RESEARCH ARTICLE

Epidemiologic Characteristics, Clinical Behavior, and Outcome of the Giant Cell Tumor of the Bone: A Retrospective Single-center Study

Khodamorad Jamshidi, MD; Amin Karimi, MD; Alireza Mirzaei, PhD

Research performed at Baharestan Square, Shafa Orthopedic Hospital, Tehran, Iran

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Abstract

Background: Giant cell tumor of bone (GCTB) is a locally aggressive lesion with an unpredictable behavior. Herein, the aim of this study was to evaluate the epidemiological characteristics, as well as clinical and functional outcomes of GCTB in a relatively large series of patients.

Methods: Patients with the diagnosis of GCTB were included in this retrospective study. Whenever the preservation of the articular surface was possible, surgical options included extended curettage; otherwise, wide resection was implemented. In case of extended curettage, the cavity was filled with cement or bone graft. In addition, the functional and oncologic outcomes of these surgical strategies were compared. The functional outcome of the patients was assessed using the Musculoskeletal Tumor Society (MSTS) scoring system.

Results: A total of 120 GCTB patients, including 55 males (45.8%) and 65 females (54.2%), were evaluated. The three involved locations with highest frequency included distal femur (26%), distal radius (22%), and proximal tibia (19%). At a mean follow-up of 125.5±49.2 months, two pulmonary metastases (1.6%) and 12 (10%) local recurrences were observed. In addition, 6 out of 12 (50%) local recurrences occurred in distal radius (P=0.04). The recurrence rate was significantly higher in extended curettage than in wide resection (P=0.05), and the same pattern was observed for allograft, compared to cement filling (P=0.05). The mean MSTS scores for extended curettage and wide resection were 94.7 and 89.1, respectively (P=0.04). Furthermore, the mean MSTS scores for bone graft filling and cement augmentation were obtained as 96 and 93.1, respectively (P=0.07).

Conclusion: Based on the findings, wide resection of GCTB was associated with superior oncologic outcome, as well as inferior functional outcome. In extended curettage, cement augmentation resulted in superior oncologic outcome when compared with allograft filling.

Keywords: Epidemiologic characteristics, Functional outcome, Giant cell tumor of bone, Oncologic outcome

Introduction

Giant cell tumor of bone (GCTB) is an osteolytic tumor which was first described by Cooper and Travers in 1818 (1). It accounts for approximately 6% of all primary bone tumors (2). Although generally considered as a benign tumor, GCTB is a locally aggressive lesion with an unpredictable behavior. It is histologically...
characterized by multinucleated giant cells in the context of mononuclear stromal cells (3). In spite of its benign nature, it has a recurrence rate of 0-65% depending on the local presentation of the tumor and the type of treatment (4).

The GCTB is also associated with histologically benign pulmonary metastases, which is estimated to occur in 1-4% of GCTB patients (4). Most of the GCTB cases occur in adults aged 20-40 years (2, 5). Distal femur, proximal tibia, and distal radius are considered as the three most common locations of GCTB, respectively (6). Several reports have highlighted a slight predominance of GCTB incidence in women in comparison with that in men (5).

Although rarely lethal, GCTB might be associated with a substantial destruction of the local bony structure. This tumor could be troublesome to manage, particularly in pre-articular regions (5). The treatment is aimed to eradicate the tumor, preserve limb function, and prevent local recurrence and distant metastasis. Historically, GCTB has been managed with intralesional curettage, with a recurrence rate of as high as 60%. On the contrary, wide excision has been associated with a lower risk of local recurrence (0-12%), while having poorer functional outcomes (5, 7, 8). However, the behavior of GCTB is unpredictable and is not always associated with surgical, radiographical, or histological characteristics of the lesion (9).

With this background in mind, the present study was conducted to evaluate the epidemiologic characteristics, clinical behavior, and functional and clinical outcomes of GCTB in a single-center study. To this end, two different surgical strategies, including wide resection and extended curettage, were adopted in this study.

Materials and Methods

The current study was approved by the review board of our institute. Informed consent was obtained from the patients or their parents for publishing their medical data. The medical records of patients diagnosed with GCTB, who were referred to our center and underwent surgery between 1996-2016, were retrospectively reviewed. The inclusion criteria were: 1) histological diagnosis of GCTB and 2) a minimum follow-up of 18 months. On the other hand, the exclusion criteria were: 1) previous surgical treatment of GCTB at other centers and 2) GCTB of the axial skeleton.

Out of a total of 156 patients, 25 cases were referred from other centers as a result of local recurrence; however, these patients were excluded from our study. Nine patients were removed from the study due to having a follow-up of fewer than 18 months and incomplete medical data. Moreover, two patients were diagnosed with axial skeleton GCTB and were excluded from the study. Consequently, the study was continued with 120 patients.

The demographic, clinical, and radiological characteristics of the patients, in addition to their functional and oncologic outcomes were evaluated. Preoperative imaging, included plain radiographs of the lesion, computed tomography (CT) scan, magnetic resonance imaging (MRI), and chest radiography. The tumor was radiologically graded, using the Campanacci staging system (10). Plain radiographs were also used to determine the width of the lesion diameter in relation to the host bone.

In the present study, surgical options included extended curettage or wide resection. Articular surface was attempted to be saved whenever possible. To this aim, extended curettage was applied to the majority of cases. Otherwise, in spite of observing an inferior functional outcome, wide resection and reconstruction were used to reduce the local recurrence rate.

Surgical techniques

For extended curettage, a longitudinal approach was chosen, depending on the most affected cortex. For type III Campanacci lesions, the soft tissue component over the involved area was removed with a margin of 5 mm. The cortical window was widened to access the entire tumor area and avoid overhanging bone ridges. The tumor was then removed with a curette, and the margin was expanded by high-speed burring about 5 mm into the normal cancellous bone and 1 mm into the normal cortical bone. There was an exception for the articular cartilage aspect when the subchondral bone was exposed.

After extended curettage, we used hydrogen peroxidase V10 as a chemical adjuvant therapy and a better visualization of the cavity. Following the extended curettage, the cavity was filled with cement or bone graft [Figure 1]. Bone graft was not used from 2008 based on the recent literature, which recommended cement augmentation, following the intralesional surgery of giant cell tumors (11).

If the cement was used as the filling agent in cases with less than 10-mm intact subchondral bone, the articular surface was supported by a 10-mm flat fresh frozen cancellous allograft (mostly from the femoral head); [Figure 2]. A similar layer of bone graft was utilized to promote the healing of pathologic fracture after reduction and cementation without hardware fixation.

En bloc wide resection was performed to manage cases in which reconstruction was not possible with extended curettage. It included tumors with more than one half of circumferential cortical loss, tumors with articular loss or defect, presence of pathologic femoral neck fracture, and tumors of expendable bones (the proximal part of the fibula or distal part of the ulna). Prostheses, osteoarthriticking allografts, or allograft-prosthesis composites were used to reconstruct the bone defects after resection.

Postoperative protocol

The patients’ follow-up was performed every 3 months for the first two years after the surgery, every 6 months until the fifth year, and every year afterward. At each follow-up session, the plain radiographs of the involved area and a chest X-ray were taken. The functional outcome of each patient was assessed using the Musculoskeletal Tumor Society (MSTS) scoring system at the last follow-up session.

Statistical analysis

Data analysis was performed in SPSS software...
The data were descriptively presented as mean±standard deviations or number and percentage. Independent t-test or its non-parametric counterpart (i.e., Mann-Whitney U test) was used for the comparison of the mean differences between the quantitative variables. In addition, the Chi-square test was used for the analysis of the potential association between two qualitative variables. Spearman’s correlation coefficient test was also utilized to evaluate potential correlations.

The measurement of the overall and recurrence-free survival of the patients was accomplished using the Kaplan-Meier survival test. Additionally, the log-rank test was used to compare the recurrence-free survival rate of different treatments. In our investigation, a P-value less than 0.05 was considered statistically significant.

Results
A total of 65 females (54.2%) and 55 males (45.8%) with the diagnosis of GCTB were evaluated in this study (a female to male ratio of 1.2:1). The mean age of the patients at the time of the diagnosis was 29.9±11.4 years (age range: 13-69 years). Based on the results, 80 (66.7%) GCTB cases were located at the lower extremity, while the remaining 40 (33.3%) cases were presented at the upper extremity. Distal femur (26%), distal radius (22%), and proximal tibia (19%) were the most three frequent locations, respectively. The mean follow-up period of the patients was 125.5±49.2 months (range: 18-240 months), and the mean width of bone involvement was 73.3±22.6% (range: 25-100%). The clinical and demographic characteristics of the patients are demonstrated in Table 1.

In this study, extended curettage was performed in 99 (82.5%) patients. The defects were augmented with cement and bone graft in 44 (36.7%) and 55 (45.8%) patients, respectively. Wide resection and reconstruction
Table 1. Clinical and demographic characteristics of patients with giant cell tumor of bone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>29.9±11.4</td>
</tr>
<tr>
<td>Bone involvement level (%)</td>
<td>73.3±22.6%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55 (45.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (54.2%)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Lower extremity</td>
<td>80 (66.7%)</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>40 (33.3%)</td>
</tr>
<tr>
<td>Involved bone</td>
<td></td>
</tr>
<tr>
<td>Distal femur</td>
<td>32 (26.7%)</td>
</tr>
<tr>
<td>Distal radius</td>
<td>27 (22.5%)</td>
</tr>
<tr>
<td>Proximal tibia</td>
<td>23 (19.2%)</td>
</tr>
<tr>
<td>Proximal femur</td>
<td>8 (6.7%)</td>
</tr>
<tr>
<td>Distal tibia</td>
<td>7 (5.8%)</td>
</tr>
<tr>
<td>Proximal humerus</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (9.1%)</td>
</tr>
<tr>
<td>Campanacci grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>29 (24.2%)</td>
</tr>
<tr>
<td>II</td>
<td>27 (22.5%)</td>
</tr>
<tr>
<td>III</td>
<td>64 (53.3%)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Extended curettage</td>
<td>99 (82.5%)</td>
</tr>
<tr>
<td>Wide resection</td>
<td>21 (17.5%)</td>
</tr>
<tr>
<td>Filling agent</td>
<td></td>
</tr>
<tr>
<td>Cement</td>
<td>44 (36.7%)</td>
</tr>
<tr>
<td>Bone graft</td>
<td>55 (45.8%)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>125.5±49.2</td>
</tr>
</tbody>
</table>

Table 2. Distribution of local recurrence with respect to the clinical and demographic characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Local recurrence Number (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8/55 (14.5%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Female</td>
<td>4/65 (6.1%)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper extremity</td>
<td>7/40 (17.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>5/80 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Involved bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal femur</td>
<td>1/33 (3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Distal radius</td>
<td>6/27 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Proximal tibia</td>
<td>1/23 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4/37 (16.2%)</td>
<td></td>
</tr>
<tr>
<td>Campanacci grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1/29 (3.4%)</td>
<td>0.03</td>
</tr>
<tr>
<td>II</td>
<td>1/27 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10/64 (15.6%)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended curettage</td>
<td>11/99 (11.1%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Wide resection</td>
<td>1/21 (4.7%)</td>
<td></td>
</tr>
<tr>
<td>Filling agent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cement</td>
<td>3/44 (6.8%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bone graft</td>
<td>8/55 (14.5%)</td>
<td></td>
</tr>
</tbody>
</table>

were performed on the remaining 21 (17.5%) patients, 3 cases (14.2%) of the resection group were done in patients presented with the GCTB of expendable bones (distal ulna or proximal fibula). Pathologic fractures were managed with wide resection in two cases and extended curettage in three patients.

In total, 12 (10%) local recurrences were observed in our series. The local recurrence rate was 14.5% (8 out of 55 patients) and 6.1% (4 out of 65 patients) in male and female patients, respectively. This difference was not statistically significant (P=0.11). The local recurrence rates were estimated at 3.4% (1 out of 29 patients), 3.7% (1 out of 27 patients), and 15.6% (10 out of 64 patients) in Campanacci grades I, II, and III, respectively (P=0.03). In addition, 6 out of 12 (50%) local recurrences were observed in the distal radius, while the remaining 6 (50%) local recurrences were observed in other anatomic locations (P=0.04).

The local recurrence rates were obtained as 11.1% (11 out of 99 patients) and 4.7% (1 out of 21 patients) in extended curettage and wide resected tumors, respectively (P=0.05). Moreover, in extended curettage group, a significant association was observed between the local recurrence and filling agent (P=0.05). In this respect, 8 out of 11 recurrences of extended curettage occurred in bone graft augmented tumors. Table 2 demonstrates the local recurrence rate with respect to the clinical and demographic characteristics of the patients. Local recurrence was managed with curettage cementation in nine patients and wide resection in the other three patients.

No significant correlation was observed between the rate of local recurrence and age of the patients (r=0.081, P=0.37). Moreover, local recurrence had no significant correlation with patient follow-up period (r=0.085, P=0.35) and the width of involvement (r=0.115, P=0.21).

Pulmonary metastasis was seen in two patients, one of whom was diagnosed with distal femur GCT and the other with proximal tibia lesion. However, both of them were managed with a thorax surgeon for metastasectomy, and are still alive.

The total mean MSTS score of the patients was 93.7%. In addition, with regard to extended curettage and wide resection, these mean scores were obtained as 94.7 and 89.1, respectively (P=0.04). Regarding the filling agent, the mean MSTS scores for bone graft filling and cement augmentation were estimated at 96 and 93.1, respectively (P=0.07).

The 5- and 10-year recurrence-free survival rates of the
patients were 94.5% and 91%, respectively [Figure 3A].
In terms of the extended curettage, the 5- and 10-year
currence-free survival rates were obtained as 94.5%
and 89%, respectively. Furthermore, the 5- and 10-year
urrence-free survival of wide resection was 100%.
Ancurrence-free survival rate was not significantly
different between extended curettage and wide resection
\[P=0.4\]; Figure 3B).

Post-operative complications
Infection occurred 3 months after the surgery in one
atient with GCTB of proximal tibia, which was initially
treated by extended curettage and cementation. In this
pect, the cement was removed and after the irrigation
of the infection site, the cavity was refilled with the
biotic-loaded cement. In this regard, no other post-
operative complications were observed in our cohort.

Discussion
The clinical behavior of GCT is still unpredictable, and
its correlation with histopathology and treatment is still
an enigma (12). Histologically, GCTs are divided into three
categories, including typical, aggressive, and malignant.
Nevertheless, many authors believe that histology alone
is a poor index for the prognosis and clinical behavior
of a tumor (13, 14). Recently, many efforts have been
made to identify the risk factors which might affect the
gressiveness of GCT. In this respect, age, pathologic
ature, and location of tumor have been associated with
the increased risk of local recurrence and metastasis of
CT in many investigations (4, 15-17).

As attempts continue to codify the clinical behavior
of GCT, cohort studies evaluating the long-term behavior
of the tumor are of great value. In the present study, the
epidemiologic and clinical characteristics of GCTB were
essed, in addition to the oncologic and functional
comes of the surgery, in a cohort of GCTB patients.

The incidence of GCTB has been reported to be
ightly higher in females than in males (4, 18, 19). Such
ediplication has also been observed in our population,
ith a male to female ratio of 1:1.2. The mean age of
CTB patients is reported to range within 20-40 years. In
accordance with the results of earlier reports, the mean
ge of our patients was 29.9 years.

Distal femur, proximal tibia, and distal radius are
sidered the most three common locations of GCTB
lvement in a decreasing order, respectively (6). These
ites were the most three common locations of GCTB
lvement in our cohort, as well. Furthermore, in our
eries, the distal radius involvement was more common
an the proximal tibial involvement (22.5% vs. 19.2%).

The local recurrence rate of GCTB has been reported
to be 0-65% depending on the type of treatment and
local presentation of the tumor (4). In this regard, the
local recurrence rate in our study was measured at
0%. Although the histological grade is not considered
reflection of the aggressiveness of the tumor, various
authors have reported an increased rate of local
urrence in grade III lesions (5, 20, 21). From a total of
local recurrences of our cohort, 10 cases occurred
patients with Campanacci grade III, which was
significantly higher than that in other grades. A higher
rate of local recurrence (22.2%) was observed in the
distal radius GCTB of our series, which could be justified
with the higher percentage of Campanacci grade III in
this group.
In a study performed by Miszczyk et al., the size of the tumor was attributed to the risk of the local recurrence of GCTB, while such association was not observed in our series. In this regard, pathologic fracture has also been attributed to the higher aggressiveness of GCT (22-24). Five cases of our series were presented with pathologic fracture, and the tumor recurred in one of them (20%).

Therefore, a considerably higher rate of local recurrence was observed in patients whose defects were filled with bone graft. Similar results of previous studies have led to a shift from the bone graft to cement afterward (11, 25). The functional outcome was not associated with the choice of filling agent (cement vs. bone graft) in our study. However, Gao et al. revealed a superior functional outcome when cement was used as the filling agent (25). Similar results were obtained in other studies as well (26, 27). While the oncologic outcome was superior in the wide resection, the functional outcome of the patients was considerably superior in extended curettage than in wide resection. The obtained result is in line with the results of earlier investigations (28, 29).

The main weakness of this study was the small number of recurrence, which might have affected the power of our statistical analysis. This issue also did not allow the implementation of multivariate statistical analysis. Hence, it is suggested to evaluate a larger series of Iranian GCTB patients in the future.

Hence, it is suggested to evaluate a larger series of Iranian GCTB patients in the future.

The epidemiological and clinical characteristics of our series were similar to earlier reported ones. Our study re-confirmed the superior functional and inferior oncologic outcomes of extended curettage in comparison with those of wide resection. Our results also highlighted the application of cement instead of bone graft to fill the cavity, which was used whenever the extended curettage is performed. Moreover, the results obtained provided a better oncologic outcome.

Khodamorad Jamshidi MD
Amin Karimi MD
Alireza Mirzaei PhD
Bone and Joint Reconstruction Research Center, Shafa Ortopedic Hospital, Iran University of Medical Science, Tehran, Iran

References