

Gingival cyst of the adult, lateral periodontal cyst, and botryoid odontogenic cyst: An updated systematic review

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The aim of the present review was to integrate the available data published on gingival cyst of the adult (GCA), lateral periodontal cyst (LPC), and botryoid odontogenic cyst (BOC) into a comprehensive analysis of their clinical/radiological features. An electronic search was undertaken in July/2017. Eligibility criteria included publications having enough clinical/radiological/histological information to confirm the diagnosis. A total of 146 publications (157 GCAs, 213 LPCs, 96 BOCs) were included. GCA and LPC presented highest prevalence in the sixth/fifth decades; BOC in the sixth/seventh decades. LPCs were larger lesions than GCAs and GCAs appeared at an older age than LPC. There was no statistically significant difference between them for other factors (location, symptoms, recurrence, follow-up time). In comparison with LPC, BOC lesions were larger, appeared more often in mandible and in older subjects, had more often a multilocular appearance, and presented a higher recurrence rate. Recurrence rates: GCA (3.2%), LPC (2.4%), BOC (21.7%). No factor seems to influence the recurrence rate of GCA or LPC. Multilocular radiological appearance seems to affect the recurrence rate of BOCs. Conservative surgical approaches seem to be enough for GCA/LPC. BOC presents a more aggressive behavior than GCA/LPC. Therefore, treatment of this lesion might involve some kind of adjunctive therapy after enucleation.

KEYWORDS

botryoid odontogenic cyst, clinical features, Gingival cyst of the adult, lateral periodontal cyst, odontogenic cysts, recurrence rate

1 | INTRODUCTION

Gingival cyst of the adult (GCA) is an odontogenic cyst that usually appears as a single, small, asymptomatic swelling with bluish color on the attached gingivae or interdental papillae. The cystic capsule is composed of fibrous connective tissue with minimal inflammation and is lined by non-keratinized epithelium (Scully & Malamos, 2015). Abrupt thickening producing plaques and clear cells are often present (El-Naggar, Chan, Grandis, Takata, & Sloopweg, 2017). Lateral periodontal cyst (LPC) is a non-keratinized, non-inflammatory, developmental cyst that occurs adjacent or lateral to the root of vital tooth (Wysocki, Brannon, Gardner, & Sapp, 1980). LPC is considered to be the intraosseous counterpart of the

extraosseous GCA. Both cysts arise probably from rests of dental lamina, but the source is still controversial. Botryoid odontogenic cyst (BOC) is considered a rare multilocular variant of LPC (El-Naggar et al., 2017).

Gingival cyst of the adult, LPC, and BOC are considered to be rare lesions, and there are limited details in the literature regarding their clinical and radiological features. A review of these rare cysts is important because it provides information that can improve diagnostic accuracy, allowing pathologists and surgeons to make informed decisions and refine treatment plans to optimize clinical outcomes (Chrcanovic, Brennan, Rahimi, & Gomez, 2017; Chrcanovic & Gomez, 2016, 2017a). Therefore, the aim of this study was to integrate the available data published in the literature on GCA, LPC or BOC into an updated

comprehensive comparative analysis of their clinical and radiological features, as well as the frequency of recurrence.

2 | MATERIALS AND METHODS

This study followed the PRISMA Statement guidelines (Moher, Liberati, Tetzlaff, Altman, & Grp, 2009).

2.1 | Search strategies

An electronic search without time restrictions was undertaken in July 2017 in the following databases: PubMed/MEDLINE, Web of Science, and Science Direct. In the database Science Direct, the appearance of the terms was limited to the fields "Abstract, Title, Keywords," since the search resulted in an excessive number of entries ($n = 5,671$) when this filter was not used. The following terms were used in the search strategies:

(gingival cyst of the adult) OR (cyst of the gingiva) OR (lateral periodontal cyst) OR (botryoid odontogenic cyst).

Google Scholar was also checked. A manual search of all related oral pathology, maxillofacial and specialist dental and oral journals was performed. The reference list of identified studies and the relevant reviews on the subject were also checked for possible additional studies. Publications with lesions identified by other authors as being GCA, LPC, and BOC, even not having the terms "gingival cyst of the adult," "lateral periodontal cyst," or "botryoid odontogenic cyst" in the title of the article, were also re-evaluated by an author (R.S.G.) of this study.

2.2 | Inclusion and exclusion criteria

Eligibility criteria included publications reporting cases of GCA, LPC, or BOC. The studies needed to contain enough clinical, radiological, and histological information to confirm the diagnosis. The definitions and criteria of the World Health Classification of Tumors—Head and Neck Tumors book (El-Naggar et al., 2017), were used to diagnose a lesion as GCA, LPC, or BOC. Some specific criteria for each lesion:

- Gingival cyst of the adult: Cystic lesions lined by a non-keratinized epithelium of few layers with focal thickenings, which may contain clear cells rich in glycogen. Cases with extensive keratinization were excluded, and any lesion showing microscopic appearance suggestive of peripheral keratocyst was excluded;
- Lateral periodontal cyst: Cysts with similar histopathological features to GCA and showing unicystic spaces. The LPC usually shows a single or double layer with focal plaque-like epithelial thickenings and clear cells. When the histology was not typical and the lesions were adjacent to non-vital teeth, the diagnosis of LPC was not considered;
- Botryoid odontogenic cyst: All the cysts showing similar microscopic appearance to LPC and with multiple cystic spaces were included.

All cases with the typical clinical presentation, even in the absence of focal thickenings, were included into the analysis.

Randomized and controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports were included. Exclusion criteria were immunohistochemical studies, histomorphometric studies, radiological studies, genetic expression studies, histopathological studies, cytological studies, cell proliferation/apoptosis studies, in vitro studies, and review papers, unless any of these publication categories had reported any cases with enough clinical, radiological, and histological information. Hybrid lesions containing parts of GCA, LPC or BOC were not considered for this study, as they may behave differently from non-hybrid lesions.

2.3 | Study selection

The titles and abstracts of all reports identified through the electronic searches were read independently by the authors. For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, the full report was obtained. Disagreements were resolved by discussion between the authors. The clinical and radiological aspects, as well as the histological description of the lesions reported by the publications, were thoroughly assessed by one of the authors (R.S.G.) of this study, an expert in oral pathology, to confirm the diagnosis of GCA, LPC, or BOC.

2.4 | Data extraction

The review authors independently extracted data using specially designed data extraction forms. Any disagreements were resolved by discussion. For each of the identified studies included, the following data were then extracted on a standard form, when available: year of publication, number of patients, patient's sex, age and race, follow-up period, duration of the lesion previously to treatment, lesion location (maxilla/mandible), anterior/posterior location (three categories: [a] anterior: lesions in the incisors/canine region; [b] premolar region; [c] posterior: lesions in the molars/retromolar region), recurrence, recurrence period, lesion size, presence of erosion of the subjacent cortical bone (for peripheral lesions), perforation of cortical bone, locularity radiological appearance (unilocular/multilocular), presence of radiopacities visible in the radiological exams, association of the lesion with a tooth (the tooth can either be erupted with the entire root(s) encompassed by the lesion or unerupted encompassing the entire tooth), tooth displacement and/or tooth root resorption due to lesion's growth, expansion of osseous region adjacent to the cyst, presence of clinical symptoms, and treatment performed (excision, curettage, marsupialization, enucleation, marginal resection). The lesion size was determined according to the largest diameter reported in the publications. Contact with authors for possible missing data was performed.

2.5 | Analyses

The mean, standard deviation (*SD*), and percentages were presented as descriptive statistics. Kolmogorov–Smirnov test was performed to

evaluate the normal distribution of the variables, and Levene's test evaluated homoscedasticity. The performed tests for two independent groups were Student's *t* test or Mann–Whitney test, depending on the normality. Pearson's chi-squared or Fisher's exact tests were used for categorical variables, depending on the expected count of events in a 2×2 contingency table. The probability of recurrence was calculated for some variables, whenever possible, in odds ratio (95% confidence interval). The degree of statistical significance was considered $p < .05$. All data were statistically analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 software (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Literature search

The study selection process is summarized in Figure S1 in Appendix S1. The search strategy in the databases resulted in 795 papers. Search in Google Scholar resulted in 18 eligible papers not found in the three main databases. A number of 244 articles were cited in more than one database (duplicates). The reviewers independently screened the abstracts for those articles related to the aim of the review. Of the resulted 569 studies, 378 were excluded for not being related to the topic or not presenting clinical cases. Additional hand-searching of journals and of the reference lists of selected studies yielded 15 additional papers. The full-text reports of the remaining 206 articles led to the exclusion of 60 because they did not meet the inclusion criteria (see Appendix S1). The excluded studies did not have enough clinical, radiological, and histological information to confirm the diagnosis. Thus, a total of 146 publications were included in the review.

3.2 | Description of the studies and analyses

The series of Moskow et al. (Moskow, Siegel, Zegarelli, Kutscher, & Rothenberg, 1970) (25 cases of GCA and LPC), Filipowicz and Page (Filipowicz & Page, 1982) (41 isolated periodontal defects, of which 20 were LPC), Cohen et al. (Cohen, Neville, Damm, & White, 1984) (31 LPC + 6 BOC), Eliasson et al. (Eliasson, Isacsson, & Kondell, 1989) (15 LPC + 3 odontogenic keratocysts + 3 cysts of inflammatory origin), Rasmusson et al. (Rasmusson, Magnusson, & Borrmann, 1991) (26 LPC + 6 BOC), Altini et al. (Altini & Shear, 1992) (9 LPC + 5 BOC + 6 glandular odontogenic cyst) included several cases of one or more of the lesions here reviewed (GCA, LPC, or BOC). However, as they did not provide information separately by lesions and some of these publications include other types of lesions that were not the aim of the present review, there was no proper way to include their cases into the present analysis. The lesions reported in publication of Bhaskar (Bhaskar, 1965) were not added to the analyses of this study, because a figure of one of the lesions that the author described as a gingival cyst was actually an odontogenic keratocyst. Therefore, it was not possible to separate this lesion from the series.

A total of 146 publications reporting 466 lesions (157 GCAs, 213 LPCs, 96 BOCs) were included in the present review. Table 1 presents

demographic and clinical features of all lesions. GCAs were more prevalent in women than in men, while LPC and BOC were equally distributed between sexes. The mean age of the patients was higher for BOC than for GCA and LPC. GCA and LPC had a similar distribution according to age, with the highest prevalence in the sixth and then fifth decade of life, while the highest prevalence for BOC was in the sixth/seventh decades of life (Figure 1). The three lesions were more prevalent at the incisive/canine and premolar regions of the mandible (Figures 2, 3, and 4 for GCA, LPC, and BOC, respectively).

In the comparison between GCA and LPC, there was no statistically significant difference for the distribution between maxilla/mandible, presence of clinical symptoms, recurrence, and follow-up time. LPCs were larger than GCAs, and patients with GCA had a higher mean age than patients with LPC.

There was no statistically significant difference between BOC and LPC for bone expansion, presence of clinical symptoms, cortical bone perforation, and tooth displacement or tooth root resorption due to lesion's growth. In the comparison to LPCs, BOCs were more often present in the mandible, more often presented a multilocular radiological appearance, the lesions were larger, the patients were older and were followed up for longer periods of time, and the lesions presented a much higher recurrence rate.

GCAs were treated mainly by surgical excision (96.5%), LPCs by enucleation (76%) and then curettage (19.4%), and BOCs by enucleation (53.8%) and then curettage (44.9%). BOCs presented a higher recurrence rate than GCAs and LPCs, regardless of when treated by curettage or enucleation (Table S1 in Appendix S1). No factor seems to have a statistically significant influence on the recurrence rate of GCAs (Table S2 in Appendix S1) or LPCs (Table S3 in Appendix S1). The difference in radiological appearance of the lesion was the only variable suggested to statistically significantly affect the recurrence rate of BOCs (Table S4 in Appendix S1). The period of time between treatment and recurrence was available for 8 BOCs, being 78.5 ± 52.7 months (min–max, 12–156). The two recurrences of LPC occurred 16 and 84 months after treatment, and the only recurrence of GCA occurred 84 months after treatment.

Table S4 in Appendix S1 shows the comparison of demographic and clinical features between recurrent and non-recurrent BOCs. The mean age of the patients with BOC who presented a recurrence was not statistically significantly different from those patients with BOC without a recurrence. Recurrent BOCs had a larger mean size than non-recurrent BOCs, although the difference was not statistically significant. Recurrent BOCs were followed up for a longer time than non-recurrent BOCs, and the difference was statistically significant. All recurrent BOC lesions were multilocular in radiological appearance.

The BOCs with a multilocular radiological appearance (3.6 ± 3.4 cm, min–max 0.8–15.0, median 2.1; $n = 26$) presented a statistically significant larger mean size than the unilocular ones (1.8 ± 1.2 cm, min–max 0.4–4.5, median 1.6; $n = 21$) ($p = .025$; Mann–Whitney test). The multilocular BOCs (46.0 ± 49.6 months, min–max 2–156, median 21; $n = 18$) were followed up for a longer mean time than the unilocular ones (15.8 ± 9.1 months, min–max 2–36, median 12; $n = 21$), but the

TABLE 1 Demographic and clinical features of gingival cysts of the adult (GCA), lateral periodontal cysts (LPC), and botryoid odontogenic cysts (BOC) described in the literature

Variables	GCA	LPC	BOC	p value ^a	p value ^b
<i>n</i>	157	213	96		
Age (years), mean ± SD (min–max)	48.6 ± 12.9 (7-79; <i>n</i> = 142)	46.8 ± 12.5 (12-81; <i>n</i> = 197)	54.0 ± 15.7 (15-85; <i>n</i> = 96)	.017 ^c	<.001 ^c
Men	43.5 ± 14.7 (7-77; <i>n</i> = 57)	47.5 ± 11.2 (12-78; <i>n</i> = 103)	54.3 ± 16.9 (15-85; <i>n</i> = 50)	.123 ^c	.002 ^c
Women	52.1 ± 10.4 (19-79; <i>n</i> = 82)	46.0 ± 14.1 (12-81; <i>n</i> = 91)	53.7 ± 14.4 (23-81; <i>n</i> = 46)	<.001 ^c	.002 ^c
<i>p</i> value ^d	<0.001	0.105	0.744		
Gender, <i>n</i> (%)					
Men	64 (41.6)	103 (52.6)	50 (52.1)		
Women	90 (58.4)	93 (47.4)	46 (47.9)	.041 ^e	.940 ^e
Unknown	3	17	0		
Jaw, <i>n</i> (%)					
Maxilla	35 (23.5)	64 (30.2)	14 (14.7)		
Mandible	114 (76.5)	148 (69.8)	81 (85.3)	.160 ^e	.004 ^e
Unknown	8	1	1		
Bone expansion, <i>n</i> (%)					
Yes	-	70 (50)	41 (56.9)		
No	-	70 (50)	31 (43.1)	-	.338 ^e
Unknown	-	73	24		
Symptomatic, <i>n</i> (%)					
Yes	8 (14.3)	15 (11.7)	15 (18.1)		
No	48 (85.7)	113 (88.3)	68 (81.9)	.628 ^e	.197 ^e
Unknown	101	85	13		
Cortical bone perforation, <i>n</i> (%)					
Yes	-	59 (48.4)	13 (55.2)		
No	-	63 (51.6)	16 (44.8)	-	.732 ^e
Unknown	-	91	67		
Bone erosion, <i>n</i> (%) ^f					
Yes	38 (50.7)	-	-		
No	37 (49.3)	-	-	-	-
Unknown	82	-	-		
Locularity, <i>n</i> (%)					
Unilocular	-	131 (98.5)	41 (53.9)		
Multilocular	-	2 (1.5)	35 (46.1)	-	<.001 ^e
Unknown	-	80	20		
Tooth displacement/unerupted, <i>n</i> (%)					
Yes	-	30 (38)	12 (37.5)		
No	-	49 (62)	20 (62.5)	-	.963 ^e
Unknown	-	134	64		
Tooth root resorption, <i>n</i> (%)					
Yes	-	3 (3.8)	2 (6.3)		
No	-	76 (96.2)	30 (93.8)	-	.449 ^e
Unknown	-	134	64		
Treatment, <i>n</i> (%)					
Excision	109 (96.5)	0 (0)	0 (0)		
Curettage	3 (2.7)	25 (19.4)	35 (44.9)		

(Continues)

TABLE 1 (Continued)

Variables	GCA	LPC	BOC	<i>p</i> value ^a	<i>p</i> value ^b
Marsupialization	0 (0)	0 (0)	1 (1.3)	-	-
Enucleation	1 (0.9)	98 (76)	42 (53.8)		
Marginal resection	0 (0)	6 (4.7)	0 (0)		
Unknown	44	84	18		
Recurrence, <i>n</i> (%)					
Yes	1 (3.2)	2 (2.4)	13 (21.7)		
No	30 (96.8)	81 (97.6)	47 (78.3)	.618 ^g	<.001 ^e
Unknown	126	130	36		
Follow-up time (months), mean ± <i>SD</i> (min–max)	14.9 ± 17.9 (1–92; <i>n</i> = 29)	15.2 ± 16.3 (1–114; <i>n</i> = 48)	34.3 ± 42.9 (2–168; <i>n</i> = 41)	.414 ^c	.045 ^c
Lesion size (cm), mean ± <i>SD</i> (min–max)	0.6 ± 0.3 (0.2–2.0; <i>n</i> = 93)	1.0 ± 0.6 (0.2–3.0; <i>n</i> = 144)	2.8 ± 2.8 (0.3–15.0; <i>n</i> = 49)	<.001 ^c	<.001 ^c

SD, standard deviation.

^aComparison between gingival cysts of the adult (GCA) and lateral periodontal cysts (LPC).

^bComparison between lateral periodontal cysts (LPC) and botryoid odontogenic cysts (BOC).

^cMann–Whitney test.

^dComparison of the mean age between men and women (Mann–Whitney test).

^ePearson's chi-squared test.

^fPeripheral lesions only.

^gFisher's exact test.

difference was not statistically significant ($p = .196$; Mann–Whitney test).

4 | DISCUSSION

Gingival cyst of the adult, LPC, and BOC are rare odontogenic cysts. They do, to some extent, share some clinical and histological features. For instance, the present study showed that GCA and LPC have the same predominant anatomic site of occurrence, both have low recurrence rates, and they are usually asymptomatic, besides the similar histological features. Some reports have combined these two entities, and this is the case of Moskow et al. (Moskow et al., 1970). They did not provide information separately by the two types of lesions, and thus, there was no proper way to include their cases into the present analysis. However, as the present review observed, besides the fact that one lesion is extraosseous GCA and the other one intraosseous LPC, LPC lesions are usually larger than GCAs, LPCs are more often observed in men, and patients with GCA had a higher mean age than patients with LPC. We found only one possible recurrent case of GCA reported in the literature (Hata et al., 2009). The secondary lesion was diagnosed 7 years after the excision of the primary lesion, but it is not possible to know whether it was a true recurrent cyst or a second lesion in the same area.

The issue of the interchangeability of features also arises between LPC and BOC. And because of that, in the same way as with GCA and LPC, some studies have combined these two entities (Altini & Shear, 1992; Cohen et al., 1984; Rasmusson et al., 1991). Once again, there was no proper way to include their cases into the present analysis. The fact is that BOC is considered as a variant of the LPC. Even though

they present similar microscopic appearance, BOC presents multiple cystic spaces—here is important to stress that BOCs have a multilocular histological presentation, which does not necessary translate into a multilocular radiological appearance. Moreover, the present review showed that these two lesions show marked differences in some features, namely lesion location (maxilla vs mandible), radiological appearance, patients' age, lesion size, and recurrence rate. BOC seems to present a more aggressive behavior than LPC.

The matter of the follow-up length deserves some comments, at least when it comes to BOC. Recurrent BOCs were followed up for a longer time than non-recurrent BOCs, and the difference was statistically significant. All recurrent BOCs were multilocular in radiological appearance, and the multilocular BOCs were followed up for a longer mean time than the unilocular ones, although the difference was not statistically significant. Still, the follow-up was 46.0 ± 49.6 months (multilocular lesions) vs 15.8 ± 9.1 months (unilocular lesions). This could have led, to some extent, to an underestimation of the actual recurrence rate of the unilocular BOC lesions, because a longer follow-up period can lead to an increase in the recurrence rate.

Many of the case reports included in the present review have a short follow-up, not only for BOC cases, but also for GCA and LPC. This is certainly a limitation of a proper assessment of recurrence. However, it is hard to define what it would be considered a short follow-up period to evaluate the recurrence of GCA, LPC, or BOC. Moreover, all included studies were retrospective reports, which reflected in gaps in information and incomplete records.

We believe it is time for the authors to review the treatment modality adopted in patients with BOC. Despite the limitations of our study, our results show clearly a relatively high recurrence rate for a benign lesion such as BOC (21.7%), which is similar to what is observed

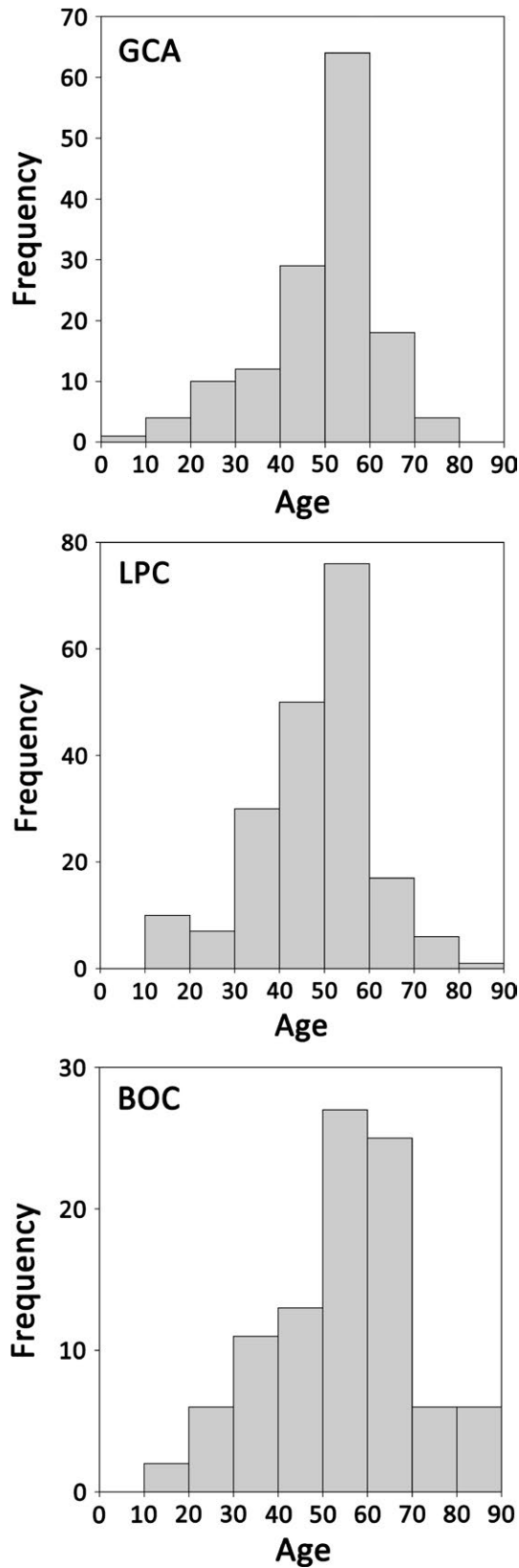


FIGURE 1 Distribution of gingival cysts of the adult (GCA), lateral periodontal cysts (LPC), and botryoid odontogenic cysts (BOC) according to age (for the cases which the patients' age was informed, $n = 435$)

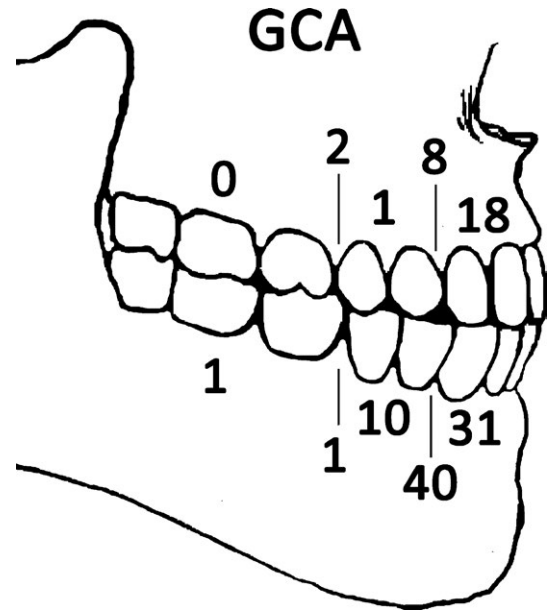


FIGURE 2 Topographical distribution of the known precise locations ($n = 112$) of gingival cysts of the adult (GCA). Numbers at the top and bottom of the lines indicate cases involving both adjoining regions: anterior/premolar, premolar/molar. For the rest of the lesions ($n = 45$), the location was the "maxilla" ($n = 6$), "mandible" ($n = 8$), "mandible incisor-canine-premolar area" ($n = 23$), "multiple lesions" ($n = 1$), and "unknown" ($n = 7$)

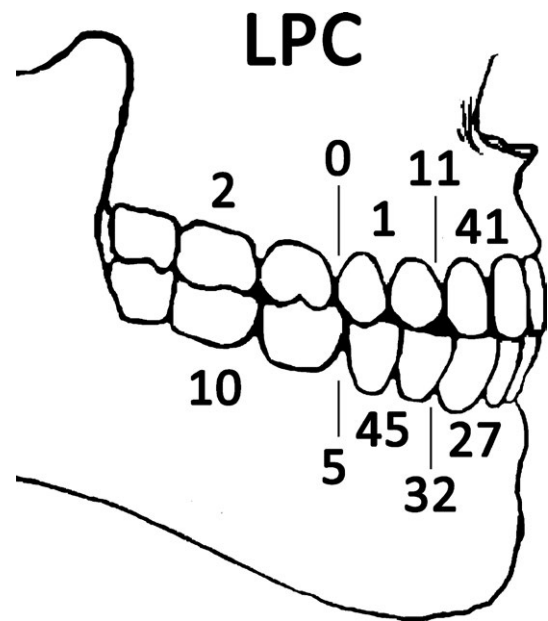


FIGURE 3 Topographical distribution of the known precise locations ($n = 174$) of lateral periodontal cysts (LPC). Numbers at the top and bottom of the lines indicate cases involving both adjoining regions: anterior/premolar, premolar/molar. For the rest of the lesions ($n = 39$), the location was the "anterior maxilla" ($n = 4$), "posterior maxilla" ($n = 3$), "anterior mandible" ($n = 4$), "posterior mandible" ($n = 1$), "mandible incisor-canine-premolar area" ($n = 26$), and "unknown" ($n = 1$)

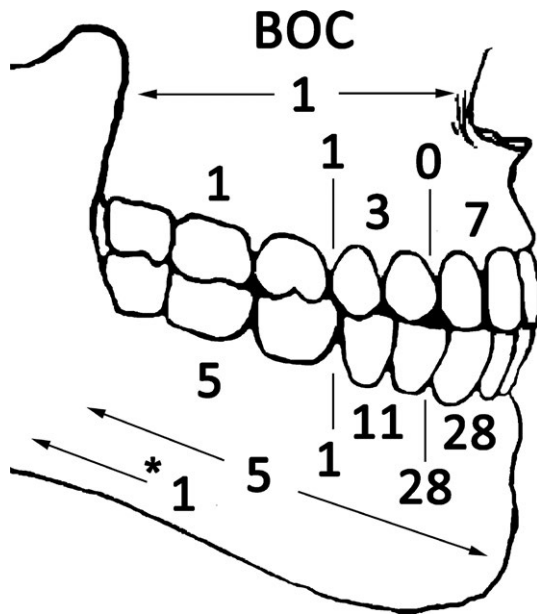


FIGURE 4 Topographical distribution of the known precise locations ($n = 92$) of botryoid odontogenic cysts (BOC). Cases involving multiple regions (or an entire quadrant) are indicated between arrows. Numbers at the top and bottom of the lines indicate cases involving both adjoining regions: anterior/premolar, premolar/molar. One asterisk (*) indicates the number of lesions from the mandibular body that reached the angle and/or ramus. For the rest of the lesions ($n = 4$), the location was “left mandible” ($n = 1$), “mandible anterior-posterior” ($n = 2$), and “unknown” ($n = 1$)

to glandular odontogenic cysts (Chrcanovic & Gomez, 2017b) and odontogenic keratocyst (Chrcanovic & Gomez, 2017c). Therefore, we suggest that the treatment of this lesion might involve some kind of adjunctive therapy after enucleation, such as peripheral osteotomy, cryotherapy, or Carnoy's solution. Future studies are necessary to prove this assumption. Conservative surgical approaches seem to be enough to keep low recidive rates for GCAs and LPCs.

5 | CONCLUSIONS

Conservative surgical approaches seem to be enough for GCA and LPC. BOC presents a more aggressive behavior than GCA and LPC. Therefore, treatment of this lesion might involve some kind of adjunctive therapy after enucleation.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTION

Bruno R. Chrcanovic involved in conception and design, acquisition of data, statistical analysis, interpretation of data, drafting the article, revising the article critically for important intellectual content, and final approval of the version to be published; Ricardo S. Gomez involved conception and design, interpretation of data, revising the article critically for important intellectual content, and final approval of the version to be published.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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