Oral and Maxillofacial Surgery
https://doi.org/10.1007/s10006-018-0737-3

REVIEW ARTICLE

Recurrence of nonsyndromic odontogenic keratocyst after marsupialization and delayed enucleation vs. enucleation alone: a systematic review and meta-analysis

Yuri Slusarenko da Silva[1] · Paul J. W. Stoelinga[2] · Maria da Graça Naclério-Homem[1]

Received: 25 September 2018 / Accepted: 16 November 2018

Abstract

Purpose This study was conducted in order to determine whether marsupialization before definitive enucleation of nonsyndromic odontogenic keratocysts (OKCs) is capable of decreasing the recurrence rate more effectively than just enucleation.

Methods We searched MEDLINE, Web of Science, Scopus, and Cochrane Library, until August 5th of 2017 for original studies reporting on the treatment of OKCs with and without previous marsupialization and the related recurrence rate. All records and data were independently assessed, meta-analysis was performed, and the odds ratio of recurrence was the effect measure; *P* value for the summary effect of < 0.05 was considered statistically significant.

Results The 748 records retrieved were reduced to 6 studies to be qualitatively assessed and 5 studies were included in the meta-analysis. The overall odds ratio of 0.57 [0.25–1.28] of the pooled values pointed that marsupialization reduced the recurrence rate in comparison to just enucleation; however, the *P* value showed that there is no strong evidence to support this statement.

Conclusions Marsupialization followed by enucleation after 12 to 18 months reduces the recurrence rate, but more studies are necessary to support this statement.

Keywords Odontogenic keratocyst · Odontogenic cysts · Decompression · Surgical · Recurrence

Introduction

Marsupialization of odontogenic keratocysts (OKCs), followed by enucleation after a certain period, has been suggested to have the potential to reduce the high recurrence rate, while the defects left after treatment are reduced in size [1]. This idea is based on the assumption that the epithelial cyst lining will undergo metaplasia, to an extent that it becomes not distinguishable from the oral mucosa [2]. The period that the cyst is exposed to the oral milieu varies in the different studies but ranges from 12 to 18 months. As a rule, the defects become much smaller, due to the decompression, which can be monitored on radiographs or scans.

✉ Yuri Slusarenko da Silva
yu.slu@hotmail.com

[1] Department of Oral and Maxillofacial Surgery, Traumatology and Prosthesis, Faculty of Dentistry of the University of São Paulo, Av Prof. Lineu Prestes 2227 Butantã, São Paulo 05508-000, Brazil

[2] Department of Oral and Maxillofacial Surgery, Radboud University, Nijmegen, the Netherlands

The abovementioned assumption is based on the idea that recurrences are due to epithelial cells of the cyst lining that are left behind when enucleating an OKC, which is known to have a rather fragile wall. It may also be due to a new cyst arising from epithelial islands in the wall of the cyst or even microcysts that are left behind. The first event would be less likely to occur after the suggested combination of marsupialization and delayed enucleation. New cyst formation because of development from microcysts or pre-existing mural proliferations is less likely to be avoided.

There is, however, ample evidence that in more than 50% of the OKC, epithelial cell nests and even microcysts are present in the mucosa overlying the OKC [3–5]. It has been suggested that these islands and/or microcysts originate from the basal layer of the epithelium of the overlying mucosa. In fact, in some occasions, a clear dropping off phenomenon can be seen of the basal layer of the mucosa both in solitary OKCs as well as in cysts developing in the nevoid basal cell carcinoma syndrome (NBCCS) [3–8]. Although OKCs are supposed to originate from remnants or offshoots of the dental lamina, as mentioned in most textbooks and even in the latest version of the *WHO classification of head*

Published online: 29 November 2018

and neck tumours [9], there certainly is a good reason to consider offshoots of the basal layer of the mucosa (hamartias), covering the alveolar processes as well as the mandibular ascending ramus and maxillary tuberosity, as an alternative source of their development. It follows that recurrences could be due to epithelial rests left behind after cyst removal, but also that new cysts develop from the microcysts or clusters of epithelial islands often found in the overlying mucosa.

Marsupialization of the OKC may have some advantages provided both theories about the occurrence of recurrences are included in the treatment plan. When marsupializing the cyst, one should include the area where the cyst is connected with the oral mucosa (Fig. 1). This area is probably always present, particularly in the posterior region of the jaws, and current modes of imaging will reveal these areas easily (Fig. 2). If this area is excised with a sufficient margin, decompression will be achieved by nibbling away some bone around the opening that has become visible. The excised mucosa, including part of the cyst membrane, should be examined for the presence of the abovementioned epithelial remnants and also to confirm the diagnosis of OKC. In theory, this treatment should reduce the recurrence rate because it tackles both pathways that allow recurrences to develop.

In a series of three articles [10–12], Al-Moraissi et al. [10] have addressed various aspects of the way OKCs are treated, including marsupialization with or without secondary enucleation. They have, however, not singled out marsupialization and delayed enucleation, which is fundamentally different from just marsupialization and, therefore, worthwhile to address separately.

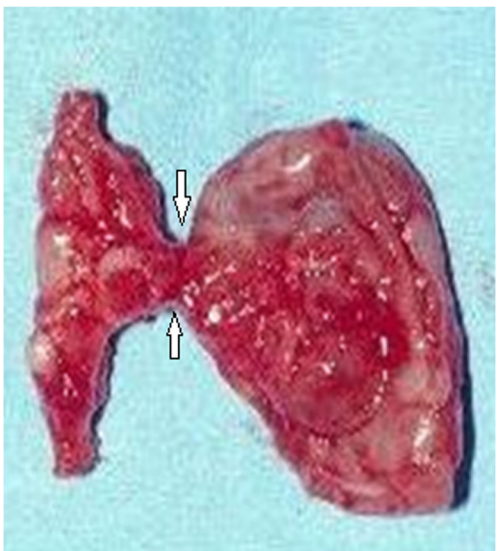

Fig. 1 Specimen of the OKC as shown in the I-Cat (Fig. 2) with the attached overlying mucosa. Note the narrow connection between the OKC and the mucosa

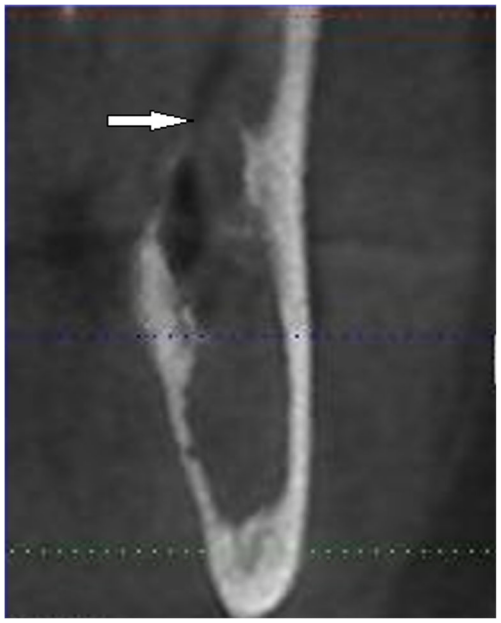

Fig. 2 I-Cat of OKC showing anterior defect in the cortical bone (arrow) which reveals the connection with the overlying mucosa

It was, thus, the prime intention of this systematic review and meta-analysis to examine the results of marsupialization and delayed enucleation of OKCs.

Materials and methods

Protocol and registration

The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—PRISMA protocol [13] and was registered in the International Prospective Register of Systematic Reviews—PROSPERO (ID: CRD42017077486).

Focused question

We intended to answer the following focused question: "Does the marsupialization before enucleation of nonsyndromic odontogenic keratocysts have the potential to reduce the risk of recurrence if compared to enucleation alone?"

Eligibility criteria

Inclusion criteria

Records that fulfilled the following PICOS criteria were included (population, intervention, comparison, outcome, and study design): P: at least six patients with primary OKC in the mandible or maxilla [14]; I: marsupialization and delayed enucleation with or without adjunctive therapy (intervention

group); C: enucleation alone with or without adjunctive therapy (control group); O: recurrence rate and a mean postoperative follow-up of at least 3 years; and S: original randomized and nonrandomized clinical trials and observational studies written in English. The excision of the overlying mucosa was considered as part of the enucleation, because when the oral mucosa is attached to the OKC, it should be excised together with the cyst.

Studies that met the inclusion criteria or those with doubtful information either in the title or abstract were selected for full-text assessment in a second round of this review.

Exclusion criteria

Records eminently concerning recurrent OKCs and orthokeratocysts were excluded. Patients with NBCCS (syndromic OKCs) were also excluded because the pattern of OKC development in syndromic patients is widely influenced by molecular/genetic alterations such as the inactivation of the tumor suppressor gene (PTCH1). A recurrent OKC could be, actually, a new, primary OKC. Reasons for rejection of studies were recorded for each report.

Search strategy

The first hit was conducted online by two independent reviewers (Yuri Slusarenko da Silva and Maria da Graça Naclério-Homem), in MEDLINE (via PubMed), Web of Science, Scopus, and Cochrane Library, from the inception until August 5th of 2017. Publications were searched using the following strategy: (((((Keratocystic Odontogenic Tumor) OR Keratocystic Odontogenic Tumour) OR Odontogenic Keratocyst)) AND treatment) AND ((recurrence) OR recurrence rate). Duplicate records were subsequently removed.

Study selection

Yuri and Maria da Graça independently selected records that remained from the first hit by reading their title and abstract (first round). Disagreements in this selection (one acceptance and one rejection) were resolved by the decision of Paul JW Stoelinga (third reviewer). Afterwards, all records screened from the first round had their full text independently assessed for eligibility by Yuri and Maria da Graça (second round). Again, split decisions were decided by P. Stoelinga.

Data collection process

Yuri and Maria da Graça separately submitted all eligible studies to a qualitative synthesis using an extraction data form including demographic and clinical characteristics of the population, number and location of primary OKC, number of surgeries with and without previous marsupialization as well as the related recurrence rate, period of recurrence (mean), and overall follow-up.

Subsequently, all extraction data forms with the results of each included study were verified together in order to calibrate validity and reliability of data collection. Disagreements in this phase were solved by consensus, and when necessary, P. Stoelinga was consulted.

Risk of bias in individual and across studies

To assess the quality of the studies, we adapted a checklist of the critical appraisal tools recommended by JBI Systematic Reviews, from the Joanna Briggs Institute (http://joannabriggs.org/research/critical-appraisal-tools.html, Accessed 24 September 2018) [15], and applied them to be used in Review Manager Software 5.3 (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The queries of the included studies are briefly explained as follows: (a) patients from the same setting of study; (b) histological diagnosis of OKC [14]; (c) same definitive treatment for the intervention and control groups; (d) adequate assessment of recurrence rate; (e) adequate postoperative follow-up; (f) marsupialization at the region of cortical perforation; and (g) histological revision of the oral mucosa plus cyst membrane of the fragment removed at marsupialization, which may contain epithelial islands or even microcysts.

For each query, the answer "Yes" meant a low risk of bias, the answer "No" meant a high risk of bias, and the answer "Unclear" meant that the information was unavailable in the text. These factors ought to be recognized and properly equilibrated with the quantitative synthesis.

Summary measures and synthesis of results

Meta-analysis was performed in the Review Manager software 5.3, and the odds ratio (OR) of recurrence (event) with a confidence interval (CI) of 95% was the effect measure.

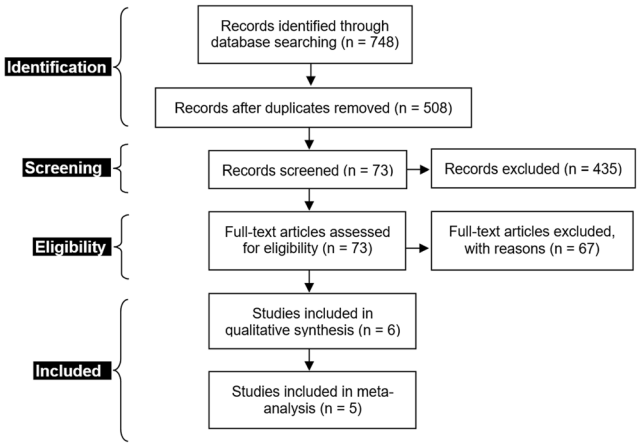

Fig. 3 Flow diagram

Table 1 Articles excluded and their reasons

Reason	Explanation	Authors	Total
Less than 6 patients in the study	Insufficient number of participants with OKC who were submitted to treatment	Alstad and Abtahi [16], Bradley and Fisher [17], Ephros and Lee [18], Eyre and Zakrzewska [19], Ogunsalu et al. [20], Rossi et al. [21], Tonietto et al. [22]	7
Possibility of duplicate data	Sample information retrieved from the same setting and between quite similar periods	Kinard et al. [23], Kinard et al. [24], Marker et al. [25], Meara et al. [26], Meara et al. [27]	5
Diagnosis is unclear	There is no specification of the quantity of OKCs among the total number of odontogenic cysts/tumors	Adebayo et al. [28], Chapelle et al. [29], Lone et al. [30]	3
Unable to distinguish OKC from orthokeratocysts	Cystic jaw lesions that are lined by orthokeratinizing epithelium do not form part of the spectrum of OKC	Marker et al. [25], Maurette et al. [31], Noy et al. [32], Pitak-Arnnop et al. [33], Rao and Kumar [34], Zachariades et al. [35]	6
Unable to distinguish OKC of nonsyndromic from NBCCS patients	The number of sporadic OKCs has been counted together with syndromic OKCs	Meara et al. [26], Lone et al. [30], Bande et al. [36], Cassoni et al. [37], Chirapathomsakul et al. [38], Dammer et al. [39], Farmand and Makek [40], Finkelstein et al. [41], Madras and Lapointe [42], Mello et al. [43], Schmidt and Pogrel [44], Tkaczuk et al. [45], Yang et al. [46]	13
Only 1 method of treatment	There is only 1 method of treatment described, i.e., only cases with or without previous marsupialization	Madras and Lapointe [42], Stoelinga and Bronkhorst [47], Stoelinga [4], Alchalabi et al. [48], Alstad and Abtahi [16], Awni and Conn [49], Bande et al. [36], Boyne et al. [50], Cassoni et al. [37], Chirapathomsakul et al. [38], Chow [51], Dashow et al. [52], El-Hajj and Anneroth [53], Ephros and Lee [18], Eyre and Zakrzewska [19], Forssell et al. [54], Gao et al. [55], Gupta et al. [56], Irvine and Bowerman [57], Jensen et al. [58], Ledderhof et al. [59], Leung et al. [60], Levorova et al. [61], Marker et al. [25], Maurette et al. [31], Meara et al. [26], Meara et al. [27], Mello et al. [43], Ogunsalu et al. [20], Partridge and Towers [62], Pejovic et al. [63], Pitak-Arnnop et al. [33], Pogrel [64], Rao and Kumar [34], Romano et al. [65], Rossi et al. [21], Sánchez-Burgos et al. [66], Schmidt and Pogrel [44], Titinchi and Nortje [67], Tonietto et al. [22], Vedtofte and Prætorius [68], Voorsmit et al. [69], Yaman and Suer [70], Zachariades et al. [35], Zecha et al. [71], Zhou et al. [72]	46
Recurrence rate is unclear for the nonsyndromic OKC	It is not possible to establish a precise relationship between the recurrence rate to the treatment of the primary OKCs because they are counted together with the treatment of syndromic OKCs	Chow [51], El-Hajj and Anneroth [53], Finkelstein et al. [41], Forssell et al. [54], Habibi et al. [73], Jattan et al. [74], Lipovec and Hren [75], Mello et al. [43], Partridge and Towers [62], Schmidt and Pogrel [44], Tkaczuk et al. [45], Yang et al. [46], Zachariades et al. [35]	13
Recurrence rate is unclear for the treatment of the primary cyst	It is not possible to establish a precise relationship between the recurrence rate to the treatment of the primary OKCs because they are counted together with the treatment of recurrent OKCs, orthokeratocysts, or other cysts/tumors	Madras and Lapointe [42], Alchalabi et al. [48], Boyne et al. [50], Farmand and Makek [40], Guler et al. [76], Irvine and Bowerman [57], Jattan et al. [74], Maurette et al. [31], Meara et al. [27], Noy et al. [32], Pitak-Arnnop et al. [33], Schmidt and Pogrel [44], Yang et al. [46], Zhao et al. [77]	14
Recurrence rate is unclear for the type of treatment	It is not possible to establish a precise relationship between the recurrence rate and the type of primary surgery	Bande et al. [36], Dammer et al. [39], Finkelstein et al. [41], González-Alva et al. [78], Jattan et al. [74], Lipovec and Hren [75], Lone et al. [30], Tkaczuk et al. [45]	8
Lack of relationship between the recurrence rate and the type of treatment	Difficulty to establish a clear relationship between the recurrence rate and the type of primary surgery	Anniko et al. [79], Bradley and Fisher [17], Dashow et al. [52], Kinard et al. [24], Vedtofte and Prætorius [68], Zhao et al. [77]	6
Follow-up of less than 3 years	The average time of follow-up is less than 3 years	Guler et al.[76], Gupta et al. [56], Habibi et al. [73], Kinard et al. [23], Maurette et al. [31], Titinchi and Nortje [67], Rao and Kumar [34], Yang et al. [46]	8
Follow-up is unclear		Alchalabi et al. [48], Awni and Conn [49], Boyne et al. [50], Bradley and Fisher [17], Cassoni et al. [37],	26

Table 1 (continued)

Reason	Explanation	Authors	Total
	There is no information regarding the follow-up period or the only available information are the minimum and/or maximum periods	Dammer et al. [39], Dashow et al. [52], El-Hajj and Anneroth [53], Ephros and Lee [18], Farmand and Makek [40], Finkelstein et al. [41], González-Alva et al. [78], Jattan et al. [74], Jensen et al. [58], Kinard et al. [24], Kolokythas et al. [80], Levorova et al. [61], Lipovec and Hren [75], Lone et al. [30], Meara et al. [26], Meara et al. [27], Mello et al. [43], Ogunsalu et al. [20], Tkaczuk et al. [45], Voorsmit et al. [69], Zachariades et al. [35]	

Mantel–Haenszel analysis was applied in a random-effect model. *P* value, from the *Z* test, for the meta-analysis summary effect of < 0.05 was considered to provide evidence to the effect estimates. The heterogeneity among studies was

Table 2 Characteristics of the included studies

Authors	Number of OKCs[a]	Surgical technique: number/recurrences	Period of marsup (months)	Site	Follow-up (years)
Berge et al. [81]	Mandible = 67 Maxilla = 25 Total = 92	Marsup + enucleation = 22/4 Enucleation = 70/23	18	Unclear	5.6
Brondum and Jensen [82]	Mandible = 34 Maxilla = 0 Total = 34[b]	Marsup + cystectomy[c] = 7/0 Cystectomy = 27/8	10	Mandible	9
Cruz et al. [83]	Mandible = 8 Maxilla = 0 Total = 8[d]	Marsup + enucleation + cryotherapy[e] = 4/1 enucleation + cryotherapy = 4/0	9.5	Mandible	5.3
Cunha et al. [84]	Mandible = 20 Maxilla = 4 Total = 24	Marsup + enucleation + peripheral ostectomy = 14/3 Enucleation + peripheral ostectomy = 10/5	15.2	Unclear	5
Nakamura et al. [85]	Mandible = 18 Maxilla = 0 Total = 33[f]	Marsup + enucleation + excision of the overlying mucosa + peripheral ostectomy = 18/5[g] Enucleation + excision of the overlying mucosa + peripheral ostectomy: **15/3[h]**	23.5	Mandible Unclear	6.6
Ribeiro et al. [86]	Mandible = 11 Maxilla = 0 Total = 11[i]	Marsup + curettage + Carnoy's solution = 2/0 Curettage + Carnoy's solution = 9/0	Unclear	Mandible Mand = 8 Max = 1	3.5
Synthesis of studies [81–86]	Mandible = 158 Maxilla = 29 Unclear site = 15[h] Total = 202	Marsupialization and delayed enucleation = 67/13 Enucleation alone = 135/39	15.25		

Period of marsup and follow-up were expressed as mean

Marsup, marsupialization; *N/A*, not applicable or not possible to describe

[a] Primary and nonsyndromic OKC

[b] Four OKCs that received marsupialization first were no longer classified as having OKCs after the cystectomy by Brondum and Jensen and further six cysts that had histologic orthokeratotic characteristics were not considered according to our protocol

[c] "Primary cystectomy with smoothing of the osseous wall of the cavity" [82]. In the present systematic review, we considered this technique as curettage

[d] Two patients had "multiple" cysts without a precise description of the OKC number and were not considered according to our protocol

[e] Refrigerant spray of a propane/butane/isobutane gas mixture stored in a pressurized can (Endo Frost, Roeko, Langenau, Germany)

[f] Five OKCs associated with the NBCCS were not considered according to our protocol

[g] Five OKCs were not considered because it received marsupialization only

[h] The site of 15 OKCs treated without previous marsupialization was unclear

[i] Eleven OKCs were associated with the NBCCS and were not considered according to our protocol. The study of Ribeiro et al. [86] was not included in the meta-analysis

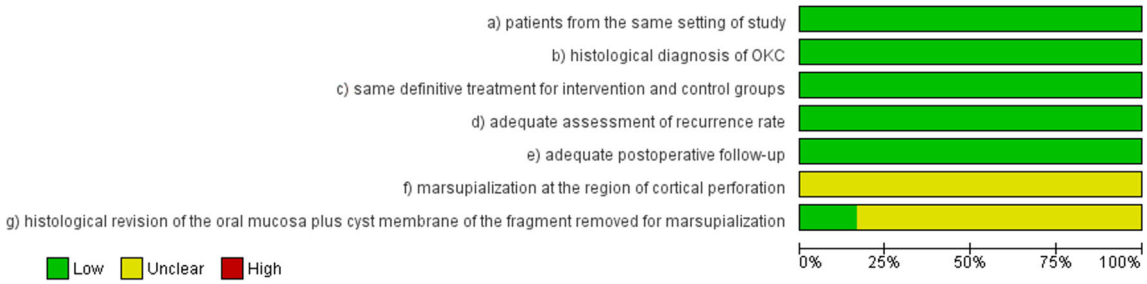

Fig. 4 Risk of bias across studies

obtained from the chi-squared test. In addition, we computed the risk ratio (RR) from the OR to facilitate statistical interpretation and also computed the relative risk reduction (RRR) to give the percentage of recurrence rate reduction.

Results

Study selection

The first hit retrieved a total of 748 records. The distribution of the searched records and the number of studies finally selected are shown in the flow diagram (Fig. 3). Excluded studies and refusal reasons are shown in Table 1.

Study characteristics and risk of bias across studies

The characteristics of the studies are shown in Table 2. Three studies were nonrandomized clinical trials [82, 85, 86] and three were retrospective observational case–controls [81, 83, 84].

Patients were treated according to the decision of the surgeon on the severity and location of OKCs, and it is expected that the same surgeons have assessed these patients in the postoperative period. Therefore, investigation of domains such as random allocation (selection bias), blinding of patients/surgeons, and blinding of outcome assessment (performance bias) is not applicable in the present systematic review. In turn, query "d" (see section "Risk of bias in individual and across studies") evaluated the domains such as incomplete outcome data (attrition bias) and selective reporting (reporting bias).

The risk of bias across studies for each query is expressed in Fig. 4. For queries "a, b, c, d, and e," all studies were at low risk of bias (100% of low risk of bias). Nonetheless, none of the studies reported if marsupialization was performed at the region of cortical perforation (100% of unclear risk of bias for query "f") and only one study histologically revised the fragments removed for marsupialization (83% of unclear risk of bias for query "g"). No study was at high risk of bias for any query.

Two studies did not report the use of adjunctive therapy after enucleation [81, 82]. On the other hand, four studies reported the use of adjunctive therapy after enucleation as follows: peripheral ostectomy [84, 85], cryotherapy [83], and application of Carnoy's solution [86].

Results of individual studies and quantitative synthesis of results

Five articles met the criteria as set for the meta-analysis [81–85], which was divided in three scenarios or subgroups. Ribeiro et al. [86] was not included in the quantitative synthesis because the odds ratio/risk ratio cannot be calculated in a study with zero recurrences in the intervention and control groups. Cruz et al. [83] was included only in the meta-analysis "scenario 3: overview of the treatments" because it would be necessary at least one more study to compare marsupialization and delayed enucleation plus cryotherapy vs. enucleation plus cryotherapy in a separate subgroup [87]. Additionally, a random-effect model was incorporated in the meta-analysis due to methodological diversity among studies and due to clinical diversity of patients presenting the disease in terms of ethnicity, age, gender, etc. The effects estimated were not identical but followed some distribution. In this way, the heterogeneity is no longer an issue [87].

Scenario 1: marsupialization and delayed enucleation vs. enucleation (without adjunctive therapy)

Marsupialization and delayed enucleation reduces the recurrence rate of the OKC in 52% over enucleation without

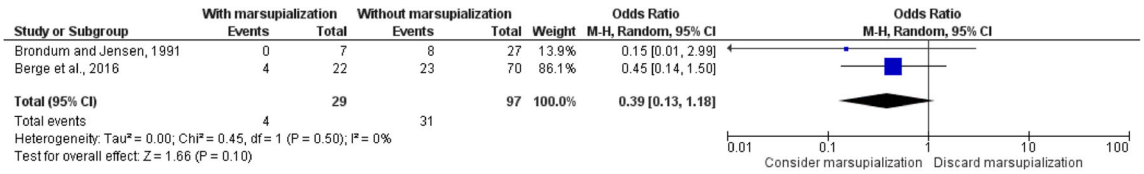

Fig. 5 Meta-analysis and forest plot of marsupialization and delayed enucleation vs. enucleation (without adjunctive therapy)

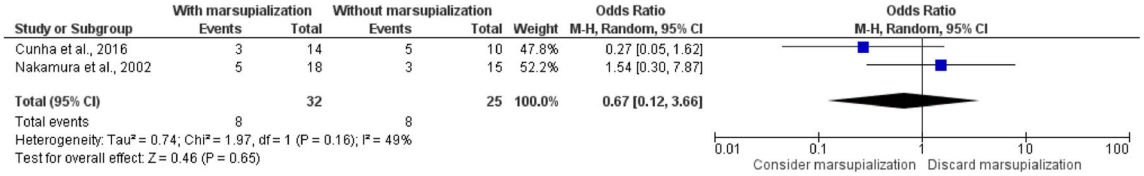

Fig. 6 Meta-analysis and forest plot of marsupialization and delayed enucleation plus peripheral ostectomy vs. enucleation plus peripheral ostectomy

adjunctive therapy (odds ratio 0.39 [0.13, 1.18] and risk ratio 0.48, $P = 0.10$) [81, 82] (Fig. 5).

Scenario 2: marsupialization and delayed enucleation plus peripheral ostectomy vs. enucleation plus peripheral ostectomy

Marsupialization and delayed enucleation plus peripheral ostectomy reduces the recurrence rate of the OKC in 26% over enucleation plus peripheral ostectomy (odds ratio 0.67 [0.12, 3.66] and risk ratio 0.74, $P = 0.65$) [84, 85] (Fig. 6).

Scenario 3: overview of the treatments

Considering all treatments, marsupialization and delayed enucleation reduces the recurrence rate of the OKC in 34% over enucleation (odds ratio 0.57 [0.25, 1.28] and risk ratio 0.66, $P = 0.17$) [81–85] (Fig. 7).

Discussion

Although all scenarios suggest that marsupialization preceding enucleation has a positive effect on the recurrence rate, one must bear in mind that the confidence intervals were wide and the P values were above 0.05, so we must conclude that further information is needed to support this notion.

In an individual study analysis, Nakamura et al. [85] and Cruz et al. [83] found that enucleation plus peripheral ostectomy or cryotherapy, respectively, is better without marsupialization, but the wide CI provided by their study did not support their suggested treatment. This must be attributed to the mechanical elimination of cystic remnants by peripheral ostectomy or pathological cell death by freezing or cryotherapy. Considering that fixation of pathological cells with Carnoy's solution after enucleation also showed positive results with or without previous marsupialization [86], it is unlikely that marsupialization will negatively interfere with the recurrence rate.

None of the studies on marsupialization reported if this technique was carried out in the area where the cyst was attached to the overlying mucosa. Thus, the results of the present systematic review cannot be assigned only to the potential benefit of performing marsupialization at the region of cortical perforation. We believe that metaplasia of the epithelial cyst lining have an important role in reducing the recurrence rate due to the conversion of OKC into a less aggressive lesion. Only Brondum and Jensen [82] did histologically examine the specimens removed after marsupialization. They did not mention the presence of epithelial islands or even microcysts but described a thin, band-like parakeratotic epithelium with cuboidal or columnar palisade-like basal cells in five out of seven fragments, with no evidence of this pattern in the enucleated lesions. They also described a parakeratotic epithelium resembling the oral mucous membrane in one fragment and a thin parakeratotic epithelium with basal cells in a nonpalisading pattern in another specimen.

Nakamura et al. [85] did find microcysts and epithelial islands in the surrounding connective tissue wall in 6 out of 28 cysts removed. In their study, however, five OKCs occurred in NBCCS patients, while five marsupialized OKCs without enucleation were grouped together, limiting our ability to properly weigh the importance or significance of their findings.

Cunha et al. [84] found parakeratinization and subepithelial split of the epithelial lining in all lesions and budding in the basal layer of the epithelium with epithelial islands next to the overlying attached mucosa in 2 out of 12 recurring lesions and in 6 out of 8 nonrecurring lesions. In their research, however, it was unclear if these patterns were present in the fragments removed for the marsupialization.

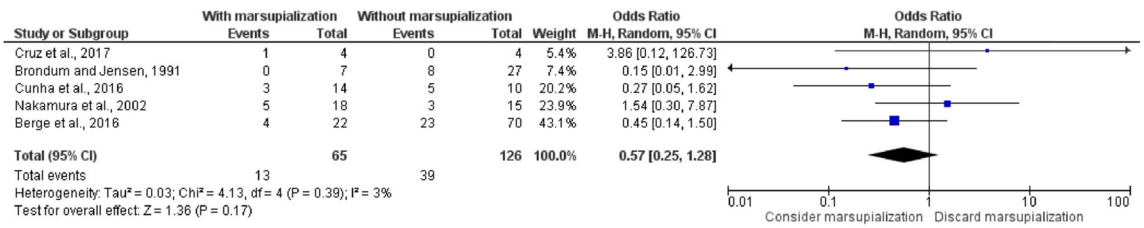

Fig. 7 Meta-analysis and forest plot of all treatments

Table 3 Main differences between the present study and previous published systematic reviews

Present study	Other systematic reviews[a]
Primary OKCs only	• Primary and recurrent OKCs [10, 12, 90, 93]
	• Primary, syndromic, and orthokeratocysts [89, 91]
Definitive treatment of OKCs with previous marsup vs. definitive treatment of OKCs without previous marsup (with meta-analysis)	• Various methods of treatment except the comparison of definitive treatment with previous marsup vs. without previous marsup with [10, 12, 92] or without meta-analysis [89–91]
	• Various methods of treatment including the comparison of definitive treatment with previous marsup/decomp vs. without previous marsup/decomp with meta-analysis [93] with the likely of an increased risk of bias [77, 80, 82]
Assessment of key points of marsupialization	• No assessment of key points of marsupialization [10, 12, 89–93]
Follow-up of a minimum of 3 years	• Follow-up of a minimum of 1 year [10, 12, 92, 93]
	• Unclear minimum follow-up [89, 91]

Marsup, marsupialization; *decomp*, decompression

[a] Systematic reviews: Al-Moraissi et al. [10], Al-Moraissi et al. [12], Blanas et al. [89], Kaczmarzyk et al. [90], Johnson et al. [91] (update of the systematic review of Blanas et al. [89]), Antonoglou et al. [92], de Castro et al. [93]

There still remains a question to be answered about the potential activity of the basal layer of the marsupialized cyst. Does it eventually become active again, since in the original OKC this layer has a high mitotic index as compared to ordinary dental cysts [88]. Microcysts and even mural proliferations, although not frequently seen in solitary OKCs, may be present in the wall of the original cyst. Stoelinga [4], however, found the epithelial islands in the wall of the cyst membrane mainly to be located in the overlying mucosa attached to the OKC.

Seven systematic reviews were found in the literature that addressed the recurrence rate after various treatments of OKC, but none of them addressed key points of marsupialization as we did [10, 12, 89–93]. To the best of our knowledge, only de Castro et al. [93] compared marsupialization/decompression and delayed enucleation vs. enucleation alone. They found similar results to ours, favoring previous marsupialization/decompression. Controversially, Al-Moraissi et al. [10] concluded that enucleation with or without adjuvant therapy is better than marsupialization with or without secondary enucleation. However, inclusion of recurrent OKCs and orthokeratocysts as well as a short-term postoperative follow-up may have influenced the direction and magnitude of their results [10, 93] (Table 3).

In short, marsupialization before enucleation can be recommended to reduce the risk of recurrence of OKCs, particularly in medium- or large-sized cysts in the mandibular ascending ramus and in the posterior maxilla, because they most likely will be OKCs [29]. However, this technique may be somewhat cumbersome for the patient because of the need of proper hygiene within the cystic cavity, which entails rinsing of the defect at regular intervals. After marsupialization, we recommend enucleation combined with excision of the overlying, attached oral mucosa, if necessary, and treatment of the defect with some adjunctive therapy to eliminate possible fragments of epithelial cyst lining left behind, which may show a high mitotic index [94]. Yearly follow-up in the first 5 years and every 2 years thereafter is strongly advocated. Possible recurrences are easily manageable without much suffering for the patient involved.

Research in this field is open for data collection from long-term prospective studies. In cases of marsupialization and delayed enucleation, the current authors advise that marsupialization should be performed at the area where the cyst is attached to the overlying mucosa, if present, while careful histological examination of the fragment containing the oral mucosa attached to the cyst membrane is histologically examined to confirm the diagnosis and also to define whether epithelial islands or even microcysts are present. Only then will we be able to support and equilibrate the concept of the hamartomas derived from the basal cell layer of the mucosa as an alternative and important source for the development and recurrence of OKCs [3].

Conclusion

Our results indicate, with a low risk of bias, that marsupialization and delayed enucleation of OKCs reduces the recurrence rate when compared with enucleation alone, but more studies are necessary to support this statement.

Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent For this type of study, formal consent is not required.

References

1. Pogrel MA (2005) Treatment of keratocysts: the case for decompression and marsupialization. J Oral Maxillofac Surg 11:1667–1673
2. Schlieve T, Miloro M, Kolokythas A (2014) Does decompression of odontogenic cysts and cystlike lesions change the histologic diagnosis? J Oral Maxillofac Surg 72:1094–1105
3. Stoelinga PJ, Peters JH (1973) A note on the origin of keratocysts of the jaws. Int J Oral Surg 2:37–44
4. Stoelinga PJ (2001) Long-term follow-up on keratocysts treated according to a defined protocol. Int J Oral Maxillofac Surg 30:14–25
5. Stoelinga PJ (2003) Etiology and pathogenesis of keratocysts. Oral Maxillofac Surg Clin North Am 15:317–324
6. Stoelinga PJ (2003) Excision of the overlying, attached mucosa, in conjunction with cyst enucleation and treatment of the bony defect with Carnoy solution. Oral Maxillofac Surg Clin North Am 15: 407–414
7. Stoelinga PJ, Peters JH, Van de Staak WJ, Cohen MM Jr (1973) Some new findings in the basal-cell nevus syndrome. Oral Surg Oral Med Oral Pathol 36:686–692
8. Shear M, Speight PM (2007) Odontogenic keratocyst. In: Shear M, Speight PM (eds) Cysts of the oral and maxillofacial regions, 4th edn. Blackwell, Ames, pp 6–58
9. Speight P, Devilliers P, Li TJ, Odell EW, Wright JM (2017) Odontogenic keratocyst. In: El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (eds) WHO classification of head and neck tumours, 4th edn. IARC, Lyon, pp 235–236
10. Al-Moraissi EA, Pogrel MA, Ellis E 3rd (2016) Enucleation with or without adjuvant therapy versus marsupialization with or without secondary enucleation in the treatment of keratocystic odontogenic tumors: a systematic review and meta-analysis. J Craniomaxillofac Surg 44:1395–1403
11. Al-Moraissi EA, Pogrel MA, Ellis E 3rd (2016) Does the excision of overlying oral mucosa reduce the recurrence rate in the treatment of the keratocystic odontogenic tumor? A systematic review and meta-analysis. J Oral Maxillofac Surg 74:1974–1982
12. Al-Moraissi EA, Dahan AA, Alwadeai MS, Oginni FO, Al-Jamali JM, Alkhutari AS, Al-Tairi NH, Almaweri AA, Al-Sanabani JS (2017) What surgical treatment has the lowest recurrence rate following the management of keratocystic odontogenic tumor?: a large systematic review and meta-analysis. J Craniomaxillofac Surg 45: 131–144
13. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097
14. Philipsen HP (2005) Keratocystic odontogenic tumour. In: Barnes L, Eveson JW, Reichart P, Sidransky (eds) World Health Organization classification of tumours. Pathology and genetics of head and neck tumours. IARC Press, Lyon, pp 306–307
15. The Joanna Briggs Institute (2018). Critical Appraisal Tools. http://joannabriggs.org/research/critical-appraisal-tools.html. Accessed 24 September 2018.
16. Alstad V, Abtahi J (2017) Surgical removal of keratocystic odontogenic tumours via a Le Fort I osteotomy approach: a retrospective study of the recurrence rate. Int J Oral Maxillofac Surg 46: 434–439
17. Bradley PF, Fisher AD (1975) The cryosurgery of bone. An experimental and clinical assessment. Br J Oral Surg 13:111–127
18. Ephros H, Lee HY (1991) Treatment of a large odontogenic keratocyst using the brosch procedure. J Oral Maxillofac Surg 49: 871–874
19. Eyre J, Zakrzewska JM (1985) The conservative management of large odontogenic keratocysts. Br J Oral Maxillofac Surg 23:195–203
20. Ogunsalu C, Daisley H, Kamta A, Kanhai D, Mankee M, Maharaj A (2007) Odontogenic keratocyst in Jamaica: a review of five new cases and five instances of recurrence together with comparative analyses of four treatment modalities. West Indian Med J56:90–95
21. Rossi D, Borgonovo AE, Vavassori V, Poli PP, Santoro F (2012) Combined treatment of odontogenic keratocysts: initial marsupialization and successive enucleation with peripheral ostectomy plus Carnoy's solution application. A five-year follow-up experience. Minerva Stomatol 61:101–112
22. Tonietto L, Borges HOI, Martins CAM, Silva DN, Sant'ana M (2011) Enucleation and liquid nitrogen cryotherapy in the treatment of keratocystic odontogenic tumors: a case series. J Oral Maxillofac Surg 69:112–117
23. Kinard BE, Chuang SK, August M, Dodson TB (2013) How well do we manage the odontogenic keratocyst? J Oral Maxillofac Surg 71:1353–1358
24. Kinard BE, Chuang SK, August M, Dodson TB (2015) For treatment of odontogenic keratocysts, is enucleation, when compared to decompression, a less complex management protocol? J Oral Maxillofac Surg 73:641–648
25. Marker P, Brondum N, Clausen PP, Bastian HL (1996) Treatment of large odontogenic keratocysts by decompression and later cystectomy—a long-term follow-up and a histologic study of 23 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82: 122–131
26. Meara JG, Li KK, Shah SS, Cunningham MJ (1996) Odontogenic keratocysts in the pediatric population. Arch Otolaryngol Head Neck Surg 122:725–728
27. Meara JG, Shah S, Li KK, Cunningham MJ (1998) The odontogenic keratocyst: a 20-year clinicopathologic review. Laryngoscope 108:280–283
28. Adebayo ET, Ajike SO, Adekeye EO (2005) A review of 318 odontogenic tumors in Kaduna, Nigeria. J Oral Maxillofac Surg 63:811–819
29. Chapelle KA, Stoelinga PJ, de Wilde PC, Brouns JJ, Voorsmit RA (2004) Rational approach to diagnosis and treatment of ameloblastomas and odontogenic keratocysts. Br J Oral Maxillofac Surg 42:381–390
30. Lone PA, Singh M, Johar HS (2015) Treatment modalities of odontogenic keratocyst of maxilla and mandible: our experience. World J Dent 6:208–212
31. Maurette PE, Jorge J, de Moraes M (2006) Conservative treatment protocol of odontogenic keratocyst: a preliminary study. J Oral Maxillofac Surg 64:379–383
32. Noy D, Rachmiel A, Zar K, Emodi O, Nagler RM (2017) Sporadic versus syndromic keratocysts—can we predict treatment outcome? A review of 102 cysts. Oral Dis 23:1058–1065
33. Pitak-Arnnop P, Chaine A, Oprean N, Dhanuthai K, Bertrand JC, Bertolus C (2010) Management of odontogenic keratocysts of the jaws: a ten-year experience with 120 consecutive lesions. J Craniomaxillofac Surg 38:358–364
34. Rao K, Kumar S (2014) The use of enucleation and chemical cauterization (Carnoy's) in the management of odontogenic keratocyst of the jaws. Indian J Otolaryngol Head Neck Surg 66:8–12

35. Zachariades N, Papanicolaou S, Triantafyllou D (1985) Odontogenic keratocysts: review of the literature and report of sixteen cases. J Oral Maxillofac Surg 43:177–182
36. Bande CR, Prashant MC, Sumbh B, Pandilwar PK (2010) Prevalence, treatment and recurrence of odontogenic keratocyst in central India. J Maxillofac Oral Surg 9:146–149
37. Cassoni A, Valentini V, Della Monaca M, Pagnoni M, Prucher GM, Baruner E, Guarino G, FaddA MT, Jamshir S, Pompa G, Ianetti G (2014) Keratocystic odontogenic tumor surgical management: retrospective analysis on 77 patients. Eur J Inflamm 12:209–215
38. Chirapathomsakul D, Sastravaha P, Jansisyanont P (2006) A review of odontogenic keratocysts and the behavior of recurrences. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:5–9
39. Dammer R, Niederdellmann H, Dammer P, Nueblermoritz M (1997) Conservative or radical treatment of keratocysts: a retrospective review. Br J Oral Surg 35:46–48
40. Farmand M, Makek M (1983) Late results following the Broschprocedure for treating large mandibular ramus cysts. J Maxillofac Surg 11:211–215
41. Finkelstein MW, Hellstein JW, Lake KS, Vincent SD (2013) Keratocystic odontogenic tumor: a retrospective analysis of genetic, immunohistochemical and therapeutic features. Proposal of a multicenter clinical survey tool. Oral Surg Oral Med Oral Pathol Oral Radiol 116:75–83
42. Madras J, Lapointe H (2008) Keratocystic odontogenic tumour: reclassification of the odontogenic keratocyst from cyst to tumour. J Can Dent Assoc 74:165
43. Mello LA, Gurgel CA, Ramos EA, de Souza RO, Schlaepfer-Sales CB, de Azevedo RA, dos Santos JN (2011) Keratocystic odontogenic tumour: an experience in the northeast of Brazil. Srp Arh Celok Lek 139:291–297
44. Schmidt BL, Pogrel MA (2001) The use of enucleation and liquid nitrogen cryotherapy in the management of odontogenic keratocysts. J Oral Maxillofac Surg 59:720–725
45. Tkaczuk AT, Bhatti M, Caccamese JF, Ord RA, Pereira KD (2015) Cystic lesions of the Jawin children a 15-year experience. JAMA Otolaryngol Head Neck Surg 141:834–839
46. Yang SI, Park YI, Choi SY, Kim JW, Kim CS (2011) A retrospective study of 220 cases of keratocystic odontogenic tumor (OKC) in 181 patients. Asian J Oral Maxillofac Surg 23:117–121
47. Stoelinga PJ, Bronkhorst FB (1988) The incidence, multiple presentation and recurrence of aggressive cysts of the jaws. J Craniomaxillofac Surg 16:184–195
48. Alchalabi NJ, Merza AM, Issa SA (2017) Using Carnoy's solution in treatment of keratocystic odontogenic tumor. Ann Maxillofac Surg 7:51–56
49. AwnI S, Conn B (2017) Decompression of keratocystic odontogenic tumors leading to increased fibrosis, but without any change in epithelial proliferation. Oral Surg Oral Med Oral Pathol Oral Radiol 123:634–644
50. Boyne PJ, Hou D, Moretta C, Pritchard T (2005) The multifocal nature of odontogenic keratocysts. J Calif Dent Assoc 33:961–965
51. Chow HT (1998) Odontogenic keratocyst: a clinical experience in Singapore. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 86: 573–577
52. Dashow JE, Mchugh JB, Braun TM, Edwards SP, Helman JI, Ward BB (2015) Significantly decreased recurrence rates in keratocystic odontogenic tumor with simple enucleation and curettage using Carnoy's versus modified Carnoy's solution. J Oral Maxillofac Surg 73:2132–2135
53. El-Hajj G, ANneroth G (1996) Odontogenic keratocysts—a retrospective clinical and histologic study. Int J Oral Maxillofac Surg 25: 124–129
54. Forssell K, Forssell H, Kahnberg KE (1988) Recurrence of keratocysts. A long-term follow-up study. Int J Oral Maxillofac Surg 17:25–28
55. Gao Z, Ni QW, Gao W, Liu YP, Zhang Q (2017) Application of endoscopy to treat mandibular keratocystic odontogenic tumors. Braz J Med Biol Res 50:e6209
56. Gupta A, Bansal P, Sharma R, Sharma SD (2016) Treatment of keratocystic odontogenic tumours: a prospective study of 30 cases. J Oral Maxillofac Surg 15:521–527
57. Irvine GH, Bowerman JE (1985) Mandibular keratocysts: surgical management. Br J Oral Maxillofac Surg 23:204–209
58. Jensen J, Sindet-Pedersen S, Simonsen EK (1988) A comparative study of treatment of keratocysts by enucleation or enucleation combined with cryotherapy. A preliminary report. J Craniomaxillofac Surg 16:362–365
59. Ledderhof NJ, Caminiti MF, Bradley G, Lam DK (2017) Topical 5-fluorouracil is a novel targeted therapy for the keratocystic odontogenic tumor. J Oral Maxillofac Surg 75:514–524
60. Leung YY, Lau SL, Tsoi KYY, Ma HL, Ng CL (2016) Results of the treatment of keratocystic odontogenic tumours using enucleation and treatment of the residual bony defect with Carnoy's solution. Int J Oral Maxillofac Surg 45:1154–1158
61. Levorova J, Machon V, Grill P, Hirjak D, Foltan R (2015) Keratocystic odontogenic tumour with extraosseal spread: evaluation of the effect Carnoy's solution. Prague Med Rep 116:303–313
62. Partridge M, Towers JF (1987) The primordial cyst (odontogenic keratocyst): its tumour-like characteristics and behavior. Br J Oral Maxillofac Surg 25:271–279
63. Pejovic M, Stepic J, Markovic A, Dragovic M, Milicic B, Colic S (2016) Retrospective study of spontaneous bone regeneration after decompression of large odontogenic cystic lesions in children. Vojnosanit Pregl 73:129–134
64. Pogrel MA (1993) The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions. J Oral Maxillofac Surg 51:269–273
65. Romano A, Orabona GD, Abbate V, Maglitto F, Solari D, Iaconetta G, CalIfano L (2016) Endoscope-assisted enucleation of mandibular odontogenic keratocyst tumors. J Craniofac Surg 27:1404–1407
66. Sánchez-Burgos R, González-Martín-Moro J, Pérez-Fernández E, Burgueño-García M (2014) Clinical, radiological and therapeutic features of keratocystic odontogenic tumours: a study over a decade. J Clin Exp Dent 6:e259–e264
67. Titinchi F, Nortje CJ (2012) Keratocystic odontogenic tumor: a recurrence analysis of clinical and radiographic parameters. Oral Surg Oral Med Oral Pathol Oral Radiol 114:136–142
68. Vedtofte P, Prætorius F (1979) Recurrence of the odontogenic keratocyst in relation to clinical and histological features: a 20-year follow-up study of 72 patients. Int J Oral Surg 8:412–420
69. Voorsmit RACA, Stoelinga PJW, Van Haelst UJGM (1981) The management of keratocysts. J Maxillofac Surg 9:228–236
70. Yaman Z, Suer BT (2013) Clinical comparison of ultrasonic surgery and conventional surgical techniques for enucleating jaw cysts. Int J Oral Maxillofac Surg 42:1462–1468
71. Zecha J, Mendes RA, Lindeboom VB, Van Der Waal I (2010) Recurrence rate of keratocystic odontogenic tumor after conservative surgical treatment without adjunctive therapies—a 35-year single institution experience. Oral Oncol 46:740–742
72. Zhou H, Hou R, Ma Q, Wu K, Ding Y, Qin R, Hu K (2012) Secondary healing after removal of large keratocystic odontogenic tumor in the mandible: enucleation followed by open packing of iodoform gauze. J Oral Maxillofac Surg 70:1523–1530
73. Habibi A, Saghravanian N, Habibi M, Mellati E (2007) Keratocystic odontogenic tumor: a 10-year retrospective study of 83 cases in an Iranian population. J Oral Sci 49:229–235
74. Jattan R, de Silva HL, de Silva RK, Rich AM, Love RM (2011) A case series of odontogenic keratocysts from a New Zealand population over a 20-year period. N Z Dent J 107:112–116
75. Lipovec A, Hren NI (2004) Keratocysts in the jaws. Radiol Oncol 38:187–192

76. Guler N, Sencift K, Demirkol O (2012) Conservative management of keratocystic odontogenic tumors of jaws. ScientificWorldJournal:1–10
77. Zhao YF, Wei JX, Wang SP (2002) Treatment of odontogenic keratocysts: a follow-up of 255 Chinese patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94:151–156
78. González-Alva P, Tanaka A, Oku Y, Yoshizawa D, Itoh S, Sakashita H, Ide F, Tajima Y, Kusama K (2008) Keratocystic odontogenic tumor: a retrospective study of 183 cases. J Oral Sci 50:205–212
79. Anniko M, Anneroth G, Bergstedt H, Ramstrom G (1981) Jaw cysts with special regard to keratocyst recurrence. A long-term follow-up. Arch Otorhinolaryngol 233:261–269
80. Kolokythas A, Fernandes RP, Pazoki A, Ord RA (2007) Odontogenic keratocyst: to decompress or not to decompress? A comparative study of decompression and enucleation versus resection/peripheral ostectomy. J Oral Maxillofac Surg 65:640–644
81. Berge TI, Helland SB, Saelen A, Øren M, Johannessen AC, Skartveit L, Grung B (2016) Pattern of recurrence of nonsyndromic keratocystic odontogenic tumors. Oral Surg Oral Med Oral Pathol Oral Radiol 122:10–16
82. Brondum N, Jensen VJ (1991) Recurrence of keratocysts and decompression treatment. A long-term follow-up of forty-four cases. Oral Surg Oral Med Oral Pathol 72:265–269
83. Cruz ELD, Tabosa AKD, Falcao ASC, Tartari T, de Menezes LM, da Costa ET, Júnior JT (2017) Use of refrigerant spray of a propane/butane/isobutane gas mixture in the management of keratocystic odontogenic tumors: a preliminary study. Oral Maxillofac Surg 21:21–26
84. Cunha JF, Gomes CC, de Mesquita RA, Goulart EMA, de Castro WH, Gomez RS (2016) Clinicopathologic features associated with recurrence of the odontogenic keratocyst: a cohort retrospective analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 121:629–635
85. Nakamura N, Mitsuyasu T, Mitsuyasu Y, Taketomi T, Higuchi Y, Ohishi M (2002) Marsupialization for odontogenic keratocysts: long-term follow-up analysis of the effects and changes in growth characteristics. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94:543–553
86. Ribeiro O, Borba AM, Alves CAF, de Gouveia MM, Coracin FL (2012) Keratocystic odontogenic tumors and Carnoy's solution: results and complications assessment. Oral Dis 18:548–557
87. Higgins JPT, Green S (2011) Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration
88. Toller P (1967) Origin and growth of cysts of the jaws. Ann R Coll Surg Eng l40:306–336
89. Blanas N, Freund B, Schwartz M, Furst IM (2000) Systematic review of the treatment and prognosis of the odontogenic keratocyst. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:553–558
90. Kaczmarzyk T, Mojsa I, Stypulkowska J (2012) A systematic review of the recurrence rate for keratocystic odontogenic tumour in relation to treatment modalities. Int J Oral Maxillofac Surg 41:756–767
91. Johnson NR, Batstone MD, Savage NW (2013) Management and recurrence of keratocystic odontogenic tumor: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol 116:e271–e276
92. Antonoglou GN, Sándor GK, Koidou VP, Papageorgiou SN (2014) Non-syndromic and syndromic keratocystic odontogenic tumors: systematic review and meta-analysis of recurrences. J Craniomaxillofac Surg 42:e364–e371
93. de Castro MS, Caixeta CA, de Carli ML, Ribeiro Júnior NV, Miyazawa M, Pereira AAC, Sperandio FF, Hanemann JAC (2017) Conservative surgical treatments for nonsyndromic odontogenic keratocysts: a systematic review and meta-analysis. Clin Oral Investig (Dec 20)
94. Stoelinga PJ (2005) The treatment of odontogenic keratocysts by excision of the overlying, attached mucosa, enucleation, and treatment of the bony defect with Carnoy solution. J Oral Maxillofac Surg 63:1662–1666