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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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Ricardo Gehrke Becker
ORCID: https://orcid.org/0000-0003-2629-9752
Federal University of Rio Grande do Sul, Brazil
E-mail: rbecker@hcpa.edu.br
Bruno Antunes Pereira
ORCID: https://orcid.org/0000-0003-1102-3083
Federal University of Rio Grande do Sul, Brazil
E-mail: bruno.pantunes@gmail.com
Carlos Roberto Galia
ORCID: https://orcid.org/0000-0003-1731-4543
Federal University of Rio Grande do Sul, Brazil
E-mail: carlosrgalia@gmail.com
Otavio Pereira Cadore
ORCID: https://orcid.org/0000-0001-6264-1143
Federal University of Rio Grande do Sul, Brazil
E-mail: otaviocadore@hotmail.com
Bruno Führ
ORCID: https://orcid.org/0000-0003-0965-592X
Federal University of Rio Grande do Sul, Brazil
E-mail: fuhr.bruno@gmail.com
Julie Francine Cerutti Santos Pestilho
ORCID: https://orcid.org/0000-0003-3630-8595
Children's Cancer Institute (ICI), Brazil
E-mail: juliefcerutti@gmail.com
Carlos Alberto Souza Macedo
ORCID: https://orcid.org/0000-0003-0412-4556
Federal University of Rio Grande do Sul, Brazil
E-mail: cmacedo@hcpa.edu.br
Willian Bernardo Spechet Rabusxke
ORCID: https://orcid.org/0000-0001-8051-6223
Federal University of Rio Grande do Sul, Brazil
E-mail: rabuskew@gmail.com
Eduardo da Silva Rodrigues
ORCID: https://orcid.org/0000-0001-5216-3504
Federal University of Rio Grande do Sul, Brazil
E-mail: edsrodrigues@hcpa.edu.br
Alex Guedes
ORCID: https://orcid.org/0000-0001-7013-7107
Federal University of Bahia, Brazil
Santa Izabel Hospital, Holy House of Mercy of Bahia, Brazil
Bone & Connective Tissue Service, Aristides Maltez Hospital, Bahiana League Against Cancer, Brazil
E-mail: alexguedes2003@yahoo.com.br

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 intralesional (with adjuvants), marginal or wide resection. Intralesional 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

aspects of patients with GCTB of wrist and hand, and to analyze the clinical and surgical aspects of patients with knee GCTB. These findings may help in the maintenance or change of national guidelines for the treatment of GCTB. This study protocol was submitted to ethical assessment under the CAAE (Ethical Appreciation Presentation Certificate) registry No. 94280918.0.0000.5327 (5th version), evaluated through the substantiated opinion No. 4.770.705, and approved by the Institutional Research Ethics Committee on June 12, 2022.
Keywords: Brazil; Denosumab; Epidemiology; Giant cell tumor of bone; Margins of excision; Surgical procedures, Operative.

Resumo

O tumor de células gigantes do osso (TCGO) representa aproximadamente 5% dos tumores ósseos primários, e mais da metade dos casos afetam indivíduos entre 20 e 50 anos de idade. Apesar de ser uma neoplasia benigna, 3 a 5% dos casos podem apresentar metástases pulmonares, além de possuir alto potencial de destruição óssea no sítio principal da lesão, muitas vezes nas epífises de ossos longos, o que pode levar a sérios problemas funcionais nos pacientes afetados. O tratamento multidisciplinar do TCGO tem sido motivo de discussão na última década devido à descoberta de medicamentos, como o denosumab, que previnem a progressão do tumor e podem ser úteis em casos de pacientes com recidivas locais e tumores não ressecáveis. A base terapêutica do TCGO permanece sendo o tratamento cirúrgico isolado por ressecção intralesional (com adjuvantes), marginal ou ampla. O tratamento intralesional apresenta maiores taxas de recidiva, porém preserva a função articular adjacente e grande parte do estoque ósseo individual. A ressecção com margens amplas apresenta menores taxas de recorrência, mas tem mostrado piores resultados funcionais e complicações frequentes nas reconstruções ósseas. O conhecimento atual dos desfechos cirúrgicos do TCGO tem sido baseado em grandes séries mundiais - faltam dados epidemiológicos e cirúrgicos brasileiros sobre esse tipo específico de neoplasia, com exceção de algumas séries de casos. O principal objetivo deste trabalho é identificar o perfil epidemiológico do TCGO; os objetivos secundários são descrever os aspectos cirúrgicos nos principais centros de diagnóstico e tratamento de tumores ósseos, analisar os aspectos clínicos e cirúrgicos dos pacientes com TCGO de punho e mão e analisar os aspectos clínicos e cirúrgicos dos pacientes com TCGO do joelho. Esses achados podem ajudar na manutenção ou mudança de diretrizes nacionais para o tratamento da TCGO. Este protocolo de estudo foi submetido à apreciação ética sob o registro CAAE (Certificado de Apresentação de Apreciação Ética) N. º 94280918.0.0000.5327 (5.ª versão), avaliado através do parecer consubstanciado N. º 4.770.705, e aprovado pelo Comitê de Ética em Pesquisa Institucional em 12 de junho de 2021.
Palavras-chave: Brasil; Denosumab; Epidemiologia; Tumor de células gigantes do osso; Margens de excisão; Procedimentos cirúrgicos operatórios.

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 epífisis de los huesos largos, lo que puede conducir a problemas funcionales graves en los pacientes afectados. El tratamiento multidisciplinario de TOCG ha sido un tema de discusión en la última década debido al descubrimiento de fármacos, como el denosumab, que previenen la progresión tumoral y pueden ser útiles en casos de pacientes con recurrencias locales y tumores no resecables. La base terapéutica de la TOCG sigue siendo el tratamiento quirúrgico aislado por resección intralesional (con adyuvantes), marginal o amplio. El tratamiento intralesional presenta tasas de recurrencia más altas, pero preserva la función articular adyacente y gran parte del stock óseo individual. La resección con márgenes amplios tiene tasas de recurrencia más bajas, pero ha 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 la 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 puño y mano, y analizar los aspectos clínicos y quirúrgicos de los pacientes con TOCG de rodilla. Estos 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. º 94280918.0.0000.5327 (5.ª versión), evaluado a través de la opinión incorporada N.º 4.770.705, y aprobado por el Comité de Ética de Investigación de la Institución el junio 12, 2021.
Palabras clave: Brasil; Denosumab; Epidemiología; Tumor óseo de células gigantes; Márgenes de escisión; Procedimientos quirúrgicos operativos.

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

Instituição (abreviatura):

Nome de quem coletou os dados: ----------

1. Iniciaismpleto do paciente:
2. N° do Registro na Instituição:
3. Gênero: ( ) Masculino ( ) Feminino
4. Data nascimento (dd/mm/aaaa):
5. Data do diagnóstico (dd/mm/aaaa- de acordo com exame anátomo):
6. Classificação de Campanacci: ( ) Grau I ( ) Grau II ( ) Grau III
7. Data cirurgia (dd/mm/aaaa):
8. *Local anatômico do tumor:

( ) Distal Fêmur	( ) Proximal Tíbia	( ) Distal Rádio	( ) Proximal Umero
( ) Proximal Fêmur	( ) Bacia	( ) Sacro	( ) Distal Ulna
( ) Fibula	( ) Distal Tíbia	( ) Metacarpal	( ) Metatarsal
( ) Distal Umero	( ) Calcâneo	( ) Outro – descrever->	

9. Metástase Pulmonar: ( ) Sim ( ) Não ( ) não descrito
10. Data Recidiva (dd/mm/aaaa – data do exame de imagem)
11. Presença de fratura patológica junto ao tumor?

( ) Sim ( ) Não ( ) não descrito

12. Tipo de cirurgia ( ) Intralesional ( ) Marginal/Ampla ( ) não realizada ( ) não descrita
13. **Tipo de preenchimento da cavidade, caso se aplique:

( ) Cimento ( ) Enxerto ósseo ( ) sem preenchimento ( ) outro, descrever _____ ( ) não descrito

14. Adjuvância, caso se aplique (possível mais de uma alternativa):

( ) curetagem estendida com broca cebolinha ( ) álcool / Fenol ( ) fulguração ( ) nitrogênio ( ) nenhuma ( ) Outra-> descrever:_____ ( ) não descrito

15. Recidiva: ( ) Sim ( ) Não ( ) não descrito
16. ***Data da 1 ° recidiva, caso se aplique (dd/mm/aaaa):
17. Data da última consulta ortopédica (dd/mm/aaaa):
18. Uso de Denosumab: ( ) Sim ( ) Não ( ) Não descrito
19. Indicação do Denosumab, caso se aplique:

( ) Tumor irressecável ( ) Recidiva ( ) Citorredução para facilitar cirurgia ( ) Tratamento de metástase ( ) Outros – Descrever _____ ( ) Não descrito

20. Óbito: ( ) Sim ( ) Não
21. Data do óbito: (dd/mm/aaaa)

Espaço para observações sobre o caso:

Versão 2_ajuste

** Nos tumores que invadem mais de um osso, marcar o sítio primário (centro geométrico). Quando não for possível determinar o local primário, descrever os ossos acometidos. ** Nos casos com mais de um tipo de preenchimento da cavidade, marcar o substituto utilizado de maior volume. *** Se mais de uma recidiva, descrever nas observações e comentários ao final do questionário.* ***Dúvidas -> Pesquisador Dr. Ricardo Becker – Fone: 51-998055644 ou rbecker@hcpa.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% ($p \leq .05$) 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.

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 Pompéia	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	Glauco 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). Proponent and team have experience in conducting projects and publishing results using the methodology specified above.

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