



## Original Article

# Epidemiological study on giant cell tumor recurrence at the Brazilian National Institute of Traumatology and Orthopedics<sup>☆</sup>



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## ARTICLE INFO

## Article history:

Received 13 August 2015

Accepted 25 August 2015

Available online 18 June 2016

## Keywords:

Giant cell tumor

Recurrence

Epidemiology

## ABSTRACT

**Objective:** Giant cell tumors are benign bone neoplasms that are relatively rare in adults and their biological behavior is still unpredictable. The incidence of local recurrence has presented variation between 0% and 65% in studies conducted worldwide, but few data are available on this complication in the Brazilian population.

**Methods:** Information on 155 patients with confirmed histological diagnoses of giant cell tumor who were treated in our institution's orthopedic oncology service between January 2000 and July 2014 was gathered. Demographic characteristics were evaluated and compared between patients who presented local recurrence during the clinical follow-up.

**Results:** Local recurrence was observed in 26 patients (16.7%), of whom 22 were female (84.6%). The most common site of local recurrence was the distal femur (38.4%). Eleven patients presented early recurrence, while 15 cases were diagnosed after 15 months, representing 42.3% and 57.7%, respectively. Metastases were identified in five patients (3.2%).

**Conclusion:** Tumor-related factors did not show any increased incidence of local recurrence of giant cell tumors. Surgical treatment with an intralesional margin is a valid option for treating local recurrences and does not show any difference in disease-free survival in relation to other types of procedures. Clinical treatment is reserved for cases of unresectable tumors or when surgical treatment is impossible.

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<http://dx.doi.org/10.1016/j.rboe.2016.06.004>

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## Estudo epidemiológico de recidiva de tumor de células gigantes no Instituto Nacional de Traumatologia e Ortopedia

### R E S U M O

#### Palavras-chave:

Tumores de células gigantes

Recidiva

Epidemiologia

**Objetivos:** O tumor de células gigantes (TCG) é uma neoplasia óssea benigna relativamente rara em adultos, porém seu comportamento biológico ainda é imprevisível. A incidência de recidiva local apresenta variação entre 0-65% em estudos internacionais, porém há poucos dados referentes a essa complicação em nossa população.

**Métodos:** Foram coletadas informações sobre 155 pacientes com diagnóstico histológico confirmado de TCG, acompanhados no serviço de oncologia ortopédica da nossa instituição, de janeiro de 2000 a julho de 2014. As características demográficas foram avaliadas e comparadas entre os pacientes que apresentaram recidiva local durante o seguimento clínico.

**Resultados:** Houve recidiva local em 26 pacientes (16,7%), dos quais 22 eram do sexo feminino (84,6%). A localização mais comum de recidiva local foi o fêmur distal (38,4%). Onze pacientes apresentaram recidiva precoce, enquanto 15 casos foram diagnosticados após 15 meses, o que representa, respectivamente, 42,3% e 57,7%. Metástases foram identificadas em cinco pacientes (3,2%).

**Conclusão:** Os fatores relacionados ao tumor não evidenciaram aumento da incidência de recidiva local de tumor de células gigantes. O tratamento cirúrgico com margem intraleisional é uma opção válida no tratamento de recidivas locais e não apresenta diferença de sobrevida livre de doença entre outros tipos de procedimentos. Tratamento clínico é reservado em casos de tumores irrissecáveis ou impossibilidade de tratamento cirúrgico.

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## Introduction

Giant cell tumor (GCT), or osteoclastoma, is a neoplasm of indeterminate malignancy with locally aggressive behavior, composed of mononuclear ovoid neoplastic tissue uniformly interposed by numerous giant cells.<sup>1-3</sup>

GCT represents approximately 5% of primary bone tumors and about 23% of benign bone tumors.<sup>2,4</sup> It occurs most often between 20 and 40 years of age, with a slight predominance in females (ratio of 1.2:1). It is considered a rare tumor in children and adolescents,<sup>5</sup> and less than 10% of cases occur in patients over 65 years.<sup>6</sup>

The most common location is the epiphyseal region of long bones in skeletally mature individuals; it can also affect the metaphyseal region of patients with open physis.<sup>1,2</sup> The most affected areas are the distal femur, proximal tibia and distal radius. Axial involvement is unusual.<sup>7</sup> Despite its benign behavior, this disease can develop with local complications and metastasis, especially into the lungs.<sup>4,8,9</sup>

Relapse is defined as symptomatic or radiologic evidence of the disease, at least three months after the treatment, and is generally detected within the first two years of follow-up.<sup>10</sup> Recurrence rates of primary GCT range from 0% to 65%, depending on the type of treatment and tumor site presentation. Despite their benign nature, pulmonary metastases occur in 2-5% of cases.<sup>11</sup>

GCT is a relatively rare benign tumor in adults; however, its biological behavior remains unpredictable. There are many published studies that report the experiences of international groups in developed countries, but there is little information about the disease's behavior in developing countries. This

article presents the epidemiological data of 155 patients, with 14 years of follow-up, in a Brazilian orthopedic reference institution.

## Methods

Data were collected on patients with confirmed histological diagnosis of GCT, followed-up at the Orthopedic Oncology Service from January 2000 to July 2014. This study was approved by the ethics committee of the institution.

Diagnostic investigation was conducted through clinical and radiological evaluation, which included conventional radiography, computed tomography, and magnetic resonance imaging. Subsequently, the patients underwent needle biopsy for histopathological definition.

The exclusion criteria were: local recurrence in less than three months after surgery; loss to follow-up; and incomplete clinical and radiological record.

The affected site, the presence of metastases and/or pathological fractures, the period of symptoms evolution, clinical and radiological staging and histopathological diagnosis were assessed, as well as the type of surgery performed, surgical margin, and the use of adjuvants. The follow-up period, disease-free time, and location/number of relapses were also assessed.

Patients were divided into three groups, A, B, and C, according to tumor site, as described by Takeuchi et al.<sup>12</sup> Group A included lesions in the femur, tibia, humerus, and radius. Group B comprised tumors located in the scapula, fibula, ulna and hand or foot. Group C included tumors located in the axial skeleton.

Tumor staging was followed the classification by Campanacci et al.,<sup>13</sup> divided as follows: I – quiescent, intraosseous lesions; II – active, presenting intact periosteum; III – aggressive, with cortex rupture and invasion of soft tissues. This classification has therapeutic utility, and was used to help define the surgical margin as intralesional, marginal, wide, or radical.

Surgical treatment followed the protocol recommended by the institution, which prioritizes less aggressive procedures that allow joint preservation. Among surgical treatments, intralesional resection associated with the use of spherical dental bur was performed, followed by local filling of bone defects with polymethylmethacrylate (PMMA), autologous bone graft, or allograft. Extensive surgery was performed in cases in which tumor extension prevented intralesional resection or in tumors located in expendable bones, such as the head of the fibula or the distal ulna.

Clinical follow-up was done after 1, 3, 6, 12, 18, and 24 months. After 24 months, evaluations were performed according to the recommendations of the attending physician. Evaluations included physical examination and radiological investigation (conventional and chest X-rays), in order to make an early diagnosis of recurrences or metastases. In case of suspected local recurrence, complementary imaging tests were ordered, which included computed tomography and magnetic resonance imaging.

The outcome of the patients included in this study were classified as favorable or unfavorable, according to the clinical follow-up. A favorable outcome indicated that the patient had no local recurrence or metastasis during follow-up. Patients who experienced these complications were placed in the unfavorable outcome group.

The data obtained was included in a database in Excel 2013 (Microsoft) and statistically assessed. The demographic profile was described as percentages, means, standard deviations, and minimum and maximum values. A comparison of the demographic characteristics of patients with and without recurrence was made using the Mann-Whitney test and the association was tested using the chi-squared test, at the 95% significance level. Event-free survival was assessed according to follow-up time in months, considering the date of the first visit until the occurrence of the event (metastasis or recurrence). Patients who remained alive were contacted, and the date of the last consultation was regarded as the end of follow-up. The cumulative survival probabilities were estimated with the Kaplan-Meier method and, for the statistical analysis of the curves between clinical groups, the log-rank test was used. All statistical tests were performed in GraphPad Prism version 5.00 for Windows (GraphPad Software – San Diego, California, USA. [[www.graphpad.com](http://www.graphpad.com)]). A *p*-value < 0.05 was considered to be statistically significant.

## Results

From January 2000 to July 2014, 158 patients were diagnosed in our institution with GCT; of these, three were excluded from the study, following the aforementioned exclusion criteria.

The analysis included 155 patients; 60 (38.7%) were male and 95 (61.3%), female. The mean follow-up period was 56.7 months (3.9–158.9). Pathological fractures were observed in 20 patients, representing 12.9% of cases.

Tumors were found mainly in long bones: 32.9% in the femur (51/155), 29% in the tibia (45/155), and 16.7% in the

**Table 1 – Demographic and tumor characteristics of 155 patients with giant cell tumor.**

Parameters	Clinical outcome		Total	<i>p</i> -value
	Favorable <i>n</i> = 129	Unfavorable <i>n</i> = 26		
Age (years)	33.4 ± 13.4	34.0 ± 14.8	33.0 ± 13.5	0.9218
Gender				
Male	43.4% (56/129)	15.4% (4/26)	60	0.0078
Female	56.6% (73/129)	84.6% (22/26)	95	
Campanacci classification				
I	4	–	4	0.4726
II	36	9	45	
III	86	15	201	
Tumor topography				
Group A	94	22	116	0.0994
Group B	14	3	16	
Group C	6	1	8	
Evolution time				
Mean ± SD (months)	12.9 ± 16.9	12.7 ± 16.8	12.9 ± 16.9	0.6592
Fracture at diagnosis				
Yes	17	2	19	0.7425
No	112	24	126	

Topography: humerus, radius, femur, tibia.

Topography B: ulna, fibula, talus.

Mean ± SD.

**Table 2 – Surgical treatment of 149 patients with giant cell tumor.**

Parameter		Primary tumor	Relapse	Total
<i>Type of surgery</i>				
1	Curettage + polymethylmethacrylate	39	15	54
2	Curettage + graft	6	1	7
3	Wide margin resection + endoprosthesis	27	3	30
4	Wide margin resection + bone lengthening	3	0	3
5	Wide margin resection + fibula transplant	8	0	8
6	Resection	12	1	13
7	Amputation	21	2	23
8	Others	8	3	11
<i>Surgical margin</i>				
1	Intralesional	42	17	59
2	Marginal	10	1	11
3	Wide	61	5	66
4	Radical	11	2	13

radius (26/155), as shown in Table 1. Group A totaled 123 cases (79.3%), while B group had 25 (16.2%). A minority of patients were included in group C (seven cases, 4.5%).

According to the Campanacci radiological classification, grades I, II, and III represented, respectively, 2.7% (4/150), 30% (45/150), and 67.3% (101/150) of the patients. Five patients had no radiographic records in the image bank, therefore were excluded due to this criterion.

One hundred and fifty patients underwent surgical treatment of the primary lesion, three of them in another institution. One of the cases was not included in the present analysis, as no information on the procedure performed could be obtained (Table 2). Five patients were not treated surgically, as they did not agree with the proposed procedure. Resection with intralesional margin was accomplished in 39.3% (59/150) of patients; 44% (66/150) underwent treatment with wide margin. Marginal and radical margins accounted for 7.3% (11/150) and 8.6% (13/150) of the cases, respectively. The most commonly performed procedure was curettage associated with the use of PMMA (36%, 54/150), followed by wide resection with use of unconventional endoprosthesis (20%; 30/150) and amputation (15.3%; 23/150).

Local recurrence was observed in 26 patients (16.7%). The demographic characteristics and treatment data of patients with and without recurrence were compared. Soft tissue lesion was identified in six cases. Fifteen patients aged between 20 and 40 years at the diagnosis of the primary tumor were identified, accounting for 57.7% of relapsed cases. Eight patients (30.7%) were aged over 40 years at initial diagnosis. Regarding the gender, 22 patients were female (84.6%).

One patient from the group that presented recurrence had pulmonary metastasis. In five years, event-free survival was 88% (Fig. 1). Considering the Campanacci groups, there was no difference in event-free survival at five years: 88.5% for Campanacci II and 91.5% for Campanacci III (Fig. 2A). Similarly, considering the topography of groups, there was also no difference in event-free survival (Fig. 2B).

The highest number of recurrences was observed in Group A ( $n=22$ ; 84.6%), followed by Group B ( $n=3$ ; 11.5%), and group C ( $n=1$ ; 3.8%). The most common site of local recurrence was the distal femur ( $n=10$ ; 38.4%). Eleven patients had early recurrence while 15 cases were diagnosed after 15 months,

representing 42.3% and 57.7%, respectively. Fifteen patients who had undergone curettage and use of PMMA developed local recurrence.

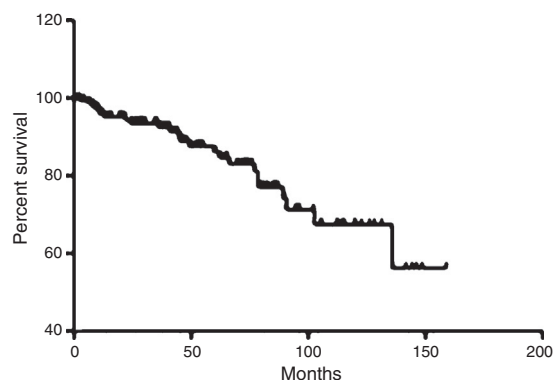
Twenty-four patients diagnosed with local recurrence were treated surgically, six of whom (25%) underwent new curettage associated with the use of PMMA. Five cases (20.8%) were treated by wide resection and use of endoprosthesis, while four patients (16.6%) underwent amputation. Two patients did not undergo surgery because they did not accept the surgical indication, and were submitted to clinical treatment with the use of bisphosphonates (alendronate). Four patients presented new recurrence after the second surgery, and one case had a third relapse.

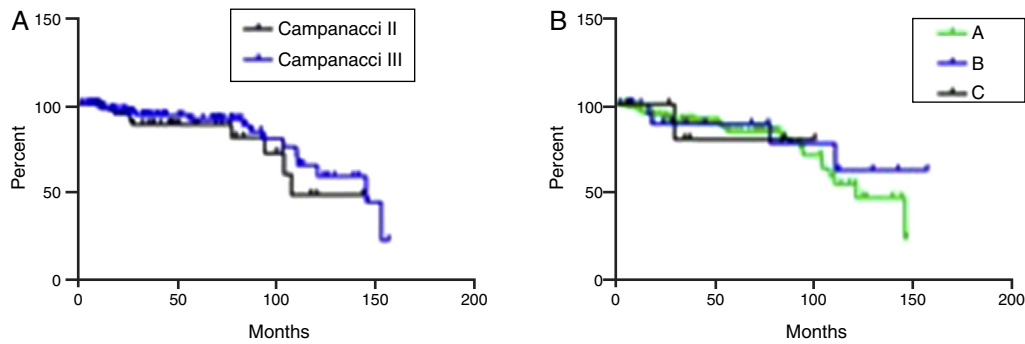
Metastases were observed in five patients (3.2%), among whom only one had local recurrence during evolution. All metastases were diagnosed in the lungs.

After clinical follow-up, 30 patients diagnosed with primary GCT (19.3%) had an unfavorable outcome; 25 with diagnosis of local recurrence, four with metastases, and one who developed both complications.

## Discussion

Gouin et al.<sup>14</sup> did not observe any tumor-related risk factors that increase the incidence of local recurrence after intralesional treatment in appendicular skeleton injuries.

**Fig. 1 – Event-free survival at five years.**



**Fig. 2 – Event-free survival in patients with giant cell tumor regarding the Campanacci classification (A) and topography (B). Group A included lesions in the femur, tibia, humerus, and radius. Group B comprised tumors located in the scapula, fibula, ulna, and bones of the hands or feet. Group C comprised tumors located in the axial skeleton.**

This indicates that the factors related to reduced risk of local recurrence were effectiveness and earliness of surgical treatment.<sup>12,14</sup> The risk of local recurrence in tumors located in the distal radius and proximal femur was higher, although it was not statistically significant. The use of autograft was considered an independent risk factor for local recurrence.<sup>14</sup> Extension to soft tissues and radiological aggressiveness were also reported as prognostic factors, what highlights the importance of the Campanacci classification.<sup>13-15</sup> In a meta-analysis, Li et al.<sup>16</sup> indicated that age younger than 20 years, tumors located in the distal radius, and intralesional surgery with or without bone grafting may be risk factors for relapse in appendicular tumors, but this was not statistically confirmed.<sup>16</sup> In the present study, the sites with highest local recurrence rate were the distal femur, proximal tibia, and distal radius. The demographic parameters evaluated herein, such as gender, age, location, and radiological classification, were not significantly related to the clinical outcome.

Several factors are important when interpreting the results. In this study, three patients who had been previously treated in other institutions were included. This may limit the conclusions about the recurrence rate of these patients, since it was not possible to obtain consistent intraoperative data. In addition, our institution is a reference that receives patients from other locations, which may affect the follow-up.

Surgical treatment with local disease control, combined with local adjuvant, is the standard care for appendicular lesions in our institution. The risk of recurrence in these cases is 12–18%, consistent with the data obtained.<sup>14,15</sup> The treatment used for primary lesions was intralesional curettage followed by enlargement of the cavity with a spherical dental bur. This surgical option is less invasive and usually allows the joint and adjacent tissue to remain disease-free. The adjuvant options are PMMA, hydrogen peroxide, phenol, and cryotherapy. PMMA is the compound most widely used in our institution due to its availability, ease of application, and proven efficacy. The impact of PMMA is related to the toxic and thermal effects that occur after application, which promote better local control.<sup>15</sup> Wide margin surgery was indicated in cases where tumor extent prevented intralesional resection or tumors involving expendable bones, such as the head of the fibula and distal ulna.<sup>11</sup>

Pelvic injuries are rare, representing approximately 1.5–6.1% of cases, but they are more associated with early recurrence and metastasis (7–75% and 2–9.1% of patients, respectively). Due to their location, some cases may be considered unresectable. There is no standard treatment for GCT in the pelvis. Although curettage preserves the integrity of the pelvis, local recurrence rate ranges from 6.3% to 43%. Wide resection is intended to prevent recurrence, but is associated with high rates of complications.<sup>17</sup> Three cases of pelvic lesions (1.9%) were found, two in the ischium and one in the acetabulum. Local recurrence occurred in one case, after tumor resection from the ischium. According to Guo et al.,<sup>17</sup> the wide resection of pelvic lesions presents a lower rate of recurrences, with good functional results. These data are consistent with the clinical outcomes observed in the present study.

GCT located in the axial skeleton represent 3–7% of cases of bone GCT and up to 4% of vertebral bone tumors. Treatment of these lesions is a challenge, as surgery with intralesional margin is considered to be a technically complex procedure with low effectiveness. Wide resection with free margins is hardly feasible, due to the associated risk. Embolization can reduce intraoperative bleeding. Radiotherapy has been successfully employed in some sacral lesions, particularly when it is a relapse.<sup>18</sup> In the present study, two sacral tumors and two lumbar tumors were observed, with overall incidence of 2.5% of cases. Two patients underwent surgical treatment: corpectomy, and anterior and posterior arthrodesis. One patient later received radiation therapy and arterial embolization. Only one patient did not undergo surgery, due to refusal of the proposed treatment. There was no evidence of recurrence during the clinical follow-up (mean of 3.8 years).

Yanagisawa et al.<sup>19</sup> described 11 cases of GCT distal to the radiocarpal and tibiotarsal joints; five patients were male and six female, with a mean of 24.7 years. The location and the most frequent radiological classification were, respectively, the metacarpals (45.45%) and Campanacci II (54.54%). In the present study, 13 patients were diagnosed with lesions in the aforementioned topography. The most common sites were the metacarpals (4/13) and tarsal bones (4/13). The patients with injuries classified as Campanacci I or II were surgically treated with intralesional margin excision. The cases

classified as Campanacci III were treated with radical margin – either amputation or en bloc resection (27.2%). There were two cases of local recurrence and one case of lung metastasis. This finding was consistent with previous studies.<sup>19</sup>

The treatment of tumor recurrence is considered controversial. According to Klenke et al.,<sup>11</sup> resection with wide margins is the most appropriate option, due to lower recurrence rates and longer disease-free survival. Nevertheless, surgery with intralesional margin is a valid option in the treatment of recurrent GCT. This treatment should be used regardless of tumor extension to soft tissues; wide margin resection should be reserved for cases where there is extensive bone involvement or injury to the neurovascular structures. Wide margin resection often requires complex bone reconstructions, associated with higher rates of surgical complications and functional deficit. The potential risk of lung metastases is not associated with the type of surgery performed.<sup>11,12</sup>

Recent studies indicate the use of specific clinical treatment in cases of tumors that are considered to be unresectable, especially those in the sacrum and spine. The recommended drugs include bisphosphonates and denosumab, which inhibit the receptor activator of nuclear factor kappa B (RANK) system.<sup>20,21</sup> In the present study, two patients diagnosed with local recurrence did not undergo surgery, as they did not accept the proposed procedure. The use of bisphosphonates (alendronate) was offered as a treatment option in these cases, achieving good local control during follow-up.

The metastasis rate found in the present study is consistent with that of the literature. Five patients (3.2%) had lung metastases, among whom only one had local recurrence during the follow-up.<sup>4,22</sup>

Metastases occur primarily in the lungs, and their incidence is between 1% and 9%.<sup>22</sup> Risk factors for this event include primary site, local recurrence, and type of primary tumor treatment. The interval between the diagnosis of the primary tumor and the detection of metastases ranges between 0 and 10 years (mean of 3.5). The most common primary metastasis sites is the distal radius, followed by the femur and sacrum. Local aggressiveness and multiple recurrences have been associated with increased incidence of metastases.<sup>22</sup> Five patients (3.2%) had lung metastases, among whom there was one case of local recurrence during follow-up. The primary sites were the distal tibia (2/5), distal radius (1/5), metacarpal (1/5), and proximal humerus (1/5). There was no statistical association between local recurrence or tumor location on the incidence of metastasis.

## Conclusion

GCT recurrence was observed in 26 patients (16.7%). The factors related to the tumor did not evidence an increased incidence of this complication, although it was more common in females. Surgical treatment with intralesional margin is a valid option for the treatment of local recurrences and presents no difference regarding disease-free survival when compared to other procedures. Clinical treatment is used in cases of unresectable tumors or surgical treatment impossibility.

## Conflicts of interest

The authors declare no conflicts of interest.

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