Recurrence probability for keratocystic odontogenic tumors: An analysis of 6427 cases

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A R T I C L E   I N F O
Article info
Paper received 6 June 2016
Accepted 10 November 2016
Available online 19 November 2016

Keywords:
Keratocystic odontogenic tumor
Marsupialization
Enucleation
Resection
Outcome
Meta-analysis

A B S T R A C T
Purpose: To investigate and compare the probability of recurrence of keratocystic odontogenic tumors (KCOTs) for different variables and treatment protocols.

Materials and methods: An electronic search was undertaken in April 2016 that included clinical series of KCOTs reporting recurrences. Untransformed proportions and meta-analyses were performed to estimate the probability/risk of recurrence, according to several variables.

Results: A total of 94 publications were included (6427 KCOTs, 1464 recurrences). Probability of recurrence: all lesions, 21.1%; nevoid basal cell carcinoma syndrome, 35.4%; males, 20.3%; females, 19.3%; maxilla, 15.3%; mandible, 21.5%; unilocular, 14.7%; multilocular, 24.4%; marsupialization/decompression, 28.7%; decompression + enucleation ± additional therapy, 18.6%; enucleation/curettage, 22.5%; enucleation + peripheral ostectomy, 18.6%; enucleation + Carnoy’s solution, 5.3%; enucleation + cryotherapy, 20.9%; marginal/segmental resection, 2.2%. The recurrence was not statistically significantly affected by lesion location (maxilla vs. mandible, risk ratio [RR] 0.92, P = 0.32) or patient’s sex (male vs. female, RR 0.94, P = 0.44), but by locularity (unilocular vs. multilocular, RR 0.67, P = 0.007). Recurrence risk for surgical managements: marsupialization vs. enucleation (RR 1.65, P = 0.0006), marsupialization vs. resection (RR 3.17, P = 0.009), enucleation alone vs. enucleation + peripheral ostectomy (RR 1.66, P = 0.05), enucleation alone vs. enucleation + Carnoy’s solution (RR 1.94, P = 0.03), enucleation alone vs. enucleation + cryotherapy (RR 0.88, P = 0.56).

Conclusions: KCOTs have a considerable rate of recurrence, which varies significantly according to some clinical, radiographic, and histopathological features, as well as surgical management.

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1. Introduction

The keratocystic odontogenic tumor (KCOT) is a benign intraosseous odontogenic tumor, with a characteristic lining of parakeratinized stratified squamous epithelium and a behavior that can potentially be aggressive and infiltrative. Radiographically, it shows a unilocular or multilocular radiolucency with well-defined borders. KCOT may appear as solitary or multiple lesions in one individual, and the latter is usually associated with the nevoid basal cell carcinoma syndrome (NBCCS) (WHO, 2005).

Pioneer studies reported recurrence rates as high as 62.5% after the removal of the lesions (Pindborg and Hansen, 1963; Rud and Pindborg, 1969; Toller, 1967), which led in the subsequent decades to the suggestion and experimentation of a variety of treatment modalities for the treatment of KCOTs. These treatments include marsupialization (also called as decompression or cystotomy) followed or not followed by enucleation, enucleation with or without adjunctive therapy (cryotherapy, Carnoy’s solution, peripheral ostectomy), and marginal/en bloc resection or resection with continuity defects. Modifications in treatment aimed to eliminate parts of the cystic lining or microcysts that are possibly left behind and are believed to increase the recidive potential (Stoelinga, 2005), as well as to balance the recurrence potential with the associated morbidity of a particular treatment (August et al., 2003). Considerable debate exists regarding the recurrence
rate and morbidity associated with each treatment modality, and there is still no adequate evidence in the literature to support any treatment modality as the most effective (Cunha et al., 2016). The lack of randomized controlled trials makes evidence-based recommendations difficult.

Thus, the aim of the present study was to investigate and compare the probability of recurrence of KCOTs for different variables and treatment protocols, based on a literature review on all published clinical series of KCOTs reporting treatment and recurrence rates.

2. Materials and methods

This study followed the PRISMA Statement guidelines (Moher et al., 2009). A review protocol does not exist.

2.1. Search strategies

An electronic search without time or language restrictions was undertaken in April 2016 in the following databases: PubMed/Medline, Web of Science, and the Cochrane Oral Health Group Trials Register. The following terms were used in the search strategies: (odontogenic keratocyst) OR (keratocystic odontogenic tumor) OR (keratocystic odontogenic tumor) OR (primordial cyst) OR (nevoid basal cell carcinoma syndrome) OR (basal cell nevus syndrome) OR (multiple basal cell carcinoma syndrome) OR (Gorlin syndrome) OR (Gorlin-Goltz syndrome).


2.2. Inclusion and exclusion criteria

Eligibility criteria included publications of clinical series of KCOT reporting recurrences. The studies needed to have a definite histologic diagnosis of KCOT, and could include single or multiple KCOTs with or without NBCCS. Randomized and controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, and case series were included. Exclusion criteria comprised case reports, immunohistochemical studies, epidemiological studies, histomorphometric studies, radiological studies, genetic expression studies, histopathological studies, cytological studies, cell proliferation/apoptosis studies, in vitro studies, and review papers.

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 solved by discussion between the authors.

2.4. Data extraction

The review authors independently extracted data using specially designed data extraction forms. The data extraction forms were piloted on several papers; these were modified as required before use. Any disagreements were solved by discussion. For each of the identified studies included, the following data were then extracted on a standard form: year of publication, study design, study setting, country, number of patients, patients’ sex, patients’ age range and average, follow-up period range and average, lesion location (maxilla/mandible), most common location, number of recurrences and total number of KCOTs per different types of treatments (main categories: marsupialization, enucleation, resection), recurrence period, presence of patients with multiple cysts, presence of KCOTs in patients with NBCCS, the presence of multilocular lesions, lesion size, and keratinization of the cyst lining. Contact with authors for possible missing data was performed.

2.5. Data analyses

Descriptive statistics were used to report the data. To standardize and clarify ambiguous data, the recurrence of KCOTs was reported for each publication. The untransformed proportion (random-effects DerSimonian-Laird method) for recurrence was calculated, considering the prevalence of KCOTs reported in the studies for the following variables: males, females, maxilla, mandible, unilocular lesions, multilocular lesions, lesions in patients with NBCCS, different types of treatments (marsupialization, enucleation, resection, and one of these with secondary adjunctive therapies), and keratinization of the cyst lining. Moreover, a meta-analysis was performed, evaluating the influence of sex, location (maxilla/mandible), locularity, different treatments, and keratinization of the cyst lining on the recurrence.

Whenever an outcome of interest was not clearly stated, the data were not used for analysis. The I² statistic was used to express the percentage of the total variation across studies due to heterogeneity. The inverse variance method was used, and a random-effects model was used for all comparisons. The reason for that was the given variability of the included studies when it comes to number of patients and KCOTs and treatment performed, among other factors. Some authors argue that, since clinical and methodological diversity always occur in a meta-analysis, statistical heterogeneity is inevitable (Higgins et al., 2003); thus, the test for heterogeneity is irrelevant to the choice of analysis; heterogeneity will always exist whether or not we happen to be able to detect it using a statistical test. The estimates of relative effect for the dichotomous outcome were expressed in risk ratio (RR) with a 95% confidence interval (CI). Only if there were studies with similar comparisons reporting the same outcome measures was meta-analysis to be attempted. In cases in which no events (or all events) are observed in both studies for the following variables: males, females, maxilla, mandible, unilocular lesions, multilocular lesions, lesions in patients with NBCCS, different types of treatments (marsupialization, enucleation, resection), and one of these with secondary adjunctive therapies), and keratinization of the cyst lining. Moreover, a meta-analysis was performed, evaluating the influence of sex, location (maxilla/mandible), locularity, different treatments, and keratinization of the cyst lining on the recurrence.
Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014).

3. Results

3.1. Literature search

The study selection process is summarized in Fig. 1. The search strategy resulted in 18,292 papers. Search in Google Scholar resulted in six eligible papers not found in the three main databases. A number of 13,458 articles were cited in more than one research of terms (duplicates). The reviewers independently screened the abstracts for those articles related to the focus question. Of the resulted 4840 studies, 4076 were excluded for not being related to the topic, resulting in 764 entries. Additional hand-searching of journals and of the reference lists of selected studies yielded four additional papers. The full-text reports of the remaining 768 articles led to the exclusion of 674 because they did not meet the inclusion criteria. Thus, a total of 94 publications were included in the review.

3.2. Description of the studies and analyses

All 94 studies (Ahlfors et al., 1984; Anand et al., 1995; Anniko et al., 1981; August et al., 2003; Balercia et al., 1983; Bataineh and al Qudah, 1998; Berge et al., 2016; Berrone et al., 1994; Blondeau et al., 1986; Bolbaran et al., 2000; Borg et al., 1974; Brannon, 1976; Browne, 1970; Brzozowski et al., 2010; Brøndum and Jensen, 1991; Calonius et al., 1972; Chemli et al., 2010; Chirapathomsakul et al., 2006; Chow, 1998; Chung et al., 1982; Crowley et al., 1992; Cunha et al., 2016; Dammer et al., 1997; Dauter, 2008; Del Corso et al., 2014; Donatsky et al., 1976; Donoff et al., 1972; Driemel et al., 2007; el-Hajj and Anneroth, 1996; Eufinger and Machtens, 1994; Eversole et al., 1975; Finkelstein et al., 2013; Forssell et al., 1974, 1988; Forssell, 1980; Francone et al., 1999; González-Alva et al., 2008; Gosau et al., 2010; Güler et al., 2012; Habibi et al., 2007; Hodgkinson et al., 1978; Irvine and Bowerman, 1985; Jensen et al., 1988; Kadlub et al., 2014; Kakarantza-Angelopoulou and Nicolatou, 1990; Klarmm, 1972; Kolokythas et al., 2007; Kuroyanagi et al., 2009; Kondell and Wiberg, 1988; Macdonald-Jankowski and Li, 2010; MacDonald et al., 2013; Machtens et al., 1972; Madras and Lapointe, 2008; Marker et al., 1996; Maurette et al., 2006; McIvor, 1972; Meara et al., 1998; Mello et al., 2011; Morgan et al., 2005; Myoung et al., 2001; Nakamura et al., 2002; Nielsen et al., 1986; Ong and Siar, 1995; Panders and Haddlers, 1969; Partridge and Towers, 1987; Payne, 1972; Pindborg and Hansen, 1963; Pippi and Vitolo, 2004; Pitak-Arnnop et al., 2010; Pogrel and Jordan, 2004; Radden and Reade, 1973; Rayne, 1971; Ribeiro Junior et al., 2012; Rud and Pindborg, 1969; Salmassy and Pogrel, 1995; Schmidt and Pogrel, 2001; Selvi et al., 2012; Shimada et al., 2013; Simiyu et al., 2013; Sortino and Buscemi, 2002; Stoelinga, 2001; Tagesen et al., 1990; Titinchi and Nortje, 2012; Toller, 1967; Tonietto et al., 2011; Vedtofte and Praetorius, 1979; Woolgar et al., 1987; Voorsmit et al., 1981; Yagyu et al., 2008; Zachariades et al., 1985; Zecha et al., 2009) were included in the review.
2010; Zhao et al., 2002, 2012; Zhou et al., 2012) were retrospective. Detailed data of the included studies are listed in Table 1 in Supplementary Material. The publications included a total of 6427 KCOTs, with 1464 lesions reported as recurrence. Table 1 shows the probability of an event (recurrence) for several variables according to the untransformed proportion. The probability of a recurrence considering all KCOTs was 21.1% (95% CI 18.4–23.7, P < 0.001), and the highest probability was for KCOTs in patients with NBCCS (35.4%, 95% CI 24.0–46.9, P < 0.001). The probability of a recurrence was quite similar between males and females, higher for KCOTs in the mandible than in the maxilla, and higher for multilocular lesions in comparison to unilocular ones in radiographic examinations. When it comes to the management of the lesions, the highest probabilities were presented by marsupialization (28.7%) and enucleation (22.5%), and the lowest probabilities of recurrence were presented by enucleation plus the use of Carnoy’s solution (5.3%) and marginal/segmental resection (2.2%). Decompression followed by enucleation decreased the probability of recurrence (11.3%) in comparison to decompression alone. Lesions with parakeratinization or orthokeratinization of the cyst lining resulted in quite distinct recurrence probabilities (22.8% and 12.1%, respectively).

Table 2 lists pairwise meta-analysis comparisons between several variables. The results suggest that the recurrence of KCOTs was not statistically significantly affected by the location of the lesion in maxilla or mandible (RR 0.92, 95% CI 0.77–1.09, P = 0.32) or by the patient’s sex (male/female, RR 0.94, 95% CI 0.80–1.10, P = 0.44). On the other hand, unilocular lesions had a lower risk to recur than multilocular lesions (RR 0.67, 95% CI 0.50–0.90, P = 0.007). Marsupialization had a statistically significant higher relative risk to recur in comparison to enucleation (RR 1.65, P = 0.0006) or resection (RR 3.17, P = 0.009). There was no difference between enucleation and resection (RR 1.04, P = 0.87). Enucleation alone had a higher risk of recurrence than when enucleation plus the secondary adjunctive therapies peripheral ostectomy (RR 1.66, P = 0.05) and the use of Carnoy’s solution (RR 1.94, P = 0.03) were performed, but not in relation to enucleation plus cryotherapy (RR 0.88, P = 0.56). There was no increased risk of recurrence for cyst lining with parakeratinization in relation to orthokeratinization (RR 1.98, P = 0.39).

Most of the funnel plots did not show a clear asymmetry for these comparisons, indicating possible absence of publication bias. There were two exceptions. The first exception was the funnel plot for the comparison between enucleation and resection, with the study of Pitak-Arnnop et al. (2010), probably presenting bias. A sensitivity analysis was performed, removing the study from the model, resulting in a different risk ratio (RR 1.63, P = 0.07). The second exception was the funnel plot for the comparison between enucleation and enucleation plus Carnoy’s solution, with the study of Dammer et al. (1997) probably presenting bias. A sensitivity analysis was performed, removing the study from the model, resulting in a higher risk ratio (RR 2.27, P = 0.005) (Table 2).

4. Discussion

The objective of the present study was to investigate and compare the probability of recurrence of KCOTs for different variables and treatment protocols. The results suggest that KCOTs have a considerable rate of recurrence, and this varies significantly according to the type of management applied.

When all lesions reviewed here were considered, there was a probability of recurrence of 21.1%, which is a figure that cannot be ignored. This number increases to 35.4% when the lesions in patients with NBCCS are isolated in the analysis. The problem is that multiple tumors in this syndrome are often not synchronous, and it may be difficult to distinguish between recurrent tumors and new ones arising in contiguous sites which were not initially detected (Partridge and Towers, 1987; Stoelinga, 2001; Woolgar et al., 1987). The probability of recurrence of KCOTs in patients with this syndrome was higher than in any other condition, which stresses an even higher importance for a closer follow-up of patients with NBCCS after the removal of KCOTs. Moreover, techniques showing lower probability/risk of lesion recurrence must preferably be used in those patients, also taking into consideration the morbidity of each treatment according to the lesion’s and patient’s conditions.

There were no apparent differences in the recurrence rates between male and female patients, and between lesions located in the maxilla and in the mandible, but a statistically significant difference disfavored multilocular lesions in comparison to lesions with a unilocular appearance. Smaller lesions tend to be unilocular, whereas larger lesions tend to be multilocular (Avril et al., 2014).

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of studies</th>
<th>Recurrence/total of lesions (% recurrence)</th>
<th>Probability of recurrence&lt;sup&gt;a&lt;/sup&gt; (95% CI), P value</th>
<th>Heterogeneity&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All KCOTs</td>
<td>94</td>
<td>1464/6427 (22.8)</td>
<td>21.1% (18.4, 23.7), P &lt; 0.001</td>
<td>$\chi^2 = 0.014$, $I^2 = 837.687$, $P = 88.898$, P &lt; 0.001</td>
</tr>
<tr>
<td>KCOTs in patients with NBCCS&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15</td>
<td>113/329 (34.3)</td>
<td>35.4% (24.0, 46.9), P &lt; 0.001</td>
<td>$\chi^2 = 0.039$, $I^2 = 82.425$, $P = 83.015$, P &lt; 0.001</td>
</tr>
<tr>
<td>Males</td>
<td>38</td>
<td>289/1171 (24.7)</td>
<td>20.3% (15.6, 25.0), P &lt; 0.001</td>
<td>$\chi^2 = 0.016$, $I^2 = 175.434$, $P = 78.909$, P &lt; 0.001</td>
</tr>
<tr>
<td>Females</td>
<td>38</td>
<td>215/873 (24.6)</td>
<td>19.3% (14.0, 24.5), P &lt; 0.001</td>
<td>$\chi^2 = 0.021$, $I^2 = 194.460$, $P = 80.973$, P &lt; 0.001</td>
</tr>
<tr>
<td>Maxilla</td>
<td>45</td>
<td>102/582 (17.5)</td>
<td>15.3% (11.3, 19.3), P &lt; 0.001</td>
<td>$\chi^2 = 0.008$, $I^2 = 104.853$, $P = 58.037$, P &lt; 0.001</td>
</tr>
<tr>
<td>Mandible</td>
<td>45</td>
<td>488/1897 (25.7)</td>
<td>21.5% (17.0, 25.9), P &lt; 0.001</td>
<td>$\chi^2 = 0.019$, $I^2 = 317.502$, $P = 86.142$, P &lt; 0.001</td>
</tr>
<tr>
<td>Unilocular</td>
<td>23</td>
<td>147/607 (24.3)</td>
<td>11.7% (10.0, 13.3), P &lt; 0.001</td>
<td>$\chi^2 = 0.009$, $I^2 = 129.779$, $P = 83.048$, P &lt; 0.001</td>
</tr>
<tr>
<td>Multilocular</td>
<td>26</td>
<td>117/547 (25.6)</td>
<td>14.3% (17.6, 31.3), P &lt; 0.001</td>
<td>$\chi^2 = 0.019$, $I^2 = 98.648$, $P = 74.657$, P &lt; 0.001</td>
</tr>
<tr>
<td>Marsupialization/decompression</td>
<td>26</td>
<td>56/226 (24.8)</td>
<td>28.7% (17.7, 39.8), P &lt; 0.001</td>
<td>$\chi^2 = 0.063$, $I^2 = 187.641$, $P = 86.677$, P &lt; 0.001</td>
</tr>
<tr>
<td>Decompression + enucleation + additional therapy</td>
<td>8</td>
<td>151/102 (14.7)</td>
<td>11.3% (3.8, 18.7), P &lt; 0.001</td>
<td>$\chi^2 = 0.003$, $I^2 = 10.556$, $P = 33.845$, P = 0.159</td>
</tr>
</tbody>
</table>

<sup>a</sup> Untransformed proportion, random-effects DerSimonian-Laird method.

<sup>b</sup> Data only from the studies reporting the number of KCOTs in patients with NBCCS.

<sup>c</sup> Data from studies reporting the number of NBCCS patients with recurrences (at the patient-level, not at the lesion-level) were not included in this analysis.
These findings could possibly suggest that recurrence is partly related to inadequate treatment, because multicellular and large lesions are difficult to access and the fragments are easily overlooked (Yagyuu et al., 2008). The present results showed that decomposition followed by enucleation decreased the probability of recurrence (11.3%) in comparison to decomposition alone (22.5%). The performance of a decomposition followed by enucleation is advantageous in cases of large cysts, especially in old or medically compromised patients (Stoelinga, 2005). A previous decomposition of the lesion may cause an enlargement of the fibrous capsule (August et al., 2003; Cunha et al., 2016; Marker et al., 1996), which facilitates the complete surgical removal of the lesion. The epithelium remaining in the cavities after marsupialization displays properties similar to those of the normal oral epithelium (Pogrel and Jordan, 2004); a dedifferentiation process of the epithelium may occur (August et al., 2003). This change of epithelium with concomitant changes in biologic behavior may explain the observed lower rates of recurrence of KCOTs (Berge et al., 2016).

Enucleation alone was associated with a recurrence rate of over 20%. The literature lists three main adjunctive therapies to enucleation that were added to the surgical technique, which are supposed to eliminate the epithelial islands and microcysts in peripheral bone and decrease the recurrence rates (Stoelinga, 2005; Tolstanov and Treasure, 2008). The results of the present study suggest that this decrease in the recurrence rates could be true for when either peripheral ostectomy or tanning of the lesion’s cavity with Carnoy’s solution is performed after the enucleation, but not for the use of cryotherapy. The lack of statistically significant difference of the recurrence risk between enucleation and enucleation plus cryotherapy may be related to the availability of only four studies for the performance of the pairwise meta-analysis, or to a true lack of improved efficacy when cryotherapy is used as a secondary adjunctive therapy. However, the fact that the untransformed proportion analysis found quite similar rates of recurrence risk for both techniques suggests that the use of cryotherapy after enucleation does not decrease the risk of recurrence when compared to enucleation alone without this adjunctive therapy.

Of the treatments described, the most likely to prevent recurrence appears to be resection. The question, however, is whether the invasive nature of resection and reconstruction of the mandible or maxilla is acceptable, given the benign nature of the disease and the low recurrence rates associated with other less invasive procedures (Blanas et al., 2000), such as enucleation plus tanning with Carnoy’s solution. Resection has been advocated for large and recurrent lesions in difficult anatomic locations (Williams and Connor, 1994). The problem with KCOTs is their capacity to infiltrate and spread over several osseous cavities of the facial skeleton, especially when the KCOT is located in the maxilla. Some surgeons might be more willing to resect the maxilla in such cases.

A surprising result from the present study was the absence of statistically significant differences for the risk of recurrence of KCOTs when the techniques enucleation and resection were directly compared by pairwise meta-analysis, even showing a recurrence rate of 22.8% and 31%, respectively, for the different surgical procedures. It is suggested that the issue here lies in the fact that the groups were extremely unbalanced (1177 enucleations vs. 130 resections) with rare events in the resection group, and the software gave almost one-third of the total weight of the studies to a study in which only one resection was performed and resulted in recurrence (Pitak-Arnnop et al., 2010). When a sensitivity analysis was performed, removing the study from the model, there was a change in the relative risk, almost reaching statistically significance. However, it is difficult to draw reliable conclusions from this analysis in particular, due to the factors previously mentioned. The authors of the present review believe that the results provided by the untransformed proportions could more reliably reflect the clinical reality, showing far better results for the resection.

The preservation of a tooth involved in the lesion after the enucleation is another important factor that may increase the chance of recurrence (Chirapathomsakul et al., 2006; Cunha et al., 2016) because the preservation of a tooth may compromise proper enucleation of the lesion. Therefore, the surgeon should consider extraction of the affected tooth in cases of root involvement by the lesion (Cunha et al., 2016). Unfortunately, the information about the removal of teeth involved in the lesions was rarely available in the included publications, and thus a proper analysis of the influence of this factor on the recurrence was not feasible.

Table 2
Pairwise meta-analysis comparisons between several variables/conditions.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of studies</th>
<th>Recurrence/total of lesions</th>
<th>Risk ratio (95% CI), P value</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxilla vs. mandible</td>
<td>46</td>
<td>108/632 vs. 504/2046</td>
<td>0.92 (0.77, 1.09), P = 0.32</td>
<td>0.00, Chi² = 13.70, I² = 10%, P = 0.001</td>
</tr>
<tr>
<td>Male vs. female</td>
<td>39</td>
<td>304/1299 vs. 222/946</td>
<td>0.94 (0.80, 1.10), P = 0.44</td>
<td>0.00, Chi² = 8.20, I² = 7%, P = 0.35</td>
</tr>
<tr>
<td>Unilocular vs. multilocular</td>
<td>23</td>
<td>147/1027 vs. 115/447</td>
<td>0.67 (0.50, 0.90), P = 0.007</td>
<td>0.01, Chi² = 3.89, I² = 9%, P = 0.05</td>
</tr>
<tr>
<td>Marsupialization vs. enucleation</td>
<td>25</td>
<td>56/216 vs. 334/1354</td>
<td>1.65 (1.24, 2.20), P = 0.0006</td>
<td>0.03, Chi² = 3.44, I² = 36%, P = 0.04</td>
</tr>
<tr>
<td>Marsupialization vs. resection</td>
<td>9</td>
<td>10/34 vs. 3/89</td>
<td>3.17 (1.34, 7.50), P = 0.009</td>
<td>0.00, Chi² = 2.13, I² = 0%, P = 0.71</td>
</tr>
<tr>
<td>Enucleation vs. resection</td>
<td>23</td>
<td>267/1711 vs. 4/130</td>
<td>1.04 (0.66, 1.63), P = 0.87</td>
<td>0.00, Chi² = 17.55, I² = 0%, P = 0.68</td>
</tr>
<tr>
<td>Enucleation vs. resection (without Pitak-Arnnop et al., 2010)</td>
<td>22</td>
<td>240/1052 vs. 3/129</td>
<td>1.63 (0.96, 2.76), P = 0.07</td>
<td>0.00, Chi² = 7.03, I² = 0%, P = 1.00</td>
</tr>
<tr>
<td>Enucleation vs. enucleation + peripheral ostectomy</td>
<td>7</td>
<td>73/243 vs. 17/86</td>
<td>1.66 (1.01, 2.74), P = 0.05</td>
<td>0.00, Chi² = 4.81, I² = 0%, P = 0.57</td>
</tr>
<tr>
<td>Enucleation vs. enucleation + Carnoy’s solution</td>
<td>13</td>
<td>127/645 vs. 21/319</td>
<td>1.94 (1.07, 3.52), P = 0.03</td>
<td>0.39, Chi² = 17.52, I² = 37%, P = 0.09</td>
</tr>
<tr>
<td>Enucleation vs. enucleation + Carnoy’s solution (without Dammner et al., 1997)</td>
<td>12</td>
<td>125/599 vs. 20/317</td>
<td>2.27 (1.43, 3.60), P = 0.0005</td>
<td>0.00, Chi² = 7.22, I² = 0%, P = 0.70</td>
</tr>
<tr>
<td>Enucleation vs. enucleation + cryotherapy</td>
<td>4</td>
<td>43/114 vs. 18/46</td>
<td>0.88 (0.56, 1.36), P = 0.56</td>
<td>0.00, Chi² = 0.25, I² = 0%, P = 0.97</td>
</tr>
<tr>
<td>Parakeratinized vs. orthokeratinized cyst lining</td>
<td>5</td>
<td>143/497 vs. 7/71</td>
<td>1.98 (0.42, 9.41), P = 0.39</td>
<td>1.62, Chi² = 8.85, I² = 66%, P = 0.03</td>
</tr>
</tbody>
</table>
The results of the present study have to be interpreted with caution because of the study limitations. First of all, all confounding factors may have affected the long-term outcomes, and not just the different treatments performed, and the impact of these variables on the recurrence rate is difficult to estimate if these factors are not identified separately between the different treatments in order to perform a meta-regression analysis. The lack of control of the confounding factors limited the potential to draw robust conclusions. Second, all included studies had a retrospective design, and the nature of a retrospective study inherently results in flaws. These problems were manifested by the gaps in information and incomplete records. Third, much of the research in the field is limited by small cohort size and short follow-up periods. This might have led to an underestimation of actual recurrences in some studies, because a longer follow-up period can lead to an increase in the recurrence rate. However, it is difficult to define what it would be considered a short follow-up period to evaluate recurrence of KCOTs. Recurrences as long as 16 (Brzozowski et al., 2010; Nakamura et al., 2002; Stoelinga, 2001; Woolgar et al., 1987), 18 (Payne, 1972), 20 (Chuong et al., 1982), 22 (Driemel et al., 2007; Pitak-Annporn et al., 2010), 23 (Berge et al., 2016; González-Alva et al., 2008), 24 (Eufinger and Machteits, 1994), 34.2 (Schmidt and Pogrel, 2001), or even 41 years (Crowley et al., 1992) after surgery of removal have been reported. Fourth, it was not uncommon a lack of control of treatment modalities used by different surgeons in different studies.

5. Conclusions

The highest probabilities of recurrence of KCOTs were presented by marsupialization and enucleation alone, and the lowest probabilities of recurrence were presented by enucleation plus the use of Carnoy’s solution and marginal/segmental resection. The recurrence was not statistically significantly affected by the location of the lesion (maxilla/mandible) or by the patient’s sex, but unilocular lesions had a lower risk of recurrence than multilocular ones. Orthokeratinized KCOTs were less likely to recur.

Conflict of interest

There are no conflicts of interest to declare.

Funding/grant support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors would like to thank Dr. Joanna Farias Cunha and Dr. Natacha Kadlub, who provided us some missing information about their studies; Dr. Francesco Sortino, who provided us his article; and Dr. Steven D. Vincent, Dr. Giacomo Del Corso, Dr. Kaustubh Natacha Kadlub, who provided us some missing information about their studies; Dr. Francesco Sortino, who provided us his article; and Dr. Steven D. Vincent, Dr. Giacomo Del Corso, Dr. Kaustubh

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcims.2016.11.010.

References


