



## Impact of Anatomical Location on Clinical and Oncological Outcome of Management of Giant-Cell Tumor

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**Received Date: September 26, 2022**

**Published Date: October 05, 2022**

**Abstract**

**Background:** *The Giant Cell Tumor is a benign aggressive tumor usually found in the meta-epiphyseal region of long bones, preferably in the distal femur and proximal tibia, but occasionally also arises in the Radius, Humerus, Vertebrae, Pelvis, Sacrum, and other rare locations. We conduct this study to analyze the impact of anatomical location on the clinical and oncological outcome of management of Giant-cell tumors among Sudanese patients.*

**Methods:** *We retrospectively reviewed the records of 43 patients with GCT of the bone treated at two orthopedics oncology centers. Patients were eligible for the study on these criteria: if the histological diagnosis of GCT was confirmed, and there was a minimum follow-up of 6 months after treatment.*

**Result:** *A total number of 43 patient records were analyzed in this study. The mean age of presentation was 28.91 years. Twenty-five were male, and eighteen patients were female. Anatomical distribution around the knee represents around 48.8 %. The distal femur location was the most common, accounting for 32.5% of cases, followed by distal radius 20.9% and proximal tibia 13.9%. Painful swelling was the most common presenting complaint of GCT reported in twenty-six patients (60.47%), and pain without an obvious swelling occurred in eleven patients (25.58%). Painless swelling was reported in six patients (13.95%). Our study found that 24 (55.8%) developed a recurrence of at least one of the clinical symptoms after surgery. However, most of them, 75% (18 out of 24 patients), did not report any impact of their complaint on their daily activity. The anatomical location has no statistically significant impact on the recurrence of the clinical symptoms after surgery. The overall incidence of local recurrence in our study was 27.9%. There was a high recurrence rate in the distal radius GCT, 55.5%, and the impact of anatomical location on GCT recurrence was statistically significant. In GCT around the knee, the distal femur location was associated with a higher rate of development of functional complaint compared to the proximal tibia (35.7 % and 0%, respectively). This finding was statistically significant (P-value, 0.03)*

**Conclusion:** *Our study concluded that anatomical location significantly impacts the local recurrence rate. We also found that in the GCT around the knee, which is the most common location, involvement of the distal femur is associated with a higher impact on the functionality of the knee joint compared to the proximal tibia location. However, anatomical location does not significantly impact the recurrence of clinical symptoms after surgery.*

## Introduction

The Giant Cell Tumor is a benign aggressive tumor of bone usually found in skeletally mature patients. [1]. The incidence of giant cell tumors is around 1.7 per million people, occurs predominantly after skeletal maturity in the third decade, and exhibits a slight female predilection in contrast to other bone tumors. [3-5] Giant cell tumors typically develop in the metaphyseal-epiphyseal region of long bones. Most commonly found in the lower end of the femur and proximal tibia represent around 50% of cases, followed by the proximal Humerus and distal Radius. [6] Other rare locations were reported as well in the literature. [7, 8] Metastatic lesions were reported in patients with c-myc oncogene or p53 gene alterations. [9]

Pain is the most common reported symptom of GCT caused by bone destruction and loss of mechanical integrity of the bone. Soft tissue swelling and deformity are associated with more extensive lesions resulting from cortical destruction and tumor progression outside the bone. Limited range of motion, synovitis, and effusion of nearby joints are also possible presentations. [6] At diagnosis, approximately 12% of patients with GCT present with pathological fractures. [13] Pathological fracture indicates a more aggressive disease with a higher risk of local recurrence and metastatic spread. [6, 10] In the literature, recurrence rates have been shown to vary from 15% to 60%. [6, 7, 11] an average estimated is 10–20%. [12,13] In most cases, recurrence occurs during the first three years after surgery, although recurrence has been reported as early as five months and late as seven years. [14] Factors affecting recurrence are the type of surgery, extra-compartmental extension, and soft tissue extension. [7, 15], whereas other studies did not show the influence of soft tissue extension on the recurrence rate. [16]

Concerning the anatomical location of the GCT, some studies showed that the tumor location is a prognostic factor for local recurrence, occurring more frequently in the distal femur and distal radius.

[5, 17] O'Donnell et al. [17] highlight a higher risk of recurrence when the tumor is located in the distal radius rather than the distal femur or proximal tibia. [17] Siddiqui MA et al. showed significantly higher recurrence with proximal tibia involvement. [18] Moore et al. described a case of GCT of the proximal femur with many local recurrences. [19] On the other hand, some studies did not find a correlation between tumor location and local recurrence. [11, 15, 20]

Most of the recommendations for the treatment of GCT are based on results from the retrospective analyses of non-randomized series from single or multiple institutions. The usual treatment of GCT of the bone is an extended curettage followed by a local adjunct aiming for local control and maintaining joint function. The cavity can be packed by bone graft or cement if needed. [5, 7, 16, 21, 22] Compared to curettage only, every adjunct can significantly reduce the local recurrence rate when used. [7] Segmental resection and reconstruction with either endo-prosthesis or fibular graft will be a better option in certain situations. [23]

Errani et al. reported a statistical significance difference in functional scores with intralesional excisions compared to wide resections followed by reconstruction. [5] No significant statistical effect on local recurrence rate was identified for the surgical margins or the type of surgery. [5] As reported in the literature, most local recurrences can be treated successfully with repeat curettage. [5, 24, 25, 26]

Several factors influence the outcome of the treatment of GCT. Therefore, we conduct this study to analyze the impact of anatomical location on the clinical presentation and oncological outcome of management of Giant-cell tumors among Sudanese patients.

### **Material and Methods:**

We retrospectively reviewed the records of 43 patients with GCT of the bone treated at the musculoskeletal oncology unit of Ibrahim Malik Teaching Hospital and Future Hospital during the period 2018 to 2020. Patients were eligible for the study if the histologic diagnosis of GCT was confirmed, and there was a minimum follow-up of 6 months after treatment. Surgical curettage with or without local adjunct (Liquid nitrogen) was the standard treatment for GCT. For GCT of the distal radius, an extended intralesional curettage without Liquid nitrogen was the standard treatment method in our center. Availability and financial constraints precluded the use of liquid nitrogen for some patients. Surgical resection and reconstruction were performed on patients with extensive lesions.

Categorical variables were expressed in percentage and frequency and assessed using cross-tabulation. (P-value < 0.05) The Chi-square test was used to assess the correlation between anatomical location and presence of functional complaint and clinical outcome (resolution of symptoms after surgery, recurrence). (P-value < 0.05) A Chi-square test was used to assess the correlation between the use of liquid nitrogen and recurrence rate after surgery. (P-value < 0.05)

## **Results**

A total number of 43 patient records were analyzed in this study. The mean age of presentation was  $28.91 \pm 10.71$  years. The youngest patient was 16 years, and the oldest was 64 years. Twenty-five patients (58.1%) were male, and eighteen patients (41.8 %) were female. Curettage was performed in thirty-eight patients with the use of liquid nitrogen in seventeen patients and without liquid nitrogen in eleven patients. Surgical resection and reconstruction were performed on five patients with extensive lesions. There was no correlation between the gender and age of presentation and the incidence of local recurrence (p 0.5, p 0.72, respectively) or resolution of clinical symptoms after surgery of GCT. (P 0.8, p 0.95 respectively). Painful swelling was the most common presenting complaint of GCT reported in twenty-six patients (60.47%), and pain without an obvious swelling occurred in eleven patients (25.58%). In comparison, painless swelling was reported in six patients (13.95%), as shown in (Figure 3). The average duration of patients' complaints before they presented for medical care was  $2.7 \pm 1.4$  months. There was no correlation between the duration of complaint and the incidence of local recurrence (p 0.42) nor the clinical outcome of GCT. (P 0.75) Twelve patients (27.9%) had hand functional complaints from the nearby joint (decrease in range movement of the nearby joint or locomotion difficulty). Five cases (11.6%) had a pathological fracture at presentation. Figure (4) shows the percentages of anatomical distribution of the GCT in our study. The distribution around the knee (proximal tibia and fibula, distal femur) represent around 48.8 % (21 patients). The distal femur location was the most common. In GCT that occurs around the knee, the distal femur location was associated with a higher rate of development of functional complaint in comparison to the proximal tibia (35.7 % and 0%, respectively). These findings were statistically significant (P-value, 0.03). Functional complaint at presentation in GCT was higher in distal Radius GCT, followed by the distal femur and proximal Humerus (33.3%). However, this finding was not statistically significant (P-value, 0.28). Our study found that 24 (55.8%) developed a recurrence of at least one of the clinical symptoms after surgery. However, most of them, 75% (18 out of 24 patients), did not report any impact of their complaint on their daily activity.

Anatomical location has no statistically significant impact on the recurrence of the clinical symptoms after surgery (p 0.14). Our study's overall incidence of local recurrence was 27.9% (12 patients) as shown in (Figure 5). There was a high local recurrence rate in the distal radius GCT of 55.5% (5 out of 9 patients). One patient was reported to have GCT of the spine, and he developed recurrence, and the two patients with GCT of the Toes both developed recurrence. The impact of anatomical location on GCT recurrence was statistically significant (p 0.03). Table (1) shows the local recurrence rate in different anatomical locations. The incidence of radiological evidence of lung metastases in the CT chest was found in 4.7% (2 Patients) of cases.

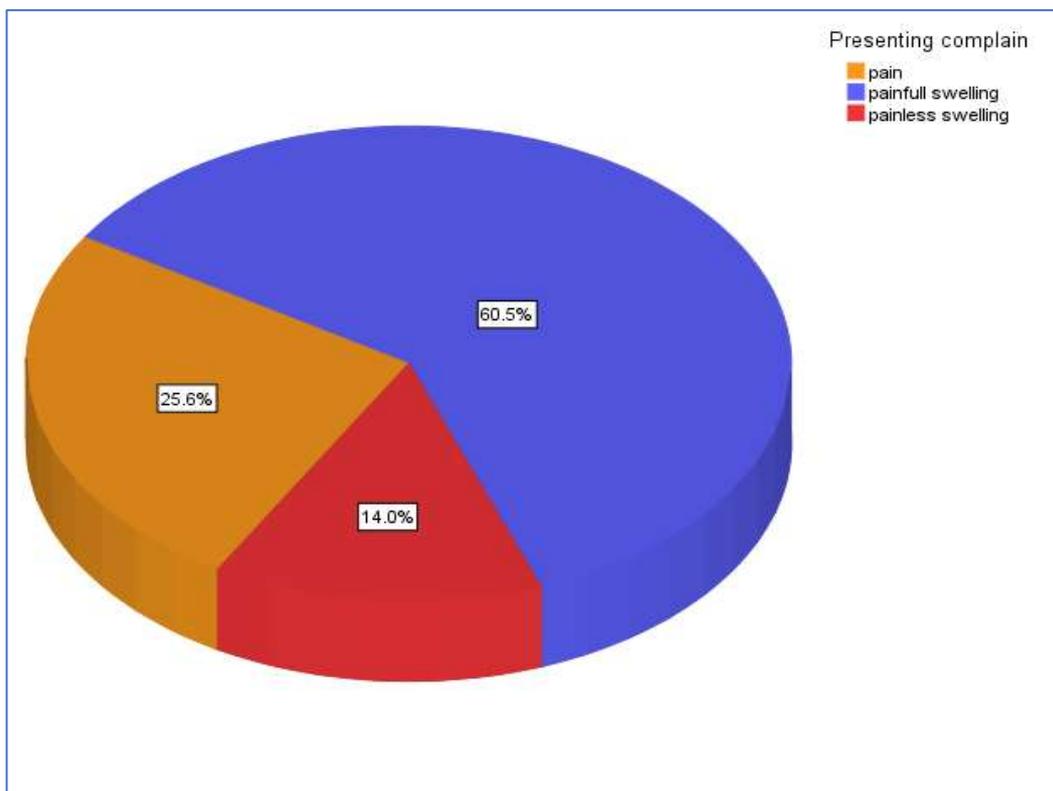
Patients treated with liquid nitrogen as an adjunct for extended curettage had a significantly lower local recurrence rate of giant cell tumors. Percentages were 10.5 % (2 out of 19 patients) in patients treated with curettage and liquid nitrogen compared to 42.1 % (8 out of 19 patients) in patients treated with curettage only (P-value 0.03). The use of liquid nitrogen was not correlated with any statistically significant functional impairment in the clinical outcome (p-value 0.63). Two of the Five Patients who had surgical resection as primary surgery developed local recurrence. (Table 2)



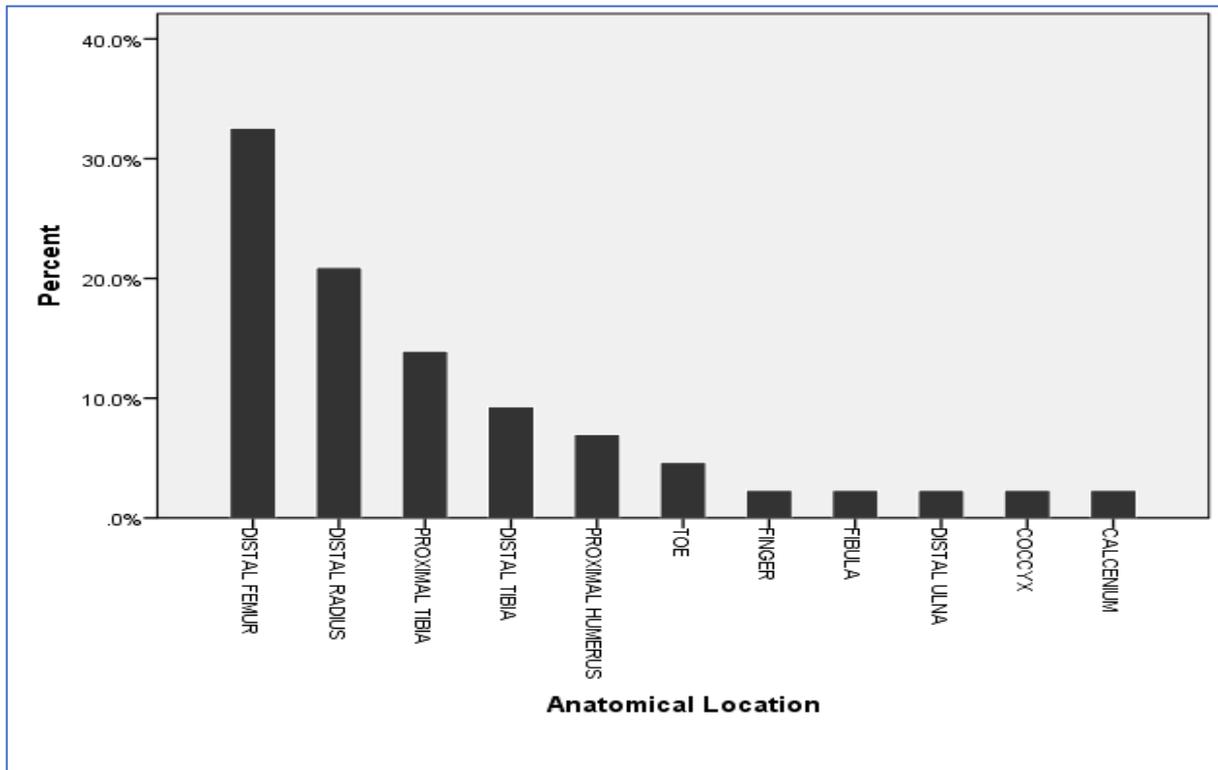
**Figure 1:** Anteroposterior (AP) and Lateral radiograph shows a Giant cell tumor of the distal radius.



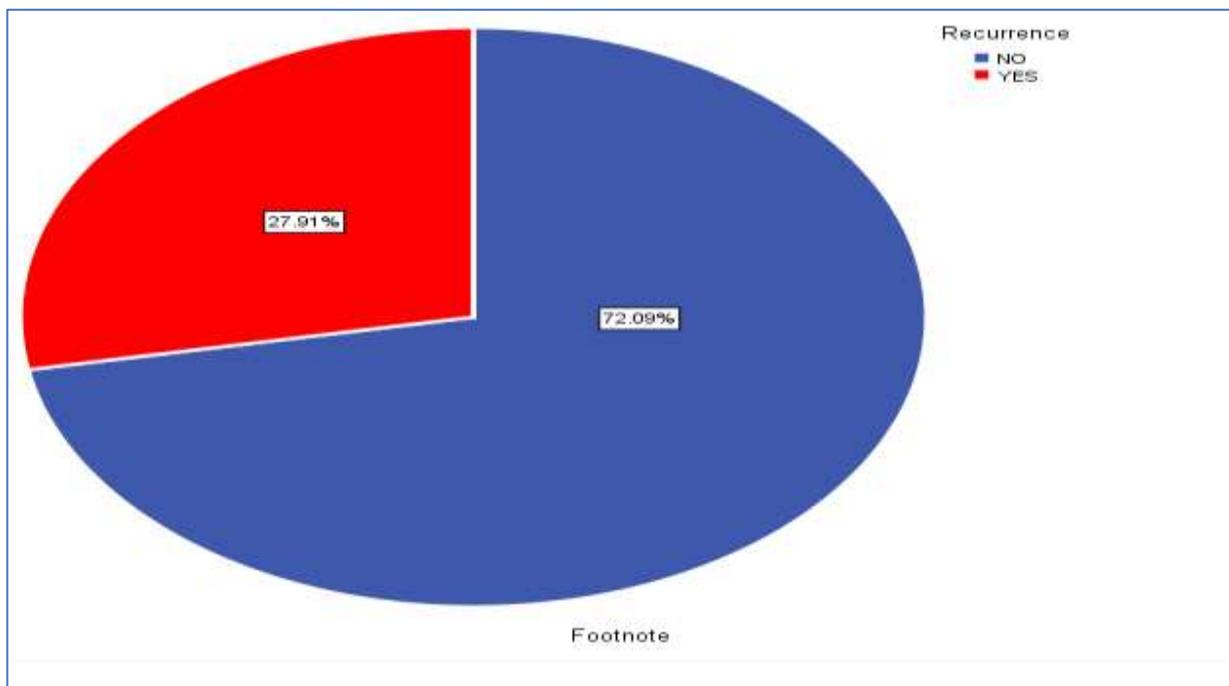
**Figure 2:** Giant cell tumor of the distal ulna show heterogeneous high intensity signal on T2 weighted images



**Figure 3:** Frequency of the different presenting complaints in patient with symptomatic GCT.



**Figure 4:** Percentages of the anatomical location distribution of the GCT



**Figure 5:** The incidence of the overall local recurrence rate of GCT after surgery.

| Anatomical Location | Total Number of patients per anatomical location | Total number of Recurrence per/ location | Percentage of Total Recurrence per/ location |
|---------------------|--|--|--|
| DISTAL RADIUS       | 9  | 5  | 55.5%  |
| PROXIMAL TIBIA      | 6  | 2  | 33.3%  |
| DISTAL FEMUR        | 14   | 2  | 14.3%  |
| DISTAL TIBIA        | 4  | 0  | 0.0%   |
| PROXIMAL HUMERUS    | 3  | 0  | 0.0%   |
| TOE                 | 2  | 2  | 100.0%                                       |
| DISTAL ULNA         | 1  | 0  | 0.0%   |
| FIBULA              | 1  | 0  | 0.0%   |
| FINGER              | 1  | 0  | 0.0%   |
| CALCENIUM           | 1  | 0  | 0.0%   |
| COCCYX              | 1  | 1  | 100.0%                                       |
| <b>Total number</b> | <b>43</b>  | <b>12</b>                                | <b>27.9%</b>                                 |

**Table 1:** Impact of anatomical location of GCT on the local recurrence rate.

|                      |                            | Recurrence  |             | Total      |
|----------------------|----------------------------|-------------|-------------|------------|
|                      |                            | NO          | YES         |            |
| Type of intervention | Curettage with liquid N    | 17<br>89.4% | 2<br>10.5%  | 19<br>100% |
|                      | Curettage without liquid N | 11<br>57.8% | 8<br>42.1%  | 19<br>100% |
|                      | Surgical resection         | 3<br>60%    | 2<br>40%    | 5<br>100%  |
| Total                |                            | 31<br>72.1% | 12<br>27.9% | 43<br>100% |

**Table 2:** Impact of the type of intervention on the incidence of local recurrence of GCT.

## Discussion

The presentation of GCT was persistently reported to be after skeletal maturity in most studies. Our study found that the average age of presentation is the end of the second decade (28-year-old), compared to the third and fourth decades as reported in previous studies. This difference can be attributed to ethnic deference or inaccurate age report, as the exact date of birth was not reported. [23, 9, 27, 28] In contrast to other studies, we noted slight male predominance. Both age and gender did not show a significant effect on GCT outcome or local recurrence rate.

In terms of GCT presentation, we found that Painful swelling was the most common presenting symptom of GCT, occurring in about 60%. The pain was attributed to the loss of mechanical integrity of the bone and progression of the tumor outside the bone with soft tissue involvement. [6] Functional limitations of the nearby joint occur in nearly 28% (27.9%). These functional limitations are reported in previous litterateurs and were related to the proximity of the anatomical location of GCT to the joint and its aggressiveness that might result in joint effusion or invasion by the tumor or joint synovitis.[6] The pathological fracture was the presenting complaint in 11.6% of the patients. It was comparable to the previously reported incidence in other studies. [10] The development of a pathologic fracture is

thought to indicate a more aggressive disease with a higher risk of local recurrence and metastatic spread. [6, 10] In GCT, occurs around the knee distal femur location was associated with a higher impact on the functionality of the knee joint in comparison to proximal tibia location. In our study, the functional impact is defined as any limitation on the range of movement in nearby joints and gait. Functional outcome data with validated scores after treatment of GCT of bone are limited; this may be due to inconsistent location of GCT. Available reports [21, 25, 26] indicated a better functional outcome with joint salvage than with resection, without showing any statistical significance. In our study, we compared the persistence of clinical symptoms, including functional limitation of the nearby joint, after surgical intervention among the different anatomical locations of GCT. We found that the impact of different anatomical locations was statistically not significant. Approximately 55% of patients developed a recurrence of at least one of the clinical symptoms after surgery. However, most of them, 75% did not report any impact of their complaint on their daily activity. The anatomical location has no statistically significant impact on the recurrence of the clinical symptoms after surgery. In literature, patients with pathological fractures have comparable functional outcomes with joint salvage surgery but may have an increased risk of developing postoperative joint fibrosis. [5] Our study's overall incidence of local recurrence was around 28% (27.9%), which was higher than the average estimate in the previous literature, 10-20%. However, some studies recorded a recurrence rate as high as 60%. [6, 7, 11, 12, 13] GCT of the Toes and distal radius have a greater tendency to local recurrence, followed by proximal tibia. The surgical intervention type, and use of liquid nitrogen as a local adjuvant, significantly influence the recurrence rate. O'Donnell et al. [17] highlight a higher risk of recurrence when the tumor is located in the distal radius rather than the distal femur or proximal tibia. Errani et al. also reported that GCT of the distal radius has a greater tendency to local recurrence [5]. Therefore, our study findings agreed with the findings in these previous studies. [5, 17] The quality of the bone and the proximity to other anatomical structures may explain the impact of anatomical location on the complication rate of the tumor or the treatment demand. [20] Other factors that affect recurrence are the type of surgery and extra-compartmental extension, and soft tissue extension. [7, 15], although some studies did not show the influence of soft tissue extension on the recurrence rate. [16] The treatment of GCT of bone remains a challenge. In our study, we found a lower recurrence rate correlated with the use of liquid nitrogen. This result agrees with most of the previously conducted studies. [5, 7, 16, 21, 22] Errani et al. reported a lower recurrence rate with surgical resection compared to curettage. [5] Deheshi et al. found no difference in local recurrence after curettage between patients with or without pathologic fracture. [24] Our study recorded radiological evidence of lung metastasis in 4.6%. Lung metastases after GCT of bone are rare, occurring in only 3% of patients, as reported in previous studies. [24, 26, 29]

Citation: Dr. Mohamed Elmubarak Awadelkarim "Impact of Anatomical Location on Clinical and Oncological Outcome of Management of Giant-Cell Tumor" MAR Orthopedics, Volume 4 Issue 1

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Pompetti F et al. reported a correlation between p53 expression and a higher risk of local recurrence and pulmonary metastases. [9] In some studies, the trend toward a higher risk of metastatic spread was associated with a more aggressive disease (stage 3 tumors undergo wide resection). [5]

## **Conclusion**

Our study concluded that anatomical location significantly impacts the local recurrence rate, but this is also influenced by the type of surgical intervention, particularly the use of adjuvant therapy. We also found that in the GCT around the knee, which is the most common location, involvement of the distal femur is associated with a higher impact on the functionality of the knee joint compared to the proximal tibia location. However, the anatomical location has no significant effect on the recurrence of clinical symptoms after surgery.

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