



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

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## 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.

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*

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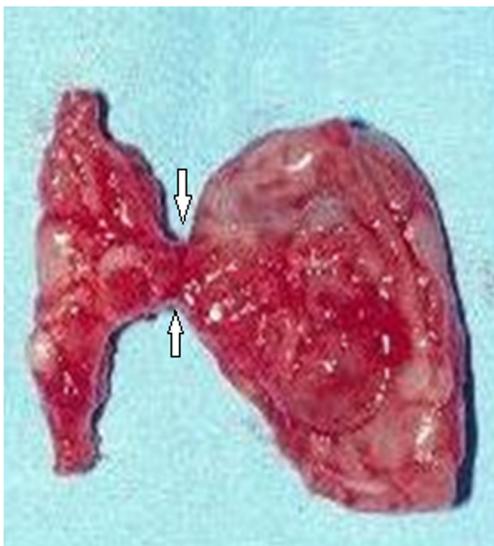
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and neck tumours [9], there certainly is a good reason to consider offshoots of the basal layer of the mucosa (hamartias), covering the alveolar processes as well as the mandibular ascending ramus and maxillary tuberosity, as an alternative source 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.

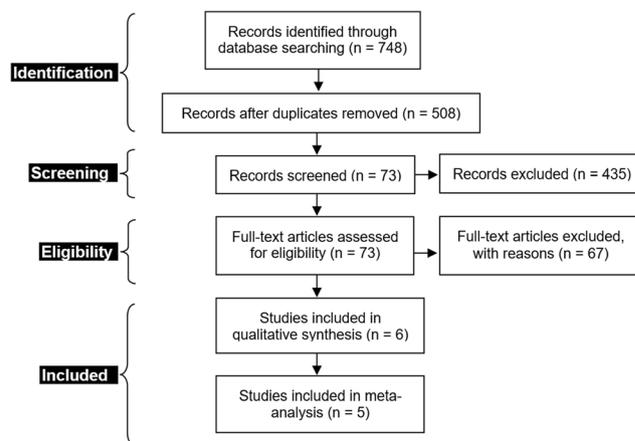


Fig. 3 Flow diagram

**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-Amnop 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], Stoeltinga and Bronkhorst [47], Stoeltinga [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-Amnop 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-Amnop 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 <sup>a</sup>	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 <sup>b</sup>	Marsup + cystectomy <sup>c</sup> = 7/0 Cystectomy = 27/8	10	Mandible	9
Cruz et al. [83]	Mandible = 8 Maxilla = 0 Total = 8 <sup>d</sup>	Marsup + enucleation + cryotherapy <sup>e</sup> = 4/1 enucleation + cryotherapy = 4/0	9.5	Mandible	5.3
Cunha et al. [84]	Mandible = 20 Maxilla = 4 Total = 24	Marsup + enucleation + peripheral osteotomy = 14/3 Enucleation + peripheral osteotomy = 10/5	15.2	Unclear	5
Nakamura et al. [85]	Mandible = 18 Maxilla = 0 Total = 33 <sup>f</sup>	Marsup + enucleation + excision of the overlying mucosa + peripheral osteotomy = 18/5 <sup>g</sup> Enucleation + excision of the overlying mucosa + peripheral osteotomy: 15/3 <sup>h</sup>	23.5	Mandible  Unclear	6.6
Ribeiro et al. [86]	Mandible = 11 Maxilla = 0 Total = 11 <sup>i</sup>	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 <sup>h</sup> 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

<sup>a</sup> Primary and nonsyndromic OKC

<sup>b</sup> 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

<sup>c</sup> “Primary cystectomy with smoothing of the osseous wall of the cavity” [82]. In the present systematic review, we considered this technique as curettage

<sup>d</sup> Two patients had “multiple” cysts without a precise description of the OKC number and were not considered according to our protocol

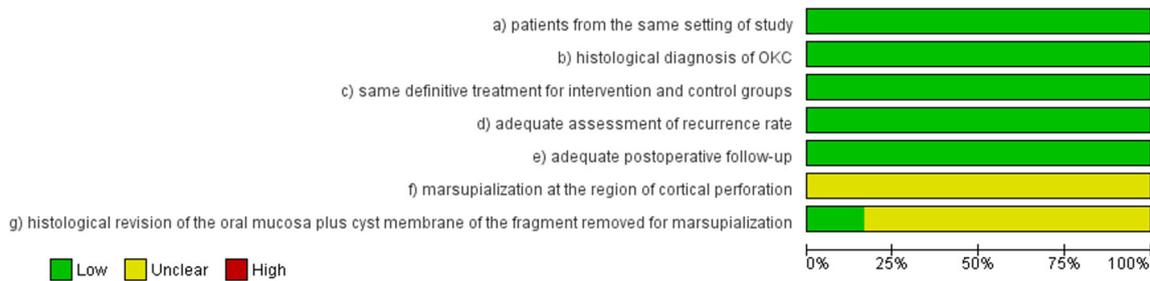
<sup>e</sup> Refrigerant spray of a propane/butane/isobutane gas mixture stored in a pressurized can (Endo Frost, Roeko, Langenau, Germany)

<sup>f</sup> Five OKCs associated with the NBCCS were not considered according to our protocol

<sup>g</sup> Five OKCs were not considered because it received marsupialization only

<sup>h</sup> The site of 15 OKCs treated without previous marsupialization was unclear

<sup>i</sup> 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 post-operative 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.

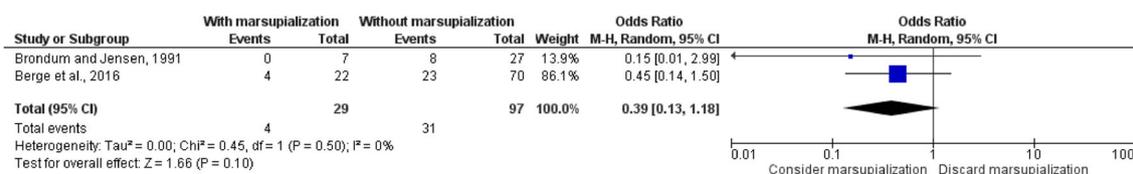
Two studies did not report the use of adjunctive therapy after enucleation [81, 82]. On the other hand, four studies reported the use of adjunctive therapy after enucleation as follows: peripheral ostectomy [84, 85], cryotherapy [83], and application of Carnoy’s solution [86].

### 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)

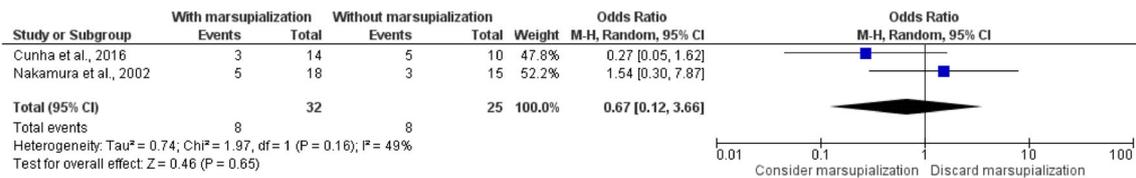


Fig. 6 Meta-analysis and forest plot of marsupialization and delayed enucleation plus peripheral ostectomy vs. enucleation plus peripheral ostectomy

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.

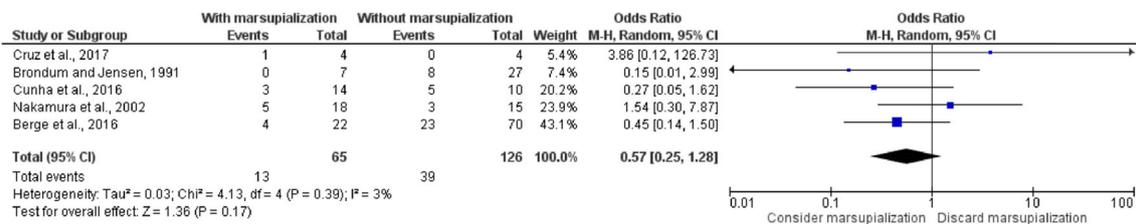


Fig. 7 Meta-analysis and forest plot of all treatments

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

Present study	Other systematic reviews <sup>a</sup>
Primary OKCs only	<ul style="list-style-type: none"> <li>• Primary and recurrent OKCs [10, 12, 90, 93]</li> <li>• Primary, syndromic, and orthokeratocysts [89, 91]</li> </ul>
Definitive treatment of OKCs with previous marsup vs. definitive treatment of OKCs without previous marsup (with meta-analysis)	<ul style="list-style-type: none"> <li>• 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]</li> <li>• 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]</li> </ul>
Assessment of key points of marsupialization	<ul style="list-style-type: none"> <li>• No assessment of key points of marsupialization [10, 12, 89–93]</li> </ul>
Follow-up of a minimum of 3 years	<ul style="list-style-type: none"> <li>• Follow-up of a minimum of 1 year [10, 12, 92, 93]</li> <li>• Unclear minimum follow-up [89, 91]</li> </ul>

*Marsup*, marsupialization; *decomp*, decompression

<sup>a</sup> 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 post-operative 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.

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