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Non-syndromic and syndromic keratocystic odontogenic tumors: Systematic review and meta-analysis of recurrences

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ABSTRACT

Background: Keratocystic odontogenic tumors (KCOTs) are locally aggressive benign tumors which occur in the bones of both jaws with a high recurrence rate.

The aim of the present study was to define and evaluate the post-treatment recurrence of KCOT lesions in non-syndromic and syndromic patients.

Methods: A systematic review of the literature and meta-analysis was conducted according to the PRISMA statement. Seven electronic databases were searched from their start up to August 2013 for clinical studies on human patients without limitation to year, language or publication status.

Results: A total of five case series studies with 323 treated KCOT lesions were included in the quantitative synthesis. The recurrence rate of KCOTs for three treatment forms ranged from 7% to 28%. Comparisons among the various treatments suggest that resection or marsupialization might be associated with fewer recurrences. However, high risk of bias and effect imprecision preclude the making of clinical recommendation. Existing evidence regarding nevoid basal cell carcinoma patients was likewise scarce.

Conclusions: The absence of studies with low risk of bias precludes the making of safe recommendations about the optimal management of KCOTs.

1. Introduction

1.1. Rationale

The keratocystic odontogenic tumor (KCOT) obtained its name in 2005 when the World Health Organization (Philipsen, 2005), decided to choose KCOT over the traditionally used term of odontogenic keratocyst. KCOTs are locally aggressive benign tumors which occur in the bone of both jaws with a notably high recurrence rate. A number of treatments have been suggested for KCOTs and various groups have attempted to determine which is the most efficacious (Blanas et al., 2000; Sharif et al., 2010; Kaczmarzyk et al., 2012; Johnson et al., 2013). One group (Johnson et al., 2013) suggests that enucleation followed by the application of Carnoy's solution and resection resulted in the lowest recurrence rates, but this left surgeons to weigh the implications of a more aggressive approach such as resection. Another group (Kaczmarzyk et al., 2012) strongly critiques the available evidence and states that it is impossible to make a strong conclusion regarding a universal treatment of choice. The gold standard for the treatment of KCOT's is still debatable, mainly because there is no reliable summary of recurrence rates associated with the treatments available to date.

1.2. Objectives

The aim of the present study was to extract the data available for solitary KCOT lesions occurring in non-syndromic patients from a large number of published studies regarding KCOTs. The authors

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aimed to investigate the association between different treatment forms and recurrence rates of solitary non-syndromic KCOT lesions. In addition to the previous aim, data were collected from trials or trial arms which included nevoid basal cell carcinoma syndrome (NBCCS) patients to determine the recurrence rates following various forms of treatment.

2. Materials and methods

2.1. Protocol and eligibility criteria

The present systematic review is conducted and reported according to the Cochrane Handbook (Higgins and Green, 2011) and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Liberati et al., 2009) and its extension for abstracts (Beller et al., 2013), respectively. Since no randomized controlled trials involving KCOTs were identified in the preliminary literature search, a systematic review of both randomized and non-randomized studies was planned. The inclusion criteria used in the present study included 1) humans diagnosed with keratocystic odontogenic tumor by histological examination, 2) at least one study arm with surgical therapy, 3) a minimum follow-up of at least 12 months after treatment, 4) treatment that was sufficiently described and could be allocated in one of the following: enucleation, enucleation plus curettage, enucleation plus Carnoy's solution, enucleation plus cryotherapy, enucleation plus peripheral ostectomy, marsupialization, resection and other or combination, and 5) prospective or retrospective, randomized and non-randomized studies with one or multiple arms. The exclusion criteria used were 1) nevoid basal cell carcinoma cases or multiple lesions 2) follow-up period unclear or not reported 3) unclear or treatment form not reported 4) cross-over clinical studies 5) non-clinical studies and all other research types (i.e. editorials, textbooks, technical reports, e.t.c).

2.2. Information sources and search

An electronic literature search on KCOT and odontogenic keratocyst was performed using MEDLINE, Scopus, LILACS, BBO, IBECS, ISI Web of Knowledge, Digital Dissertations and Cochrane Database of Systematic Reviews using and combining the following keywords: keratocyst, keratocystic tumor, recurrence, relapse, therapy, treatment outcome and surgical management. No limitations regarding publication language, year or publication status (i.e. published in journal or not) were applied. In addition complementary searches were conducted in Google Scholar and hand-searching of relevant journals for the following years 2000–2013 (i.e. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, Journal of Oral and Maxillofacial Surgery, International Journal of Oral and Maxillofacial Surgery, British Journal of Oral and Maxillofacial Surgery, and Journal of Cranio-Maxillofacial Surgery). Citation lists of previously published reviews and included studies were scanned to identify missed reports. Additional searches in grey literature were performed.

2.3. Study selection, data collection process and data items

The selection process of the articles and their evaluation was performed by two independent judges (G.A. and V.K.) blind to each other's activities (Fig. 1). The resolution-plan for any disagreements between the two judges was to be sought from a third party (G.K.S.).

In the first round (screening) the authors excluded studies that were not clinical trials treating KCOTs by screening the titles and abstracts of the search results (Fig. 1). When a clear decision could not be made, the full text of the article was obtained and the decision was made based upon it. In the second round, the authors excluded studies which did not meet the criteria regarding participants, intervention characteristics, comparisons, outcome measures and study design (PICOS) (Table 1).

Included studies were summarized and analyzed qualitatively. Extracted characteristics included year of publication, study design, ethnic origin of the patients, treatment form and post-surgical follow-up period. Included studies with a minimum follow-up of three years were also analyzed quantitatively.

Only solitary cyst-like lesions were recorded and multicystic lesions were initially excluded. Multiple or solitary lesions diagnosed in patients with Gorlin–Goltz or NBCCS and these cases were termed syndromic.

The primary outcome of this systematic review was the recurrence of KCOTs. Recurrence rates were recorded for solitary lesions and at the patient level. Event rates were calculated considering the recurrence after the treatment form described in each report. The goal was to provide a homogeneous summary of recurrence rates. Recurrence rates for syndromic and for non-syndromic patients were assessed separately.

Treatment forms initially planned to be assessed in this systematic review included: enucleation, enucleation plus curettage, enucleation plus Carnoy's solution, enucleation plus cryotherapy, enucleation with peripheral ostectomy, marsupialization, resection, other or combination of the previous. As however, limited studies were identified, treatment forms were grouped together in the following groups: enucleation, enucleation plus adjunctive therapy (including enucleation plus curettage, enucleation with Carnoy's solution, enucleation with cryotherapy and enucleation with peripheral ostectomy and Carnoy's solution), marsupialization (no recurrence), resection (no recurrences), other or combinations of the previous. The category of other or combinations of treatment forms was created to include treatment forms that were a combination of those listed or could not be allocated to any of the categories.

2.4. Risk of bias in individual studies

Risk of bias for randomized trials was to be assessed using the Cochrane Risk of Bias Tool according to the Cochrane Handbook. Risk of bias of case-series was assessed with the tool developed by the National Institute for Health Care and Excellence (NICE) in the United Kingdom especially designed for case-series.

2.5. Summary measures and synthesis of results

Included studies on the recurrence rate of non-syndromic patients with a minimum follow-up of 36 months were summarized with a random-effects model, as response to treatment was expected to differ according to treatment form.

Recurrence event rates and their corresponding 95% Confidence Interval (CIs) were calculated and pooled for each included treatment. Relative Risk (RR) of KCOTs with its corresponding 95% CI was used as a summary measure of comparing recurrence between two treatments. The extent and impact of between-study heterogeneity was assessed by calculating the tau^2 and the I^2 statistic, respectively. For meta-analyses of at least 3 studies, the 95% CIs around I^2 were to be calculated according to the non-central χ^2 approximation of Q and 95% prediction intervals were to be calculated. All analyses were performed in Stata version 10 (StataCorp LP, College Station, TX). All P values are 2-sided with a level of significance set at 5%, except for the tests of between-studies heterogeneity (at 10%).

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