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**CISTO ODONTOGÊNICO CALCIFICANTE: *UM ESTUDO  
MULTICÊNTRICO***

**Faculdade de Odontologia  
Universidade Federal de Minas Gerais  
Belo Horizonte  
2019**

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MULTICÊNTRICO***

Dissertação apresentada ao Colegiado de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Mestre em Odontologia – área de concentração em Estomatologia

**Orientador:** Prof. Ricardo Alves de Mesquita

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## FOLHA DE APROVAÇÃO

**CISTO ODONTOGÊNICO CALCIFICANTE: UM ESTUDO MULTICÊNTRICO**

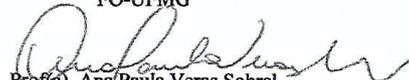
**JOSÉ ALCIDES ALMEIDA DE ARRUDA**

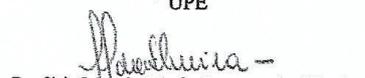
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“A doença é a zona noturna da vida, uma cidadania mais onerosa. Todos que nascem têm dupla cidadania, no reino dos sãos e no reino dos doentes. Apesar de todos preferirmos só usar o passaporte bom, mais cedo ou mais tarde nos vemos obrigados, pelo menos por um período, a nos identificarmos como cidadãos desse outro lugar.”

Susan Sontag

## RESUMO

Este estudo investigou a frequência do cisto odontogênico calcificante (COC) submetido à análise histopatológica em diferentes regiões geográficas do Brasil. Em uma análise retrospectiva (1953-2016), arquivos de biópsias de 10 centros de Patologia Oral e Maxilofacial localizados em diferentes estados do Brasil: Goiás, Minas Gerais, Pará, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina e São Paulo foram analisados. Dados demográficos, características clinicopatológicas, aspectos radiográficos e tipos de biópsia foram avaliados descritivamente. O teste Mann-Whitney foi utilizado para determinar a associação entre sintomas, tempo de evolução e tamanho da lesão. A significância estatística foi estabelecida como  $p < 0,05$ . O diagnóstico do COC foi de acordo com a classificação da Organização Mundial de Saúde (2017). Adicionalmente, uma revisão da literatura de série de casos de COC foi realizada em quatro bases de dados eletrônicas (PubMed, Medline Ovid, Web of Science e Scopus). Dos 198.350 espécimes de biópsias exploradas, 268 casos de COC foram avaliados, representando 0,1% das lesões orais dos centros estudados. Em geral, indivíduos do sexo feminino ( $n=142$ , 54.0%), na segunda década de vida ( $n=76$ , 31.0%) com acometimento da maxila ( $n=141$ , 54.4%) foram os mais afetados. O tamanho médio das lesões dos indivíduos sintomáticos foi maior que o dos casos assintomáticos ( $p=0,026$ ). A revisão da literatura apresentou maior frequência dos casos de COC na Ásia (186 casos) e na Europa (68 casos), acometendo principalmente os homens ( $n=247$ , 56.2%) na terceira década de vida. O COC é uma lesão rara. Novos dados sobre as características clinicopatológicas de 268 casos foram adicionados à literatura. Os dados referentes ao gênero e idade dos pacientes brasileiros aqui relatados são diferentes dos achados de séries de casos relatados já na literatura. Este estudo fornece informações que podem ajudar os clínicos, patologistas e cirurgiões no diagnóstico e manejo do COC.

**Palavras-chave:** Cistos. Neoplasias. Anormalidades da Boca. Arcada Osseodentária. Medicina Bucal. Patologia Bucal. Epidemiologia.

## ABSTRACT

### Calcifying odontogenic cyst: a multicenter study

This study investigated the frequency of calcifying odontogenic cyst (COC) submitted to histopathological analysis in different geographic regions of Brazil. In a retrospective analysis (1953-2016), biopsy files of 10 Oral and Maxillofacial Pathology centers located in different states of Brazil: Goiás, Minas Gerais, Pará, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina and São Paulo were analyzed. Demographic data, clinicopathological characteristics, radiographic aspects and treatment were evaluated descriptively. The Mann-Whitney test was used to determine the association between symptoms, evolution time and lesion size. Statistical significance was set as  $p < 0.05$ . The diagnosis of COC was according to the classification of the World Health Organization (2017). In addition, a literature review of case series was carried out in four electronic databases (PubMed, Medline Ovid, Web of Science and Scopus). Of 198,350 specimens of biopsies analyzed, 268 cases of COC were surveyed, representing 0.1% of the oral lesions at the centers studied. Overall, female patients ( $n=142$ , 54.0%) in their second decade of life ( $n=76$ , 31.0%) and the maxilla ( $n=141$ , 54.4%) were more affected. The mean lesion size of symptomatic individuals was larger than that of cases without symptoms ( $p=0.026$ ). The literature review showed a higher frequency in Asia (186 cases) and Europe (68 cases), mainly affecting men ( $n=247$ , 56.2%) in the third decade of life. COC is a rare lesion. Additional data on the clinicopathological features of 268 cases have been added to the literature. Data regarding gender and age of the Brazilian patients reported herein are different with findings of case series and retrospective studies reported in the literature. This study provides information that could help clinicians, pathologists, and surgeons in the diagnosis and management of COC.

**Keywords:** Cysts. Neoplasms. Mouth Abnormalities. Jaw. Oral Medicine. Oral Pathology. Epidemiology.

## LISTA DE ABREVIATURAS E SIGLAS

COC	Calcifying Odontogenic Cyst
COC	Cisto Odontogênico Calcificante
OMS	Organização Mundial de Saúde
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

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## 1 CONSIDERAÇÕES INICIAIS

A primeira descrição detalhada do cisto odontogênico calcificante (COC) foi publicada em 1962 por Gorlin *et al.* (1962), seguida de uma descrição por Gold em 1963 (GOLD, 1963), na ocasião, a lesão foi denominada como cisto de Gorlin. Entretanto, o COC já havia sido descrito anteriormente por Thoma nos Estados Unidos. O autor apresentou a primeira evidência radiológica do COC associada a um odontoma. Rywkind na Rússia, Bloodgood nos Estados Unidos e Sato no Japão também documentaram esse cisto odontogênico (IDE *et al.*, 2015).

Algumas nomenclaturas foram atribuídas ao COC devido as distintas características clínicas, radiográficas e microscópicas. Gorlin *et al.* (1962) o denominaram como uma entidade patológica distinta e de lesão cística não-neoplásica. No entanto, Praetorius *et al.* (1981) propuseram uma nova classificação e revisaram o potencial dessa lesão. Em 2005, a Organização Mundial de Saúde (OMS) denominou essa lesão como tumor odontogênico cístico calcificante, além de definir as outras variáveis, tumor dentinogênico de células fantasmas e carcinoma odontogênico de células fantasmas, como entidades patológicas distintas (BARNES *et al.*, 2005). No entanto, em 2017, a OMS definiu o COC como uma lesão cística simples revestida por epitélio tipo ameloblastomatoso, que contém acúmulos focais de células-fantasma (EL-NAGGAR *et al.*, 2017).

Os COCs representam aproximadamente 1% dos cistos dos maxilares (ARRUDA *et al.*, 2018; DE SOUZA *et al.*, 2010; JAEGER *et al.*, 2017; JOHNSON *et al.*, 2014; JONES, CRAIG e FRANKLIN, 2006). Mesmo raro, alguns casos de COC periféricos acometendo gengiva/rebordo alveolar em indivíduos jovens foram descritos na literatura (DE ARRUDA *et al.*, 2018a). Recentemente, dados demográficos, características clinicopatológicas, achados radiográficos, tratamento e recorrência dos COCs foram discutidos em uma revisão sistemática da literatura (DE ARRUDA *et al.*, 2018a). Aproximadamente 367 casos foram reportados, sendo os continentes com maior número de casos a Ásia, seguido da Europa e da América do Norte. De forma geral, homens e mulheres foram afetados igualmente, numa relação homem-mulher de 1,0:1, com predileção para a segunda década de vida. Interessantemente, a grande maioria dos casos de COC são totalmente assintomáticos e, diagnosticados fortuitamente durante o exame radiológico. Quando

sintomáticos, um discreto aumento de volume tem sido descrito como o principal achado clínico (BUCHNER, 1991; LUCCHESI *et al.*, 2011). Ademais, as lesões ligeiramente ocorrem na mandíbula, com discreta ocorrência pela região anterior dos maxilares (DE ARRUDA *et al.*, 2018a; GORLIN *et al.*, 1964; HABIBI *et al.*, 2011; IIDA *et al.*, 2006; IRANI e FOROUGH, 2017; LUCCHESI *et al.*, 2007; SHAMASKIN, SVIRSKY e KAUGARS, 1989).

Radiograficamente, pode se apresentar como imagem radiolúcida uni ou multilocular (DE ARRUDA *et al.*, 2018a; GALLANA-ALVAREZ *et al.*, 2005; IRANI e FOROUGH, 2017; LUCCHESI *et al.*, 2007). As margens podem variar de bem definidas e corticalizadas, como pobremente definidas (CHINDASOMBATJAROEN *et al.*, 2007; DE ARRUDA *et al.*, 2018a; MARQUES *et al.*, 2010). Além de poder apresentar evidência de pequenos focos de massa calcificada que aparecem como áreas salpicadas brancas ou grânulos pequenos e homogêneos; ou mostrar-se como massa sólida e amorfa (WHITE e PHAROAH, 2015). A calcificação é uma importante característica radiográfica na interpretação dessa lesão, porém sendo detectada em apenas cerca da metade dos casos. As características microscópicas confirmam que as massas calcificadas podem não necessariamente ser observadas no exame radiográfico, embora possam ser encontradas microscopicamente (DANIELS, 2004; MARQUES *et al.*, 2010). Em quase um terço dos casos de COC, as lesões radiolúcidas estão associadas a dentes não erupcionados, sendo mais frequente o canino em ambos os maxilares. Muitos desses cistos apresentam-se com um diâmetro aproximadamente de dois a quatro centímetros e reabsorção radicular e divergência dos dentes adjacentes tem sido observadas com certa frequência (DE ARRUDA *et al.*, 2018a; IRANI e FOROUGH, 2017; ROJO *et al.*, 2017).

Histologicamente, o COC é caracterizado por uma camada basal bem definida no revestimento epitelial, com um estrato subjacente composto por células epiteliais que se assemelham ao retículo estrelado do órgão do esmalte e massas de células epiteliais fantasmas localizadas no revestimento epitelial cístico ou na cápsula fibrosa. Dentina displásica e áreas de formação de tecido mineralizado dental podem ocasionalmente ser detectadas (EL-NAGGAR *et al.*, 2017; LEDESMA-MONTES *et al.*, 2008; YOSHIDA *et al.*, 2001). Ainda, o COC pode ser identificado em associação a outras lesões odontogênicas, como odontoma, fibroma ameloblástico, cisto dentífero, tumor odontogênico adenomatóide, ameloblastoma, fibro-odontoma ameloblástico,

ceratocisto odontogênico e cisto odontogênico ortoceratinizado (DE ARRUDA *et al.*, 2018a; IDE *et al.*, 2019; LEDESMA-MONTES *et al.*, 2008; LUCCHESI *et al.*, 2011).

O tratamento para os COCs é a excisão cirúrgica. A recomendação para as modalidades intraósseas geralmente é conservadora e consiste na enucleação com curetagem (DANIELS, 2004; DE ARRUDA *et al.*, 2018; MARQUES *et al.*, 2010; TOMICH, 2004). As recidivas do COC são baixas e o prognóstico é considerado bom na maioria dos casos (DE ARRUDA *et al.*, 2018). Mesmo sendo raro, alguns casos de tumor dentinogênico de células fantasmas e de carcinoma odontogênico de células fantasmas foram reportados como sendo lesões recorrentes do COC (DE ARRUDA *et al.*, 2018).

Alguns estudos epidemiológicos com grande número de casos de COC foram publicados fornecendo o conhecimento necessário para conhecer e determinar o perfil clínico, radiográfico e histopatológico do COC nas diferentes regiões geográficas do mundo (HABIBI *et al.*, 2011; IRANI e FOROUGH, 2017; LEDESMA-MONTES *et al.*, 2008; LUCCHESI *et al.*, 2011). No entanto, os relatos de séries de casos de COC na América do Sul são incomuns (ARRUDA *et al.*, 2018; FREGNANI *et al.*, 2003; GOMES DA SILVA *et al.*, 2014). Além de que, estudos multicêntricos epidemiológicos com base em laudos histopatológicos de biópsias orais e maxilofaciais são de grande importância por fornecer informações úteis que podem ajudar os clínicos, os patologistas orais e maxilofaciais, bem como os cirurgiões no diagnóstico e manejo dos indivíduos afetados com lesões bucais (DE ARRUDA *et al.*, 2017; DE ARRUDA *et al.*, 2018b; DE ARRUDA *et al.*, 2019; SILVA *et al.*, 2017; SILVA *et al.*, 2018; SILVA *et al.*, 2018; VASCONCELOS *et al.*, 2018).

Nesse contexto, o objetivo deste estudo multicêntrico foi determinar a frequência do COC entre as lesões que foram submetidas a exame histopatológico em cinco regiões geográficas do Brasil. Adicionalmente, os dados demográficos, as características clinicopatológicas, os aspectos radiográficos e tratamento dos COCs foram comparados com os estudos obtidos através de uma revisão da literatura.

## 1.1 Objetivos da pesquisa

### 1.1.1 Objetivos gerais

Este estudo investigou a ocorrência do COC com base nos arquivos de biópsias de centros de Patologia Oral e Maxilofacial localizados em diferentes estados do Brasil: Goiás, Minas Gerais, Pará, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina e São Paulo. Ademais, os dados analisados dos COCs foram comparados com as informações dos estudos obtidos através de uma revisão da literatura.

#### 1.1.2 Objetivos específicos

- a) Analisar os dados demográficos, as características clinicopatológicas, os aspectos radiográficos e tipo de biópsia dos COCs;
- b) Realizar uma revisão da literatura de estudos retrospectivos e séries de casos de COCs.

## 2 METODOLOGIA EXPANDIDA

### 2.1 Estudo multicêntrico

#### 2.1.1 Considerações éticas

O estudo foi aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (Número do Parecer: 2.692.400 e CAAE: 89194618.0.1001.5149) (Anexo A), e foi realizado de acordo com os princípios éticos Declaração de Helsinque (BELSEY, 1978).

#### 2.1.2 Desenho do estudo

Este foi um estudo do tipo observacional retrospectivo.

#### 2.1.3 População e seleção da amostra

Foram avaliados laudos histopatológicos de biópsias de COC. Os dados foram obtidos de 10 centros de referência de patologia oral e maxilofacial no Brasil:

- a) Departamento de Diagnóstico Oral e Patologia Geral da Faculdade de Odontologia da Universidade Federal Fluminense (Rio de Janeiro). Período da análise dos casos entre 2014 a 2016;
- b) Laboratório de Patologia Bucal do Centro Universitário do Pará (Pará). Período da análise dos casos entre 2008 a 2016;
- c) Laboratório de Patologia Bucal, Centro Goiano de Doenças da Boca da Faculdade de Odontologia da Universidade Federal de Goiás (Goiás). Período da análise dos casos entre 1996 a 2016;
- d) Departamento de Semiologia e Clínica da Faculdade de Odontologia da Universidade Federal de Pelotas (Rio Grande do Sul). Período da análise dos casos entre 1959 a 2016;

- e) Departamento de Clínica, Patologia e Cirurgia Odontológicas da Faculdade de Odontologia da Universidade Federal de Minas Gerais (Minas Gerais). Período da análise dos casos entre 1953 a 2016;
- f) Departamento de Patologia e Diagnóstico Oral da Faculdade de Odontologia da Universidade Federal do Rio de Janeiro (Rio de Janeiro). Período da análise dos casos entre 1975 a 2016;
- g) Departamento de Odontologia, Programa de Pós-graduação em Patologia Oral da Universidade Federal do Rio Grande do Norte (Rio Grande do Norte). Período da análise dos casos entre 1978 a 2016;
- h) Departamento de Odontologia Conservadora, Disciplina de Patologia Bucal da Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul (Rio Grande do Sul). Período da análise dos casos entre 1953 a 2016;
- i) Departamento de Patologia do Centro de Ciências da Saúde da Universidade Federal de Santa Catarina (Santa Catarina). Período da análise dos casos entre 2006 a 2016;
- j) Departamento de Estomatologia, Disciplina de Patologia Oral e Maxilofacial da Faculdade de Odontologia da Universidade de São Paulo (São Paulo). Período da análise dos casos entre 1996 a 2016.

#### 2.1.4 Critérios de inclusão, análise histopatológica e critérios de exclusão

As lesões foram analisadas de acordo com os critérios de diagnósticos do COC de acordo com a última classificação da OMS (EL-NAGGAR *et al.*, 2017). Adicionalmente, foram notificados os casos de tumor dentinogênico de células fantasmas e carcinoma dentinogênico de células fantasmas. Os registros com falta de informação sobre o diagnóstico histopatológico foram excluídos.

#### 2.1.5 Análise dos dados demográficos, características clínicas, aspectos radiográficos e tipo de biópsia

Foram avaliados sexo, idade, cor da pele (branca ou não-branca). As lesões foram analisadas de acordo com o tempo de evolução (em meses), sintomatologia

(assintomático ou sintomático), localização anatômica (região anterior: lesão nas regiões de incisivos e caninos; região posterior: lesão nas regiões de pré-molares, molares, ramo da mandíbula e região do seio maxilar; lesões extra-ósseas/periféricas), achados radiográficos através de radiografias convencionais ou de tomografia computadorizada de feixe cônico (radiolúcida/hipodensa ou mista ou radiopaca/hiperdensa; unilocular ou multilocular), tamanho da lesão (determinado de acordo com o maior diâmetro), alteração na cortical óssea (expansão e/ou perfuração), associação com um dente (impactado, deslocamento e ou reabsorção da raiz), tipo de biópsia e recorrência (WHITE, 1989).

## 2.2 Revisão da literatura

### 2.2.1 Fontes de informações, critérios de elegibilidade e buscas

Uma revisão da literatura foi realizada para investigar estudos sobre COC. Os critérios de inclusão foram: estudos retrospectivos e séries de casos que incluíram pelo menos 10 casos de COC, sem restrição do ano de publicação.

Os critérios de exclusão foram estudos em outras línguas que não o inglês, espanhol ou português, bem como estudos sem textos completos disponíveis. As bases de dados eletrônicas utilizadas foram PubMed (National Library of Medicine), Medline Ovid (Wolters Kluwer), Web of Science (Thomson Reuters) e Scopus (Elsevier).

A busca foi realizada em março de 2018, utilizando as seguintes palavras-chave e entretermos: *calcifying odontogenic cyst OR calcifying cystic odontogenic tumour OR Gorlin cyst OR dentinogenic ghost cell tumour OR odontogenic ghost cell tumour OR ghost cell odontogenic carcinoma OR epithelial odontogenic ghost cell tumour OR calcifying ghost cell odontogenic tumour*.

As referências recuperadas foram exportadas para o software (Thompson Reuters, New York, NY, EUA). Após a remoção dos duplicados, a seleção dos estudos foi realizada em duas fases. Na fase 1, foram incluídos títulos/resumos que atendiam aos critérios de elegibilidade. Se um título/resumo forneceu informações insuficientes para uma decisão sobre inclusão/exclusão, o texto completo foi obtido e avaliado na

fase 2. Aqueles que preencheram os critérios de elegibilidade também foram incluídos.

### 2.2.2 Extração de dados e itens

Os seguintes dados foram extraídos dos artigos incluídos na revisão de literatura: autor e ano de publicação, país, número de casos relatados, sexo e idade dos indivíduos, localização anatômica, características radiográficas, dente associado à lesão, tratamento fornecido e recorrência da lesão.

### 2.3 Análise dos dados

A análise dos dados foi realizada no software Statistical Package for the Social Sciences (SPSS), versão 23.0 (SPSS Inc., Chicago, IL, EUA). A estatística descritiva foi realizada para caracterizar os casos quanto ao sexo, idade, cor da pele, sintomatologia, localização anatômica, tempo de evolução, tipo de biópsia, tamanho e tipo de manifestação (i.e., primária ou recorrente). O teste de Kolmogorov-Smirnov mostrou que as variáveis quantitativas (tempo de evolução e tamanho da lesão) apresentaram distribuição não normal. Dessa forma, o teste não paramétrico de Mann-Whitney foi utilizado para determinar a associação entre sintomas, tempo de evolução e tamanho da lesão. Significância estatística foi estabelecida em  $p < 0,05$ .

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# A multicentre study of 268 cases of calcifying odontogenic cysts and a literature review

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## Abstract

**Objectives:** To investigate the frequency of calcifying odontogenic cysts (COCs) that have been submitted for microscopic examination from representative geographic regions of Brazil and to compare it with literature data.

**Materials and Methods:** A retrospective study was conducted on biopsies obtained from 1953 to 2016 at 10 Brazilian oral and maxillofacial pathology centres. A total of 198,350 biopsy specimens were analysed. Demographic data and histopathological diagnosis were evaluated descriptively and statistically. In addition, a literature review of case series was carried out in four electronic databases.

**Results:** A total of 268 cases of COC were surveyed, representing 0.1% of the oral lesions at the centres studied. Female patients in their second decade of life and the maxilla were more affected. The mean lesion size of symptomatic individuals was larger than that of cases without symptoms ( $p = 0.026$ ). The literature review showed



a higher frequency in Asia and Europe, mainly affecting men in the third decade of life.

**Conclusions:** COC is a rare lesion. Novel data on the clinicopathological features of 268 cases have been added to the literature. Data regarding gender and age of the Brazilian patients reported herein contrast with findings of case series and retrospective studies reported elsewhere.

**KEYWORDS**

calcifying odontogenic cyst, diagnosis, epidemiology, Gorlin cyst, jaw cysts, odontogenic cyst

## 1 | INTRODUCTION

The first detailed description of calcifying odontogenic cyst (COC) was published in 1962 by Gorlin, Pindborg, Odont, Clausen, and Vickers (1962), followed by a description by Gold in 1963 (Gold, 1963). However, COC had already been reported five decades earlier by Thoma in the United States. The author presented the first radiological evidence of such a lesion associated with odontoma. Rywkind in Russia, Bloodgood in the United States and Sato in Japan also provided previous contributions to this issue (Ide et al., 2015).

Calcifying odontogenic cyst is a rare lesion of the jaws and has been defined as a simple cyst lined with ameloblastoma-like epithelium containing focal ghost cells, which are also found in the dentinogenic ghost cell tumour (DGCT) and in the ghost cell odontogenic carcinoma (GCOC) (Barnes, Eveson, Reichart, & Sidransky, 2005; Chrcanovic & Gomez, 2016; Hong, Ellis, & Hartman, 1991; Ledesma-Montes et al., 2008). There has been much debate about whether COC is a neoplasm or a developmental cyst (Ledesma-Montes et al., 2008; Li & Yu, 2003; Toida, 1998). The histogenesis and clinicopathological features of COC strengthen the hypothesis of a developmental cyst arising from the dental lamina (Ledesma-Montes et al., 2008; Li & Yu, 2003).

The incidence of COC is estimated at 1%–3% of all odontogenic cysts and tumours (Buchner, Merrell, & Carpenter, 2006a; Jaeger et al., 2017; Luo & Li, 2009), with a slight prevalence among males in their 30 s (Ledesma-Montes et al., 2008). The lesion usually presents as a painless swelling with a unilocular and scalloped radiographic border (Buchner, 1991; Li & Yu, 2003). Displacement of teeth and root resorption are relatively common (Buchner, 1991; Chindasombatjaroen, Poomsawat, & Klongnoi, 2012; Ledesma-Montes et al., 2008). Extraosseous lesions may also occur and are usually found in the anterior region of either jaw (Hong et al., 1991). The treatment of COC is a conservative approach. The literature has recommended enucleation associated with curettage (Buchner, 1991; Shamskin, Svirsky, & Kaugards, 1989), and marsupialization/decompression has also been used for the treatment of large COCs in order to reduce the cyst size and to mitigate the extent of surgery, improving the prognosis (Emam, Smith, Briody, & Jatana, 2017; Kim, Choi, & Ko, 2016; Souza et al., 2007). Low recurrence rates of approximately 5% have been reported (Buchner, 1991; Daniels, 2004).

Some epidemiological studies with a larger number of COC cases have been published in the English literature (Irani & Foroughi, 2017; Ledesma-Montes et al., 2008), providing the data necessary to know and determine the clinical, radiographic and histopathological profile of the COC in the different geographic regions of the world. However, reports of case series of COC in South America are uncommon (Fregnani et al., 2003; Gomes da Silva, Ribeiro Bartholomeu Dos Santos, Cabral, Azevedo, & Pires, 2014). Thus, the scope of this multicentre study was to determine the frequency of COC among lesions that have been submitted for microscopic examination in five geographic regions of Brazil. Moreover, the data were compared with those obtained from a review of the literature.

## 2 | MATERIALS AND METHODS

### 2.1 | Multicentre study

#### 2.1.1 | Study design and ethical approval

A total of 198,350 histopathological records of oral and maxillofacial biopsies were analysed in a retrospective study. The records were obtained from a consortium of 10 services of oral and maxillofacial pathology in five Brazilian regions: north, north-east, south, south-east and midwest (Table 1). The study was approved by the Ethics Committee of the Federal University of Minas Gerais (Approval No. 016/2003). Patient's anonymity was guaranteed according to the Helsinki Declaration. Furthermore, a literature review of cases series of COC published in four electronic databases was conducted.

#### 2.1.2 | Sample

A total of 268 biopsy records of COC were retrieved. Affected individuals were analysed regarding gender, age and skin colour (white or nonwhite). Lesions were analysed in terms of evolution time [month(s)], symptoms (symptomatic or asymptomatic), anatomical location [data were detailed according to the following parameters: (anterior: lesions in the incisor/canine region; posterior: lesions in the premolar/molar/retromolar/ramus/maxillary sinus region; and extraosseous/peripheral lesion), radiological features (radiolucent; mixed; or radiopaque and unilocular or multilocular), size [determined according to the largest

**TABLE 1** Information regarding the sources of the reviewed cases

Service	State	Geographic area (km <sup>2</sup> ) <sup>a</sup>	Population (million)	Period	Number of biopsied lesions	COC (n)	COC (%) <sup>b</sup>	Odontogenic cysts (n)	COC in relation to the odontogenic cysts (%)
USP <sup>c</sup>	São Paulo	248.209	45.094.866	1996-2016	65,385	70	0.10	4,507	1.55
UFMG <sup>d</sup>	Minas Gerais	586.528	21.119.536	1953-2016	34,046	53	0.15	2,618	2.02
UFRN <sup>e</sup>	Rio Grande do Norte	52.797	3.507.003	1978-2016	15,007	40	0.26	1,661	2.40
UFPEL <sup>f</sup>	Rio Grande do Sul	281.748	11.322.895	1959-2016	23,893	14	0.05	4,419	0.31
UFG <sup>g</sup>	Goiás	340.086	6.778.772	1996-2016	10,246	30	0.29	1,078	2.78
UFRJ <sup>h</sup>	Rio de Janeiro	43.696	16.718.956	1975-2016	13,780	25	0.18	1,361	1.83
UFRGS <sup>i</sup>	Rio Grande do Sul	281.748	11.322.895	1953-2016	31,163	19	0.06	3,934	0.48
CESUPA <sup>j</sup>	Pará	1.248.000	8.366.628	2008-2016	1,280	10	0.78	185	5.40
UFSC <sup>k</sup>	Santa Catarina	95.346	6.778.772	2006-2016	2,703	5	0.18	324	1.54
UFF <sup>l</sup>	Rio de Janeiro	43.696	16.718.956	2014-2016	847	2	0.23	43	4.65
Total	-	-	-	-	198,350	268	0.13	20,130	1.33

Note. <sup>a</sup>Data according to the Brazilian Institute of Geography and Statistics (Brazilian Institute of Geography and Statistics (IBGE), 2017); <sup>b</sup>percentage of the whole sample; <sup>c</sup>Department of Oral Medicine and Oral Maxillofacial Pathology, School of Dentistry of the Universidade de São Paulo (south-east region); <sup>d</sup>Department of Oral Surgery and Pathology, School of Dentistry of the Universidade Federal de Minas Gerais (south-east region); <sup>e</sup>Post-Graduation Program in Oral Pathology of the Universidade Federal do Rio Grande do Norte (north-east region); <sup>f</sup>Diagnostic Centre for Oral Diseases of the Universidade Federal de Pelotas (south region); <sup>g</sup>Department of Stomatology (Oral Pathology), School of Dentistry of the Universidade Federal de Goiás (Midwest region); <sup>h</sup>Department of Oral Diagnosis and Pathology, School of Dentistry of the Universidade Federal do Rio de Janeiro (south-east region); <sup>i</sup>Department of Oral Pathology, School of Dentistry of the Universidade Federal do Rio Grande do Sul (south region); <sup>j</sup>Department of Oral and Maxillofacial Pathology, School of Dentistry of the Centro Universitário do Pará (north region); <sup>k</sup>Health Sciences Centre, School of Dentistry of the Universidade Federal de Santa Catarina (south region); <sup>l</sup>Department of Oral Medicine and Pathology, School of Dentistry of the Universidade Federal Fluminense (south-east region).

diameter (White, 1989)], alteration in the cortical bone (expansion and/or perforation), association with a tooth (impacted, tooth displacement and/or tooth root resorption), type of biopsy, recurrence and histopathological diagnosis. COC associated with other odontogenic cysts and/or tumours was also recorded.

The lesions were classified according to the 2017 classification of the World Health Organization (WHO) (El-Naggar, Chan, Grandis, Takata, & Slootweg, 2017). The cases were analysed individually by 10 oral and maxillofacial pathologists. Each oral and maxillofacial pathologist had more than 20 years of experience in microscopic diagnosis. Records with lack of information regarding histopathological diagnosis were excluded.

## 2.2 | Literature review

### 2.2.1 | Information sources, eligibility criteria and search

A review of the literature was carried out to retrieve studies on COC. The inclusion criteria were retrospective studies and case series that included at least 10 cases of COC, with no restriction of year of publication.

Exclusion criteria were studies in languages other than English, Spanish or Portuguese and studies with no available full texts. PubMed (National Library of Medicine), Medline Ovid (Wolters Kluwer), Web of Science (Thomson Reuters) and Scopus (Elsevier) electronic databases were examined to identify studies. The search was undertaken in March 2018 using the following entry terms and keywords: calcifying odontogenic cyst OR calcifying cystic odontogenic tumour OR Gorlin cyst OR dentinogenic ghost cell tumour OR odontogenic ghost cell tumour OR ghost cell odontogenic carcinoma OR epithelial odontogenic ghost cell tumour OR calcifying ghost cell odontogenic tumour. The retrieved references were exported to the EndNote software (Thompson Reuters, New York, NY, USA). After removal of duplicates, the selection of the studies was performed in two phases. In phase 1, titles/abstracts that met the eligibility criteria were included. If a title/abstract provided insufficient information for a decision about inclusion/exclusion, the full text was obtained and assessed in phase 2. Those who met the eligibility criteria were also included.

### 2.2.2 | Data extraction and items

The following data were extracted from the articles included in the literature review: author and year of publication, country, number of cases reported, participants' gender and age, anatomical location, radiographic features, impacted tooth associated, treatment provided and recurrence of lesions.

### 2.2.3 | Data analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0 (SPSS Inc., Chicago, IL,

USA). Descriptive statistics was carried out to characterize the cases regarding patient's gender, age, skin colour as well as symptoms, anatomical location, evolution time, type of biopsy, size, and type of manifestation. The Kolmogorov-Smirnov test showed that the quantitative variables (evolution time and lesion size) presented non-normal distribution. Therefore, the nonparametric Mann-Whitney test was used to determine the association between symptoms, evolution time and lesion size. Statistical significance was set at  $p < 0.05$ .

## 3 | RESULTS

A total of 198,350 histopathological records of oral and maxillofacial biopsies were diagnosed at the 10 referral services studied; 20,130 were odontogenic cysts (10.1%), and of these, 268 (0.1% of all records and 1.3% of all odontogenic cysts) were COC. The distribution of COC cases by centre is shown in Table 1. One hundred and forty-two (53%) cases occurred in females and 121 (45.1%) in males (female-to-male ratio: 1.2:1). In five patients, no information regarding gender was available. Children and adolescents (0-19 years) accounted for 35.1% of the sample, adults (20-59 years) accounted for 47.3%, and elderly people ( $\geq 60$  years) accounted for 17.5%. The entire information on patient's gender, age and skin colour as well as symptoms, anatomical location, type of biopsy, recurrence, evolution time, radiological features and size is provided in Table 2. Impacted teeth were documented in 17 COC cases (6.3%). The canine was the most frequent unerupted tooth ( $n = 10$ ).

Seven cases were peripheral COC (PCOC) (<3% of the sample), and most were found in the maxilla. Three COC were associated with odontomas, and one case was associated with ameloblastoma.

Regarding radiographic aspects, 128 cases (47.8%) were radiolucent, 66 were mixed (24.6%), and 11 cases (4.1%) were radiopaque. Information concerning internal structure was obtained in only 35 cases. Of these, 25 cases were unilocular and 10 were multilocular. Thirty-two cases presented well-defined borders, and one case was ill-defined. In 33 cases (12.3%), osseous expansion was observed and six cases showed tooth resorption. Tooth displacement was not notified in any case. Figure 1 illustrates the radiographic aspect of COC.

Grossly, COC consisted of soft tissue with the presence of mineralized white structures in the luminal interior of the surgical piece (Figure 2). Microscopic evaluation of routine haematoxylin-eosin (H&E)-stained COC issues revealed that the lesions were lined with epithelium of variable thickness (Figure 3a). The epithelium consisted of a well-defined basal layer of palisading columnar cells and a thick overlying layer resembling the stellate reticulum and with the presence of ghost cells that became calcified (Figure 3b and c). Cases associated with odontomas exhibited dentin, pulp, cementum and periodontal ligament, while the case associated with ameloblastoma showed the classical proliferation of ameloblastoma.

Table 3 displays the results of the Mann-Whitney test. Symptoms were associated with lesion size. The mean lesion size of

**TABLE 2** Sociodemographic and clinical characteristics of the sample

	Number (%)
Gender	
Male	121/263 (46)
Female	142/263 (54)
Age (years) <sup>a</sup>	Mean: 33.1 ± 20.47 Range: 6-85
0-9	10 (4.0)
10-19	76 (31.0)
20-29	44 (18)
30-39	36 (14.7)
40-49	22 (9)
50-59	14 (5.8)
60-69	24 (9.8)
70-79	16 (6.5)
80-89	3 (1.2)
Skin colour	
White	147/232 (63.4)
Nonwhite	85/232 (36.6)
Symptoms	
Symptomatic	41/193 (21.2)
Asymptomatic	152/193 (78.8)
Anatomical location <sup>b</sup>	
Maxilla	Anterior: 64/141 (45.4) Posterior: 19/141 (13.5) Peripheral: 5/141 (3.5) Maxillary sinus: 2/141 (1.4) NI: 51/141 (36.2)
Mandible	Anterior: 36/118 (30.5) Posterior: 48/118 (40.7) Peripheral: 1/118 (0.8) NI: 33/118 (28)
Type of biopsy	
Incisional	55/237 (23.2)
Excisional	182/237 (76.8)
Recurrence <sup>c</sup>	10
Evolution time (months)	Mean: 24.9 ± 32.3 Range: 1-180
Radiological features	Radiolucent: 128 (47.8) Mixed: 66 (24.6) Radiopaque: 11 (4.1) NI: 63 (23.5)
Size (millimetres)	Mean: 33.2 ± 25.1 Range: 1-100

Notes. NI: not informed.

<sup>a</sup>Values representing 245/268 cases; in other cases, these data were not informed. <sup>b</sup>In one case of peripheral calcifying odontogenic cyst, there was no information about anatomical location. <sup>c</sup>Recurrence was not available in some cases.

symptomatic individuals was larger than that of asymptomatic subjects ( $p = 0.026$ ). No significant association was observed between time of evolution and symptoms ( $p = 0.091$ ).

Also, nine cases of DGCT were identified across the sample. Most individuals were males (55.6%) and white (55.6%), ranging in age from 12 to 64 years (mean 27.6 years). The most frequent location was the mandible (66.7%), and many of the patients were asymptomatic (77.8%). No case of GCOC was diagnosed.

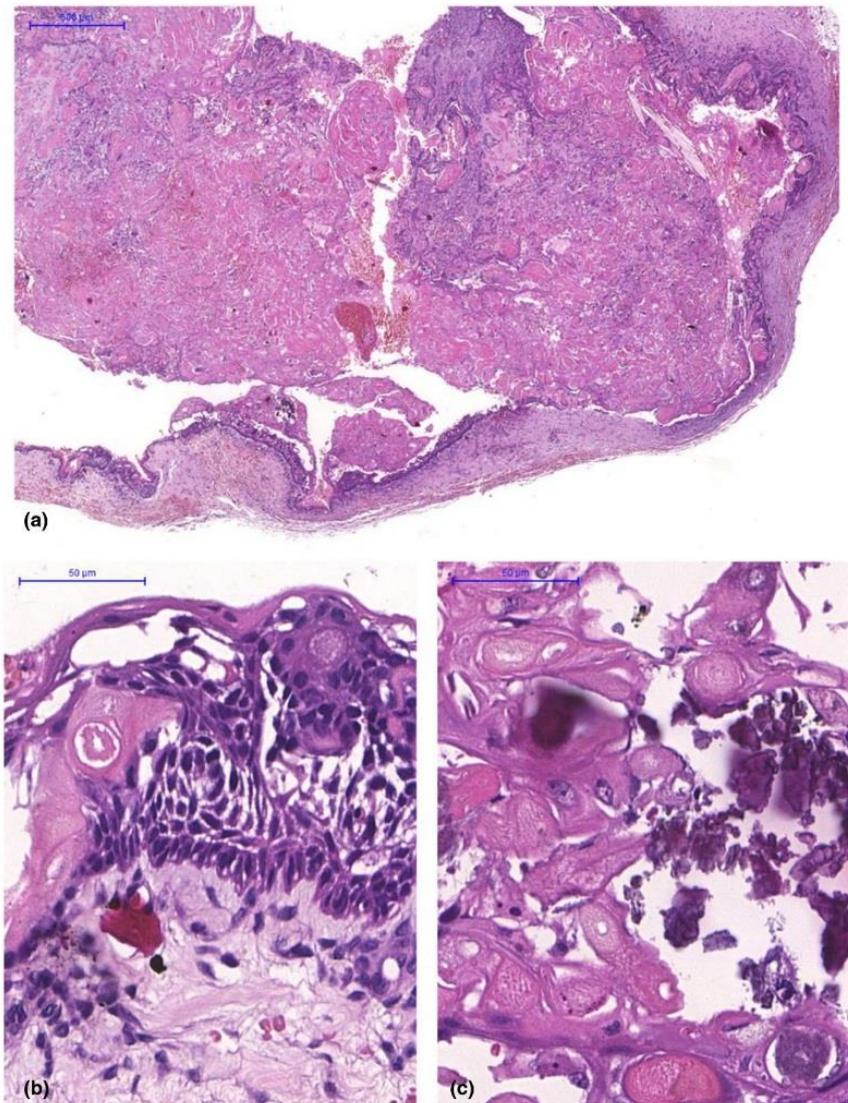
The literature review yielded 1,620 articles. Inclusion and exclusion criteria were applied, and a total of 16 articles reporting 443 cases of COC were selected. The studies were conducted on different continents: Asia (186 cases), Europe (68 cases) and Americas (64 cases). A multicentre study from Europe, Africa, Oceania and the Americas (125 cases) was also retrieved. Thirteen articles showed that COC mostly affected patients in the third decade of life. The review showed an involvement of 247 males (56.2%) and 192 females (43.8%). Concerning localization, 217 (51.4%) cases occurred in the mandible and 205 (48.6%) in the maxilla. Of the cases with radiographic data, 118 (91.4%) were unilocular lesions and 11 (8.5%) were multilocular. Regarding



**FIGURE 1** Panoramic radiograph of a calcifying odontogenic cyst in the left maxilla located from the first premolar to the third molar. The image shows a unilocular and radiolucent lesion, with a well-defined, punched-out border. Root resorption is also observed



**FIGURE 2** Calcifying odontogenic cyst. Gross aspect of the surgical specimen and luminal interior. Note the presence of mineralized white structures (blue arrows) [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]



**FIGURE 3** (a) Fibrous capsule, lining of odontogenic epithelium and solid cystic contents of a calcifying odontogenic cyst (H&E staining, 2x magnification). (b) The basal cells of the epithelial lining are columnar and similar to ameloblasts. The overlying layer of loosely arranged epithelium is similar to the stellate reticulum (H&E staining, 40x magnification). (c) Presence of variable numbers of ghost cells within the epithelial component and calcification (H&E staining, 40x magnification) [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 3** Association between symptoms, evolution time and size of calcifying odontogenic cyst cases

	Symptoms		Total	p-value
	Asymptomatic	Symptomatic		
Evolution time (months)	64/84	20/84	84/108	0.091 <sup>*</sup>
	Mean: 25.0 ± 29.8	Mean: 16.3 ± 19.5		
	Median: 12	Median: 9		
	Range: 2-168	Range: 1-72		
Size (millimetres)	106/128	22/128	128/169	<b>0.026<sup>*</sup></b>
	Mean: 31.9 ± 23.9	Mean: 47.7 ± 31.4		
	Range: 1-100	Range: 7-100		
	Median: 30.0	Median: 35.0		

Note. <sup>\*</sup>Mann-Whitney test: Bold indicates statistical significance.

radiological appearance, 132 (65%) were radiolucent and 69 (34%) were mixed. Ten articles (57 cases) provided information about association with an impacted tooth. Information about treatment

was provided in 11 articles. Treatment essentially consisted of enucleation. Among the 443 cases with information available, only 10 (2.2%) showed recurrence (Table 4).

**TABLE 4** Demographic data of series with more than 10 cases of calcifying odontogenic cyst published in the literature

Author (year of publication)	Country	Number of cases	Mean age <sup>a</sup> (Range)	Gender <sup>a</sup>		Anatomical location <sup>a</sup>	
				Male	Female	Maxilla	Mandible
Gorlin et al. (1964)	USA/Denmark/Australia	12	46.2 (10-77)	5	7	5	7
Praetorius et al. (1981)	Denmark	16	32.2 (1-78)	11	5	6	10
McGowan and Browne (1982)	UK	12	44.2 (11-87)	5	7	5	7
Shamaskin et al. (1989)	USA	20	25.5 (5-74)	10	10	9	11
Yoshida, Kumamoto, Ooya, and Mayanagi (2001)	Japan	16	23 (9-72)	9	7	11	5
Fregnani et al. (2003)	Brazil	10	28.9 (7-61)	6	4	10	0
Li and Yu (2003)	China	21	NI	11	10	12	9
Iida et al. (2006)	Japan	11	26.9 (12-82)	7	4	4	7
Lucchese et al. (2007)	Italy	15	37.0 (5-75)	6	9	6	9
Ledesma-Montes et al. (2008)	Mexico/South Africa/Denmark/USA/Brazil/Guatemala/Peru	113	NI (4-76)	61	49	54	38
Tosios, Prountzos, Katsoulas, Koutlas, and Sklavounou-Andrikopoulou (2012)	Greece	12	27.8 (8-56)	8	4	7	5
Habibi et al. (2011)	Iran	60	23.0 (6-80)	37	23	14	46
Lucchese et al. (2011)	Italy	13	36.0 (5-73)	6	7	5	8
Etemad-Moghadam, Baghaee, Dadafarid, and Alaeddini (2014)	Iran	37	39.4 (12-82)	22	14	25	12
Gomes da Silva et al. (2014)	Brazil	23	NI	12	11	13	10
Irani and Foroughi (2017)	Iran	52	27.9 (8-61)	31	21	19	33
Total	-	443	-	247	192	205	217

Notes. NI: not informed; UK: The United Kingdom; USA: The United States of America.

<sup>a</sup>Data were not available in some cases.

## 4 | DISCUSSION

The first attempt to classify odontogenic cysts and tumours was published by the French physician Dr Paul Pierre Broca, nearly 150 years ago (Imran, Jayanthi, Tanveer, & Gobu, 2016). During the twentieth century, classification systems of jaw cysts were proposed. At the last WHO classification of Odontogenic and Maxillofacial Bone Tumours, the COC was reincorporated into the cyst classification, as it had been classified as a neoplasm in 2005 (Barnes et al., 2005; El-Naggar et al., 2017). In this current multicentre study, 268 COC cases have been added to the literature. To the best of our knowledge, this is the first and largest multicentre study reporting the frequency of COC submitted for microscopic examination in a South American country.

Although COCs are widely known lesions, they are not very common. In this Brazilian survey, COC represented 0.1% of cases among the entire sample of diagnosed oral and maxillofacial lesions and 1.3% of cases among all odontogenic cysts. Two single-centre studies from Iran (Habibi, Saghravani, Salehinejad, & Jafarzadeh, 2011; Irani &

Foroughi, 2017) and an international collaborative study involving 14 institutions of Europe, Africa and America (Ledesma-Montes et al., 2008) also provided a large case series of this lesion. The strength of our study regards the report of the frequency of COC identified across 10 reference services in a multicentre collaboration. Our data concur with findings of previous studies of COC in the Americas, Asia and Europe, which have demonstrated that COC represents less than 1% of all lesions diagnosed at oral and maxillofacial pathology services (Gallana-Alvarez, Mayorga-Jimenez, Torres-Gómez, Avellá-Vecino, & Salazar-Fernandez, 2005; Jaeger et al., 2017; de Souza et al., 2010).

According to our literature review, comparison of the prevalence of this lesion across different regions may be difficult due to the different periods of analysis in each population and the scarcity of epidemiological studies about COC. It is important to highlight that the studies included in this literature review were based on the 2005, 1992 or 1971 WHO classification (Philipsen & Reichart, 2006; Wright & Vered, 2017), while the present multicentre study was based on the latest 2017 WHO classification (El-Naggar et al., 2017).



Radiographic features <sup>a</sup>					Impacted tooth associated <sup>a</sup> (n)	Treatment <sup>a</sup>	Recurrence <sup>a</sup> (n)
Unilocular	Multilocular	Radiolucency	Radiopaque	Mixed			
2	NI	2	NI	2	1	Enucleation, segmental mandibulectomy	1
NI	NI	NI	NI	NI	3	Marsupialization, cystectomy, extirpation, resection	2
NI	1	1	1	3	3	Enucleation	NI
NI	NI	NI	NI	NI	NI	Enucleation	NI
NI	NI	3	NI	13	5	Enucleation	NI
NI	NI	NI	NI	NI	4	Enucleation	None
15	3	18	0	3	NI	Enucleation or curettage	2
10	1	11	0	0	5	Enucleation	None
NI	NI	NI	NI	NI	NI	NI	None
NI	NI	NI	NI	NI	NI	NI	NI
NI	NI	NI	NI	NI	NI	Enucleation	NI
35	3	38	0	11	15	NI	2
NI	NI	NI	NI	NI	2	Enucleation	None
18	3	21	1	3	9	NI	3
8	NI	8	0	12	10	NI	NI
30	0	30	0	22	NI	NI	NI
118	11	132	2	69	57	-	10

The classification and terminology used to designate COC have evolved historically (Gorlin et al., 1962; Gold, 1963; Fejerskov & Krogh, 1972; Freedman, Lumerman, & Gee, 1975; Praetorius, Hjørting-Hansen, Gorlin, & Vickers, 1981; Ellis & Shmookler, 1986; Colmenero, Patron, & Colmenero, 1990; Hirshberg, Kaplan, & Buchner, 1994; Shear, 1994; Toida, 1998). Therefore, inconsistencies in the terminology have occurred over time, reflecting the lack of precise knowledge about the pathogenesis, histology and behaviour of the lesions, as well as the overlapping definitions of tumours and cysts (Yukimori et al., 2017). In 2005 and until 2017, the WHO reclassified two odontogenic cysts (odontogenic keratocyst and COC) as neoplasms. While the WHO provided evidence for the reclassification of odontogenic keratocysts, it is important to highlight that no justification was provided for the reclassification of COC. For this reason, many authors chose to continue classifying COC as cysts and not as neoplasms (Iida et al., 2006; Lucchese, Scivetti, Pilolli, & Favia, 2007; de Souza et al., 2010).

The present study demonstrated a wide age range of affected people. The youngest recorded patient was 6 years old, and the oldest was 85. Most individuals were in the second decade of life, in agreement with the largest international collaborative study (Ledesma-Montes et al., 2008) and with a study in Iran (Habibi et al., 2011). In the study by Ledesma-Montes et al. (2008), cases were diagnosed according to the guidelines of the 2005 WHO classification (Barnes et al., 2005) and were further typified using a modified version of the classification proposed by Praetorius et al. (1981). Most lesions in their study were classified as a calcifying cystic odontogenic tumour type 1, that is, a simple cystic lesion, and most patients were between 10 and 19 years of age. This feature has been confirmed by Habibi et al. (2011). Interestingly, Praetorius et al. (1981) stated that individuals between 10 and 19 years and those between 60 and 69 years are significantly affected. The authors raised the hypothesis that they were dealing with two distinct entities: cystic-type (COC) and neoplastic-type (DGCT) lesions.

Although some previous reports have not shown a gender preference of COC (Gomes da Silva et al., 2014; Lucchese et al., 2011; Shamaskin et al., 1989), others have demonstrated a male prevalence (Irani & Foroughi, 2017; Ledesma-Montes et al., 2008). In our multicentre study, there was a slight female prevalence (female-to-male ratio: 1.2:1), diverging from the present literature review that showed 247 males (56.2%) among the 439 informed cases (male-to-female ratio: 1.2:1). It is difficult to infer the reasons that could explain this slight discrepancy between genders. To our knowledge, this multicentre study involves a significant number of cases, and the discrepancy between genders, indeed, might not exist, a fact also supported by a Japanese study with a smaller sample (Nagao, Nakajima, Fukushima, & Ishiki, 1983).

With respect to symptoms and lesion size, this multicentre study showed a statistically significant association between these variables. Symptomatic individuals presented larger lesions. Otherwise, no significant association between evolution time and symptoms was observed. It is important to note that, in this survey, more than 80% of the cases were asymptomatic. Therefore, this could be interpreted as additional evidence as the patients spent an average of 2 years to be diagnosed with such lesion. Our data are in agreement with previous studies. Some cases are fully asymptomatic and are diagnosed fortuitously during radiological examination (Buchner, Merrell, Hansen, & Leider, 1991; Lucchese et al., 2011).

When the patients were referred to the diagnostic centres, swelling was the most frequent complaint and occurred in more than half of the cases reported (Habibi et al., 2011). Bone expansion, tooth displacement and resorption can be observed more frequently than pain (Gallana-Alvarez et al., 2005; Lucchese et al., 2011). Herein, osseous expansion was observed in more than 10% of the sample, and few cases were notified as being associated with tooth resorption. Our data showed no case of tooth displacement. According to the literature review, almost 13% of cases had information about an impacted tooth associated with COC. In our series, this was found in approximately 6% of cases. However, these data should be interpreted with caution. It is impossible to know whether clinicians, surgeons and physicians recorded accurately all clinical and radiographic data in the biopsy reports. This is a limitation of this study as we relied on biopsy records, and greater attention to this information is encouraged when reporting future cases.

Regarding anatomical location, in our study, COC was more commonly found in the anterior maxilla followed by the posterior mandible. In relation to the studies with more than 10 cases, the mandible was slightly more affected; however, information regarding lesion location was missing in 21 of 443 cases of the literature review (Gorlin, Pindborg, Redman, Williamson, & Hansen, 1964; Habibi et al., 2011; Iida et al., 2006; Irani & Foroughi, 2017; Lucchese et al., 2007; Shamaskin et al., 1989).

Our study identified seven cases of peripheral COC (PCOC). Gingiva and the alveolar ridge mucosa are rare sites for COC. Herein, the maxilla was most affected. According to Chrcanovic and Gomez (2016), the great majority of cases described in the literature appear as isolated case reports or small case series. Buchner et al. (1991)

provided an excellent review of 45 cases of PCOC published in the English literature and found that patients were most affected in their 60 s, 70 s and 80 s. Individuals in their 20 s were also significantly affected. This was the same age distribution observed by Brazilian researchers in 2016 (Chrcanovic & Gomez, 2016). Most individuals complain of painless swelling (Buchner et al., 1991; Resende, Brito, Souza, Gomez, & Mesquita, 2011), and the clinical appearance of these lesions was variously described as sessile, nodular, smooth-surfaced, firm, of soft consistency or as a fibrous mass (Buchner et al., 1991; de Lima, Kitakawa, Almeida, Brandão, & Anbinder, 2012; Resende et al., 2011). The erosion of the underlying alveolar bone was not so commonly seen in peripheral COC (Chrcanovic & Gomez, 2016). The clinical differential diagnosis of PCOC includes common gingival growths of a non-neoplastic nature and other peripheral odontogenic tumours (Buchner, Merrell, & Carpenter, 2006b). The literature has emphasized that it has been difficult to compare clinical and histological features of peripheral and intraosseous lesions, as most studies recognize them as a single entity (Buchner et al., 1991; Fejerskov & Krogh, 1972; Freedman et al., 1975; Gorlin et al., 1962; Johnson, Fletcher, Gold, & Chen, 1997; Ledesma-Montes et al., 2008; Resende et al., 2011).

Radiographically, the common presentation of COC is a well-limited unilocular radiolucency of different size, shape and possible radiopacity. Root resorption or displacement and cortical expansion and/or perforation may be observed (Irani & Foroughi, 2017; Rojo, Prados-Frutos, Gutierrez Lázaro, & Herguedas Alonso, 2017). In the present study, 128 (47.8%) cases appeared as unilocular lesions followed by mixed lesions (24.6%), which partially agrees with the data from the studies listed in Table 4, showing that a unilocular lesion was present in 129 cases (91.4%); however, a radiolucent lesion was present in 203 cases (65%), followed by mixed lesions (34%). Interestingly, we observed that the radiolucent, mixed and radiopaque lesions had increasing sizes (i.e., mean: 32.0, 36.0 and 50.0 mm, respectively). It is hypothesized that the deposition and number of calcifications may be related to the size of the lesion; that is, as the lesions grow, there is a greater deposition of material. However, further studies are encouraged to confirm this hypothesis. Although suggestive, radiographic appearance does not define the diagnosis, and perhaps these features are not diagnostic. A series of lesions exhibit the same characteristics. When radiographic appearance is radiolucent/radiopaque, COC may resemble an adenomatoid odontogenic tumour or calcifying epithelial odontogenic tumour (Buchner et al., 1991). However, the radiographic appearance may be exclusively radiolucent; therefore, other diagnoses should be included such as other odontogenic cysts (radicular, residual, dentigerous and keratocysts), tumours (unicystic ameloblastoma, odontogenic fibroma and odontogenic myxoma) and even a sinus mucocele. In cases of predominantly radiopaque radiographic appearance, the differential diagnosis may include ameloblastic fibro-odontoma and odontoma, as well as a group of fibro-osseous lesions (Buchner et al., 1991; Gadipelly, Reddy, Sudheer, Kumar, & Harsha, 2015; Rojo et al., 2017; de Santana Santos, Frota, de Souza Andrade, de Oliveira, & Silva, 2013).



Herein, three cases of COC were associated with odontomas. Odontomas are mixed epithelial and mesenchymal tumour-like malformations (hamartomas) composed of hard and soft dental tissue (El-Naggar et al., 2017). The epithelial lining of the COC has the ability to induce the formation of dental tissue in the connective tissue wall (Buchner, 1991). Ledesma-Montes et al. (2008) reported 113 COC cases, 22.1% of which were associated with odontomas. In a literature review by Buchner (1991), 52 of 200 cases (26%) with available histological confirmation exhibited such an association. However, the study of Buchner (1991) was restricted to the review of isolated case reports or to reports of small case series. Moreover, in both articles, it is impossible to determine the frequency of this association in each country. Small case series from Brazil displayed three and four cases, respectively (Fregnani et al., 2003; Gomes da Silva et al., 2014). Thus, the real frequency of COC associated with odontoma demonstrated by our multicentre study in fact is low. It is possible to infer that geographic variation does not help to explain some differences observed.

Because of the potential for growth, displacement of associated teeth and root resorption, marsupialization or decompression is indicated for extensive lesions (Fregnani et al., 2003; Li & Yu, 2003; Sheikh, Cohen, Ramer, & Payami, 2017). Considering the low recurrence risk, another approach is conservative treatment with local excision. However, long-term follow-up is recommended (Emam et al., 2017; Kim et al., 2016; Sheikh et al., 2017; Souza et al., 2007). Our study consisted of 182 excisional biopsy samples of COC, obtained from different services across Brazil. Taking into account the nonstandardization of the treatment performed and follow-up, it is unfeasible to estimate accurately the recurrence rate of COC. This is another limitation of this study due to the data collection strategy adopted in this multicentre survey.

Extrapolation of our results should be taken with caution. Although this study analysed a large number of COC biopsy records, it also faced missing data due to its retrospective nature. The main reason for this weakness is the lack of protocols used to report patient information across institutions and among clinicians. Thus, initiatives to use well-designed instruments for data collection should be encouraged. Furthermore, small lesions and/or those located peripherally might be neglected. As they usually do not show the clinical appearance of malignant alteration, histopathological analysis may not be requested. This may contribute to the underdiagnosis of COC cases.

In summary, this multicentre study showed that COC is a rare lesion observed in oral biopsy samples. This study has added 268 cases of COC to the literature, providing novel data on the clinicopathological features of such a rare condition. In our study, differences regarding gender and age of the affected individuals were found in comparison with case series and retrospective studies reported elsewhere. However, the data presented herein are restricted to those lesions which were submitted for microscopic evaluation.

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## CONFLICT OF INTEREST

None to declare.

## AUTHOR CONTRIBUTIONS

José Alcides Almeida de Arruda, João Luiz Gomes Carneiro Monteiro, Lauren Frenzel Schuch, Rodrigo Finger de Carvalho Pinho, and Leorik Pereira da Silva conducted a literature review and organized the data of the clinical cases. Suzana Cantanhede Orsini Machado de Sousa, Bruno Augusto Benevenuto de Andrade, Mario José Romañach, Simone de Queiroz Chaves Lourenço, Aline Carvalho Batista, Elismauro Francisco de Mendonça, Manoela Domingues Martins, Pantelis Varvaki Rados, Elena Riet Correa Rivero, Lélia Batista de Souza, Maria das Graças Rodrigues Pinheiro, Ana Paula Neutzling Gomes, and Ana Carolina Uchoa Vasconcelos contributed cases from their services and reviewed and classified all cases. Leni Verônica de Oliveira Silva contributed to the design of the work, while Lucas Guimarães Abreu was responsible for data interpretation. Ana Paula Veras Sobral and Ricardo Alves Mesquita contributed to the conception of the work. All authors drafted the article, approved the final version of the manuscript as submitted and agreed to be accountable for all aspects of the work.

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#### 4 CONSIDERAÇÕES FINAIS

Neste estudo multicêntrico brasileiro, 268 casos de COC foram analisados. O COC é uma lesão rara, representando 0,1% dos casos em toda a amostra de lesões orais e maxilofaciais diagnosticadas e 1,3% dos casos entre todos os cistos odontogênicos. COC exibiu predileção por indivíduos do sexo feminino na segunda década de vida com acometimento na maxila. Ademais, alguns casos foram totalmente assintomáticos e diagnosticados fortuitamente durante o exame radiológico, ao passo que os indivíduos sintomáticos apresentaram lesões maiores. Radiograficamente, as lesões exibiram aspecto radiolúcido com margens bem definidas e uniloculares. Ainda, a revisão da literatura de série de casos de COC revelou maior frequência dos casos na Ásia e na Europa, afetando principalmente os homens na terceira década de vida.

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## ANEXO A – Aprovação do comitê de ética em pesquisa

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### PARECER CONSUBSTANCIADO DO CEP

#### DADOS DO PROJETO DE PESQUISA

**Título da Pesquisa:** CISTO ODONTOGÊNICO CALCIFICANTE: ESTUDO MULTICÊNTRICO

**Pesquisador:** Ricardo Alves de Mesquita

**Área Temática:**

**Versão:** 2

**CAAE:** 89194618.0.1001.5149

**Instituição Proponente:** UNIVERSIDADE FEDERAL DE MINAS GERAIS

**Patrocinador Principal:** Financiamento Próprio

#### DADOS DO PARECER

**Número do Parecer:** 2.692.400

#### Apresentação do Projeto:

O objetivo desse estudo é analisar a prevalência do cisto odontogênico calcificante (COC) com base nos arquivos de biópsias de centros de patologia oral e maxilofacial localizados em diferentes estados do Brasil: Goiás, Minas Gerais, Pará, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina e São Paulo. Trata-se de uma análise retrospectiva. Serão avaliados gênero, idade, raça, localização anatômica, aspectos sintomáticos, aspectos radiográficos, tamanho da lesão, tratamento e recidiva dos COCs. Os laudos histopatológicos de COC de todos os referidos centros, serão analisados de acordo com a classificação da OMS (2017). Os dados serão descritos através de métodos de estatística descritiva. Espera-se observar uma prevalência muito baixa no Brasil, por tratar-se de uma lesão rara. Os dados obtidos desse estudo adicionam à literatura achados importantes para novas pesquisas que viabilizem correlacionar os aspectos clínicos com marcadores moleculares a dessa lesão.

#### Objetivo da Pesquisa:

Hipótese:

Dados epidemiológicos do COC na população brasileira é diferente das populações distribuídas em outras regiões do mundo.

Objetivo Primário:

Analisar a prevalência do COC com base nos arquivos de biópsias de centros de patologia oral e

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maxilofacial localizados em diferentes estados do Brasil: Goiás, Minas Gerais, Pará, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina e São Paulo.

**Objetivo Secundário:**

Analisar gênero, idade, raça, localização anatômica, aspectos sintomáticos, aspectos radiográficos, tamanho da lesão, tratamento e recidiva dos COCs.

Analisar os laudos microscópicos de COC de todos os referidos centros.

**Avaliação dos Riscos e Benefícios:**

**Riscos:**

No caso de coleta de dados através de fichas de arquivos, considera-se o risco de identificação do indivíduo. Entretanto, nós nos responsabilizamos no anonimato desses indivíduos em todo momento da pesquisa.

**Benefícios:**

O COC faz parte de um espectro de lesões caracterizadas por epitélio odontogênico contendo células-fantasma, que depois podem sofrer calcificações. Embora a maioria cresça em um formato cístico, algumas lesões se apresentam como crescimentos sólidos similares a neoplasias (NEVILLE et al., 2016). Sua etiologia e natureza ainda não são completamente compreendidas (FREGNANI et al., 2003; DE OLIVEIRA et al., 2008), contudo, a última classificação da OMS o reclassificou como lesão cística e não mais neoplásica (EL-NAGGAR et al., 2017). Nesse sentido, os achados deste estudo epidemiológico podem elucidar a nova denominação desse cisto odontogênico. Esta diversidade de nomenclatura tem levado à incerteza na terminologia e classificação e, por isso, alguns autores têm buscado titular essa lesão, de acordo com suas características clínicas e histopatológicas (ORSINI et al., 2002; LI e YU, 2003; WRIGHT et al., 2014; WRIGHT e VERED, 2017).

**Comentários e Considerações sobre a Pesquisa:**

Pesquisa relevantes para as áreas de Estomatologia e Patologia Bucal. Término previsto para 20/02/2019. Trata-se do projeto da dissertação de Mestrado do pós-graduando José Alcides Almeida de Arruda, sob orientação do Prof. Dr. Ricardo Alves de Mesquita. O estudo será retrospectivo, multicêntrico. Todos os dados dessa pesquisa serão oriundos de arquivos de biópsias de 10 centros de referência de patologia oral e maxilofacial localizados em diferentes regiões do Brasil.

As solicitações do COEP foram atendidas:

- os riscos da pesquisa foram adequadamente descritos;

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- os pesquisadores complementaram a solicitação de dispensa do TCLE, assegurando a preservação da identidade dos participantes da pesquisa.

**Considerações sobre os Termos de apresentação obrigatória:**

Foram anexados os seguintes documentos para apreciação:

- Informações Básicas do Projeto;
- Carta resposta à diligência;
- Parecer consubstanciado aprovado pelo Colegiado do Programa de Pós-graduação em Odontologia, e posteriormente aprovado "ad referendum" pela câmara departamental;
- Autorização dos centros participantes para utilização dos dados e declaração de responsabilidade pela busca dos dados pelos professores responsáveis; os centros participantes são pertencentes às seguintes instituições: USP, UFSC, UFRN, UFRJ, UFRGS, UFPel, UFMG, UFG, UFF e CESUPA;
- Orçamento;
- Cronograma;
- Projeto Detalhado / Brochura Investigador e
- Folha de Rosto.

**Recomendações:**

Recomenda-se a aprovação do projeto de pesquisa.

**Conclusões ou Pendências e Lista de Inadequações:**

Somos favoráveis à aprovação do projeto "CISTO ODONTOGÊNICO CALCIFICANTE: ESTUDO MULTICÊNTRICO" do pesquisador responsável Prof. Dr. Ricardo Alves de Mesquita.

**Considerações Finais a critério do CEP:**

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

Tipo Documento	Arquivo	Postagem	Autor	Situação
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**Endereço:** Av. Presidente Antônio Carlos, 6627 2º Ad Sl 2005

**Bairro:** Unidade Administrativa II **CEP:** 31.270-901

**UF:** MG **Município:** BELO HORIZONTE

**Telefone:** (31)3409-4592

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Continuação do Parecer: 2.692.400

Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1071751.pdf	28/05/2018 12:11:32		Aceito
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Outros	Aprove.pdf	04/04/2018 15:40:55	josé alcides almeida de arruda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	USP.pdf	04/04/2018 15:40:25	josé alcides almeida de arruda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	UFSC.pdf	04/04/2018 15:39:50	josé alcides almeida de arruda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	UFRN.pdf	04/04/2018 15:39:34	josé alcides almeida de arruda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	UFRJ.pdf	04/04/2018 15:39:17	josé alcides almeida de arruda	Aceito
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TCLE / Termos de Assentimento / Justificativa de Ausência	UFG.pdf	04/04/2018 15:37:55	josé alcides almeida de arruda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	UFF.pdf	04/04/2018 15:37:43	josé alcides almeida de arruda	Aceito
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Orçamento	orcamento.docx	04/04/2018	josé alcides	Aceito

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Orçamento	orcamento.docx	15:36:50	almeida de arruda	Aceito
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Outros	891946180parecerassinado.pdf	05/06/2018 14:06:04	Vivian Resende	Aceito

**Situação do Parecer:**

Aprovado

**Necessita Apreciação da CONEP:**

Não

BELO HORIZONTE, 05 de Junho de 2018

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**Assinado por:**  
**Vivian Resende**  
**(Coordenador)**

**Endereço:** Av. Presidente Antônio Carlos, 6627 2º Ad SI 2005

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