Giant cell tumor of bone: Epidemiological profile (fifth version) – A study protocol

Tumor de células gigantes do osso: Perfil epidemiológico (quinta versão) – Um protocolo de estudo

Tumor óseo de células gigantes: Perfil epidemiológico (quinta versión) - Un protocolo de estudio

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Abstract
The giant cell tumor of bone (GCTB) represents approximately 5% of primary bone tumors, and more than half of cases affect individuals between 20 and 50 years of age. Despite being a benign neoplasm, 3 to 5% of cases may show pulmonary metastases, besides it has high potential for bone destruction at the main site of the lesion, often in the epiphyses of long bones, which may lead to serious functional problems in affected patients. Multidisciplinary treatment of GCTB has been a cause for discussion in the last decade due to the discovery of drugs such as denosumab that prevent tumor progression and may be useful in cases of patients with local recurrences and unresectable tumors. The therapeutic basis of GCTB remains the isolated surgical treatment by intraslesional (with adjuvants), marginal or wide resection. Intraslesional treatment presents higher rates of recurrence, however it preserves the adjacent joint function and much of the individual bone stock. Resection with wide margins presents lower recurrence rates but has shown worse functional results and frequent complications in bone reconstructions. Current knowledge of GCTB surgical outcomes has been based on major world series - there is a lack of Brazilian epidemiological and surgical data on this specific type of neoplasm, except for a few series of cases. The primary objective of this paper is to identify the epidemiological profile of GCTB; the secondary objectives are to describe the surgical aspects in the main diagnostic centers and treatment of bone tumors, to analyze the clinical and surgical
Resumen
El tumor óseo de células gigantes (TOCG) representa aproximadamente el 5% de los tumores óseos primarios, y más de la mitad de los casos afectan a individuos entre 20 y 50 años. A pesar de ser una neoplasia benigna, del 3 al 5% de los casos pueden presentarse con metástasis pulmonares, además de tener un alto potencial de destrucción ósea en el sitio principal de la lesión, a menudo en las epífises de los huesos largos, lo que puede conducir a problemas funcionales graves en los pacientes afectados. El tratamiento multidisciplinar de TOCG ha sido un tema de discusión en la última década debido al descubrimiento de fármacos, como el denosumab, que previenen la progresión del tumor y pueden ser útiles en casos de pacientes con recurrencia más altas, pero han mostrado peores resultados funcionales y complicaciones frecuentes en las reconstrucciones óseas. El conocimiento actual de los resultados quirúrgicos de TOCG se ha basado en grandes series mundiales; faltan datos epidemiológicos y quirúrgicos brasileños sobre este tipo específico de neoplasia, con excepción de algunas series de casos. El objetivo principal de este trabajo es identificar el perfil epidemiológico del TOCG; los objetivos secundarios son describir los aspectos quirúrgicos en los principales centros de diagnóstico y tratamiento de tumores óseos, analizar los aspectos clínicos y quirúrgicos de los pacientes con TOCG de punho y mão e analisar os aspectos clínicos e quirúrgicos dos pacientes com TCGO do joelho. Los hallazgos pueden ayudar a mantener o cambiar las pautas nacionales para el tratamiento del TOCG. Este protocolo de estudio fue sometido a evaluación ética bajo el CAAE (Certificado de Presentación de Apreciación Ética) N.° 94280918.0.0000.5327 (5.ª versión), evaluado a través de la opinión incorporada N.° 4.770.705, e aprobado por el Comité de Ética em Pesquisa Institucional em 12 de junho de 2021.

Palabras clave: Brasil; Denosumab; Epidemiología; Tumor óseo de células gigantes; Margens de excisión; Procedimientos quirúrgicos operatórios.
1. Introduction

The giant cell tumor of bone (GCTB) was first described in 1818 by Cooper. Years later, Nelaton and Virchow described, respectively, the local aggressiveness pattern and the potential for malignancy of this lesion. GCTB represents approximately 5% of primary bone tumors, and more than half of the cases affect individuals between 20 and 50 years of age; 3 to 5% of cases may present with pulmonary metastases and, despite being a benign neoplasm, it has high potential for bone destruction at the primary site of the lesion. The characteristic local aggressiveness of GCTB may be responsible for serious functional issues in affected patients. This is due to the frequent location in the long bones epiphyses, that is, in periarticular regions such as knee, wrist, hip, shoulder, among others (Bertoni, et al., 1985; Eckardt & Grogan, 1986; Siebenrock et al., 1988; Turcotte, 2006).

Multidisciplinary treatment of GCTB has been a cause for discussion in the last decade due to the discovery of drugs that prevent tumor progression and may be useful in cases of patients with local recurrences and unresectable tumors. Some studies have shown interesting results regarding the use of drugs such as denosumab in preoperative cytoreduction.

On the other hand, the therapeutic basis of GCTB remains the isolated surgical treatment (Luengo-Alonso et al., 2019). The most common surgical resection options are intralesional resection (curettage) and wide (or marginal) resection. Intralesional treatment presents higher rates of tumor recurrence, however it preserves the adjacent joint function and much of the individual bone stock. After curettage, cavity filling is often performed with bone cement or graft, to prevent subcondral bone collapse and provide structural support. Despite the controversy regarding the reduction of relapses, adjuvants such as absolute alcohol, phenol, liquid nitrogen and bone cement have been widely used. Although GCTB resection with wide margins presents lower recurrence rates, it has shown worse functional results and often presents complications in bone reconstructions. Reconstructions are usually performed with structural grafts, prosthetic solutions or both methods (O'Donnell et al., 1994; Prosser et al., 2005; Lackman et al., 2009).

Current knowledge of GCTB surgical outcomes has been based on major world series (Deheshi et al., 2007; Balke et al., 2009; Ferraz et al., 2016). On the other hand, there is a lack of Brazilian epidemiological and surgical data on this specific type of neoplasm, except for a few series of cases (Camargo et al., 2001; Baptista et al., 2001; Catalan et al., 2006; Rigollino et al., 2017).

The primary objective of this paper is to identify the epidemiological profile of GCTB. The secondary objectives are to describe the surgical aspects of treatment in the main diagnostic centers and treatment of bone tumors, to analyze the clinical and surgical aspects of patients with wrist and hand GCTB, and to analyze the clinical and surgical aspects of patients with knee GCTB. These findings may help in the maintenance or change of guidelines within the country for the treatment of GCTB.

2. Materials and Methods

2.1 Type of Study

A retrospective, multicenter national cohort study based on the data analysis from medical records of patients diagnosed with GCTB from co-participating centers.

2.2 Data Collection

Data collection will be performed locally from the printed clinical form (Figure 1) to all patients included in the study.
Figure 1. Data collection sheet (text in Portuguese).

**Ficha de coleta de dados: Tumor de Células Gigantes Ósseo – Estudo Epidemiológico**

**Instrução (abreviações):**

Nome de quem coletou os dados: ________________________________

1. Iniciante do paciente: ________________________________
2. N° de Registro na Instituição: ________________________________
3. Gênero: ( ) Masculino ( ) Feminino
4. Data de nascimento (dd/mm/aaaa): ________________________________
5. Data de diagnóstico (dd/mm/aaaa) - de acordo com exame anatômico:
6. Classificação de Conquista: ( ) Grau I ( ) Grau II ( ) Grau III
7. Data cirúrgica (dd/mm/aaaa):
8. **Local anatomático do tumor:**
   - ( ) dana Úmero
   - ( ) Proximal Tibia
   - ( ) Distal radio
   - ( ) Proximal Úmero
   - ( ) Distal Femor
   - ( ) Capitão
   - ( ) Sacro
   - ( ) Transmetacarpal
   - ( ) Metatarsal
   - ( ) Distal Úmero
   - ( ) Calcâneo
   - ( ) Outro – Descrever:
9. **Máscara Residual:** ( ) Sim ( ) Não ( ) não descrito
10. **Data Recidiva (dd/mm/aaaa – data de escama da imagem):** ________________________________
11. **Presença de fratura patológica junto ao tumor?**
   - ( ) Sim ( ) Não ( ) não descrito
12. **Tipo de cirurgia:** ( ) Interna ( ) Marginal ( ) Ampla ( ) não realizada ( ) não descrito
13. **Tipo de preenchimento da caridade, caso se aplique:**
   - ( ) Cimento ( ) Fardo ( ) sem preenchimento ( ) outro – Descrever ________________________________ ( ) não descrito
14. **Adjuvância, caso se aplique (posível mais de uma alternativa):**
   - ( ) Cetamento externa com braço celiático ( ) álcool ( ) Fisioterapia ( ) nitrogênio ( ) amônia ( ) Outro – Descrever ________________________________ ( ) não descrito
15. **Radicada:** ( ) Sim ( ) Não ( ) não descrito
16. **Data da 1ª recídua, caso se aplique (dd/mm/aaaa):** ________________________________
17. **Data da última caridade ortopédica (dd/mm/aaaa):** ________________________________
18. **Usado de Denominação:** ( ) Sim ( ) Não ( ) não descrito
19. **Indicação de Denominação, caso se aplique:**
   - ( ) Tumor irresolúvel ( ) Recidiva ( ) Cirurgia para facilitar cirurgia ( ) Tratamento de metástase ( ) Outro – Descrever ________________________________ ( ) não descrito
20. **Outro:** ( ) Sim ( ) Não
21. **Data de obite (dd/mm/aaaa):** ________________________________

**Espaço para observações sobre o caso:**

**Versão 3 ajuste:**

* Nos tumores que invadem mais de um osso, marcar o osso principal (centro geométrico). Quando não for possível determinar o local principal, descrever os ossos acompanhados. ** Nos casos com mais de um tipo de preenchimento de caridade, marcar o substâncias utilizadas: de maior volume. *** Se mais de uma recidiva, descrever nas observações e comentários ao final do questionário. Damnels – Dr. Edorado Reszker – Fone: 11-999999844 ou drerdor@iquopa.edu.br

Source: Authors.

2.3 Data Analysis

Data will be collected and sent to the coordinating center - Hospital de Clínicas de Porto Alegre (HCPA) - and then, it will be analyzed.
2.4 Eligibility Criteria

2.4.1 Inclusion Criteria

2.4.1.1 Patients diagnosed with GCTB confirmed by pathological examination.
2.4.1.2 Patients in any age group.
2.4.1.3 Primary tumors in any bone anatomical site.
2.4.1.4 Localized or metastatic disease.

2.4.2 Exclusion Criteria

2.4.2.1 Patients with conclusive diagnosis of secondary GCTB.
2.4.2.2 Absence of pathological examination confirming the diagnosis.

2.5 Sample Size

Considering a confidence level of 95% and error of 5%, we estimate a sample of 385 Patients. About 20 collaborating centers will be contacted and invited to participate, contributing approximately 20 cases each. Sampling will be for convenience. The calculation sample size was performed in the WinPEPI (Programs for Epidemiologists) version 11.65.

The sample size calculated at the beginning of the project will be maintained.

2.6 Statistical Analyses

Descriptive variables will be represented by absolute and relative frequency. Quantitative variables will be represented by mean and standard deviation.

Analyses of Kaplan-Meier curves will be used to describe and compare the groups.

Representations of this analysis will be made with mean and confidence interval.

To compare the groups (tumor site, gender, age group, etc.) the analysis of uni/multivariate Cox regression, being calculated the hazard ratio (HR).

Bivariate analyses will have their significance determined by chi-square, Student’s t-test, according to the type of data involved.

The level of significance adopted will be 5% (p≤.05) and the analyses will be carried out in the SPSS program, version 18.0.

2.7 Study Co-Participants Centers

The Study Co-Participants Centers are described in the Table 1.
| Study Co-Participants Centers list. |
|-----------------------------------|
| **Name** | **Hospital** | **Principal Researcher** |
|---------------------------------------------------------------|
| Hospital de Clínicas de Porto Alegre (COORDINATING CENTER) | | Ricardo Gehrke Becker |
| Hospital São Marcos | | Marcelo Barbosa Ribeiro |
| Hospital de Amor | | Eduardo Areas Toller |
| Hospital das Clínicas de Ribeirão Preto | | Edgard Eduard Engel |
| Hospital da Baleia/ Fundação Benjamin Guimarães | | Rodrigo de A. Gandra Peixoto |
| AC Camargo Cancer Center | | Suely Akiko Nakagawa |
| Hospital São Lucas PUC | | Osvaldo André Serafini |
| Santa Casa de Porto Alegre | | Alexandre David |
| Universidade de Passo Fundo - Vice-Reitoria de Pesquisa e Pós-Graduação | | Marcos Ceita Nunes |
| Hospital Santa Izabel - Santa Casa de Misericórdia da Bahia | | Alex Guedes |
| Instituto de Ortopedia e Traumatologia – Hospital das Clínicas – Faculdade de Medicina da Universidade de São Paulo (IOT-HC-FMUSP) | | André Mathias Baptista |
| Hospital Nossa Senhora de Pompeia | | Gustavo de Almeida Nunes Gil |
| Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA) | | Roberto André Torres de Vasconcelos |
| Faculdade de Medicina de Botucatu - Universidade Estadual de São Paulo | | Fabio Fernando Elói Pinto |
| Investiga/Beneficência Portuguesa | | Valter Penna |
| Hospital Haroldo Joaçaba - Instituto do Câncer do Ceará (ICC) | | Jose Marcello Sales Bruno |
| Hospital Ophir Loyola | | Fernando Brasil do Couto Filho |
| Hospital Erasto Gaertner | | Glaucio José Pauka Mello |
| Hospital Universitário da Universidade Federal de Sergipe | | Adonai Pinheiro Barreto |

Source: Authors.

2.8 Ethical Aspects

This research will begin after approval of the project by the Research Ethics Committee of HCPA, which will be the coordinating center of this study. The present study design was developed as recommended by the Resolution No. 466/2012 of the National Health Department. The researchers request waiver of a free and informed consent form and an assent term, since only the data contained in the patient's medical records will be accessed.

The researchers will sign a term of commitment for data use.

There are no known risks to this research, except those related to the possible confidentiality. However, the researchers involved are committed to ensuring the confidentiality of the data collected and published.

As for the benefits of this research, we can say that there is no direct benefit to participants of this research, as they have already undergone clinical treatment. However, future research participants will therefore benefit from education through a more complete possible will have an impact on reliable and safe results.

The new researchers involved in the project are committed to maintaining the confidentiality of information of the research participants already inserted in this project.

3. Budget

Financial resources will be requested for the implementation of this research through the Children's Cancer and Research and Events Incentive Fund and national research funding agencies, according to a budget spreadsheet.

Additional figures with statistical analyses, papers preparation and translation will be responsibility of the researchers.
4. Schedule

Due to the new objectives included in the project, it was necessary to adjust its schedule, as described in the Table 2.

Table 2. Adjusted project schedule.

| Discrimination Activity                      | Start      | Ending     |
|---------------------------------------------|------------|------------|
| CEP approval for 5th version                | 20/03/2021 | 20/04/2021 |
| Specific data analysis for master's degrees | 30/04/2021 | 30/04/2022 |
| Manuscripts preparation for publication     | 30/06/2021 | 30/06/2022 |
| Publication of articles                     | 30/06/2022 | 30/12/2022 |

Source: Authors.

5. Basic Infrastructure and Technical Support

The proposed trials have an adequate physical area and computers with statistical and biostatistical programs provided by the HCPA (Orthopedics and Traumatology Service, Research and Graduate Group, Clinical Pathology Service, Multi-tissue Bank). Proposent and team have experience in conducting projects and publishing results using the methodology specified above.

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