors<sup>4,22,29</sup> reported that the recurrence rate was higher in stage 3 GCTs, but Campanacci et al.<sup>30</sup> showed that the risk of recurrence was unrelated to the stage of the lesion. Recurrences seem to reflect inadequacy of treatment and appropriate removal of the tumor seems to be the most important predictive factor.<sup>31,32</sup> The recurrence rate found in the present study was not statistically correlated with the tumor stage, although it only occurred in stages 2 or 3. We found most local recurrences can be treated successfully with repeat curettage as reported in the literature.<sup>14,30,33,34</sup>

The tumor in most cases recurs during the first three years after surgery.<sup>4,6,8</sup> The vast majority of local recurrences in this series occurred within 2 years, but the longest took 7 years to develop. Therefore, we suggest that patients should be checked until the 10th year following the final surgery.

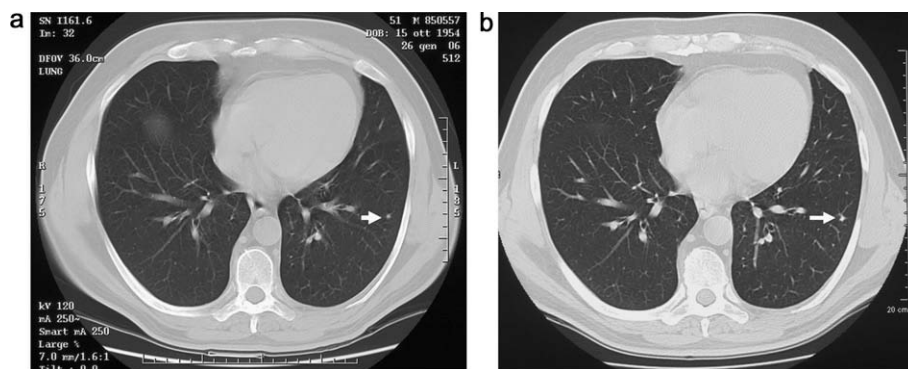
O'Donnell et al.<sup>29</sup> highlight a higher risk of recurrence when the tumor is located in the distal radius rather than distal femur or proximal tibia. The quality of the bone at that site and the proximity to other small bones of the carpus and the ulna make the complication rate of the tumor or the treatment greater than in other sites.<sup>35,36</sup> Aside from the finding of local recurrence, which was much lower after resection than curettage, there was little difference in outcome.<sup>37</sup> On the basis of our study, GCT of the distal radius has a greater tendency to local recurrence. Therefore, we agree with others authors<sup>37</sup> to recommend curettage and cement application for Campanacci stage 2 GCT, where the structural alteration of the bone is minimal, and wide resection and allograft distal radial replacement for Campanacci stage 3 GCT.

There is limited data in the literature comparing local recurrence rates between patients with and without pathologic fracture through GCT lesions of bone.<sup>4,33</sup> Dreinhofer et al.<sup>33</sup> underlined that a pathological fracture is not a contraindication for intralesional excision and cement. Dehesi et al.<sup>34</sup> found no difference in local recurrence after curettage between patients



with or without pathologic fracture. Patients with a pathologic fracture have equivalent functional outcomes after joint salvage, but may have a slightly increased risk of developing postoperative arthro-fibrosis.

Masui et al.<sup>38</sup> reported that there is a correlation between p53 expression and a higher risk of local recurrence and pulmonary metastases. Metastases after GCT of bone are rare, occurring in only 3% of patients.<sup>8,30,34,39</sup> Like the primary lesion, the natural his-



**Fig. 1.** A 46-year-old man with GCT of the distal femur: (a) Computed Tomography of the lung 4 years later the first surgery around the knee presenting a metastasis in the left area (marked by an arrow). (b) Follow-up of the metastasis two years later (marked by an arrow) without significant progression.



**Fig. 2.** GCT of the right proximal femur on a 17-year-old girl: (a) and (b) Anteroposterior and laterolateral preoperative radiographs suggestive of stage 3 GCT involving the right proximal femur. (c) Anteroposterior radiograph showing the result after curettage and filling the bone defect with cement and bone allografts. (d) and (e) Anteroposterior and laterolateral radiograph show a local recurrence after 8 months of follow-up. (f) Anteroposterior radiograph shows the result after resection of the proximal femur and reconstruction with bipolar hip arthroplasty.

tory of metastases is also unpredictable.<sup>40</sup> In our study, the overall metastatic rate was 4%. Based on our data, the trend towards a higher risk of metastatic spread was associated with a more aggressive disease (stage 3 tumors undergo wide resection). Histologically, the metastases were identical to the primary bone lesions and had a good long-term prognosis (Fig. 1).<sup>41</sup>

Functional outcome data with validated scores after treatment of GCT of bone are limited in the literature. Available reports<sup>1,2,8,14,19,30,34</sup> indicate a better functional outcome and a lower rate of non oncological complications with joint salvage compared to joint resection, without showing any statistical significance. Turcotte et al.<sup>8</sup> showed no significant difference in the Musculoskeletal tumor society scores between patients who received cement and patients receiving other types of filler after curettage. We reported that there was a statistical significance in functional scores with intralesional excisions compared to wide resections followed by reconstruction. But we did not find a difference in functional scores after joint salvage between patients who received cement and patients receiving bone grafts. Therefore, we believe that there is no good evidence that proves the use of cement can damage cartilage causing subsequent degenerative arthritis.<sup>24</sup>

The limitations of our study include retrospective analysis of prospective data, and the inclusion of patients treated by different surgeons over a 16-year period.

The treatment of GCT of bone remains a challenge, since there are no clinical, radiographic or histological aspects that allow one to accurately predict the trend of a single lesion to recur or to metastasize.<sup>42</sup> Enneking's and Campanacci's classifications<sup>1,2</sup> are helpful in planning the initial surgical treatment.

The ideal treatment of the GCT consists in excising the tumor and sparing the joint. Therefore, conservative surgery and careful curettage should be considered the treatment of choice when feasible. In fact, intralesional excision preserves joint integrity with excellent functional results.<sup>1,2,6,8,10,14,19,30,42,43</sup> Literature<sup>4,6,8,26</sup> is controversial about filling the bone defect with bone grafts or cement. There were never any prospective randomized studies showing the effects of different methods of filling the cavity. Because of the special operative techniques involved, we believe that a randomized controlled trial inclusion of patients treated by single surgeon is needed.

We were unable to prove the putative value of single adjuvants. However, the review of our series documents that after curettage, the association of phenol, alcohol and cement proved useful to reduce the recurrence rate in a disease not easily predictable for its aggressiveness. We think that this unpredictable course justifies a more aggressive surgical procedure where the use of local adjuvants does not alter functional outcome. Furthermore, the positive role of cement is threefold: first, as a local adjuvant; second, for mechanical support; lastly, to allow an earlier detection of recurrence. Gitelis et al.<sup>18</sup> confirmed that it is more difficult to see recurrences when a bone graft has been used. An early diagnosis of local recurrence allows further excision in most cases, avoiding resection and reconstruction.<sup>1,6,7,12,42,43</sup>

In our series, tumor location significantly affected prognosis. In 1943 Moore et al.<sup>44</sup> described a case of GCT of the proximal femur with many local recurrences, finally treated by resection and replacement with vitallium prosthesis. However, our observation on the statistic correlation of the GCT located in the proximal femur and risk of local recurrence is new.

Literature<sup>7</sup> demonstrated how 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. The actual incidence of these events is unknown due to the difficulties associated with the choice of surgical techniques. Numerous methods of reconstructions have been reported.<sup>7,29,45,46</sup> Among these, total hip arthroplasty (THA) or bipolar hip arthroplasty (BHA)

should be avoided when possible as more cases are observed in young patients. We do not address different approach for the proximal femur. GCT in the proximal femur is much more difficult to treat than in other sites, but if curettage is feasible, the best way is to save the joint with a higher risk of local recurrence, knowing that the sacrifice of the hip articulation in case of recurrence is always possible with THA or BHA (Fig. 2).

The correct surgical indications and a meticulous surgical procedure are mandatory in the treatment of GCT, as in any other musculoskeletal tumor. The selection of which treatment method according to which tumor site is not always easy. The main aim is, when feasible, to remove the tumor saving the joint. Special attention must be given to GCT, not only in the distal radius, but also in the proximal femur.

### Conflict of interest statement

We confirm that there are not relationships with other people or organizations that could inappropriately influence our work.

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