ORAL SURGERY

Oral Surgery ISSN 1752-2471

ORIGINAL ARTICLE

Treatment options for keratocyst odontogenic tumour (KCOT): a systematic review

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Key words:
keratocystic odontogenic tumour, odontogenic keratocyst, odontogenic tumours, recurrence, treatment

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Accepted: 12 September 2016

doi:10.1111/ors.12250

Abstract

Background: The keratocystic odontogenic tumour (KCOT) is a benign intraosseous odontogenic lesion relatively frequent in the oral cavity. It has a locally aggressive behaviour and exhibits a high propensity to recur after treatment. All the singular characteristics of this pathology have originated controversy in the scientific community regarding the most appropriate surgical approaches for the successful treatment of this tumour.

Objectives: To analyse the optimal treatment choice for this tumour, ensuring high success rates of treatment, preventing future recurrences and allowing the maintenance of the patient's quality of life.

Materials and methods: A search was conducted in *Cochrane* – 1 result – and in *PubMed* – 756 results. The selection of articles was based on abstracts and inclusion and exclusion criteria. Three research studies were considered for the final analysis.

Results: One hundred and nineteen lesions were identified (73 males and 46 females). Twenty-nine tumours were found in the maxilla and 91 in the mandible; the applied therapeutic methods were: marsupialization/decompression, marsupialization followed by enucleation and adjunctive therapies (peripheral ostectomy and *Carnoy's* solution), solely enucleation, enucleation and *Carnoy's* solution, enucleation followed by peripheral ostectomy and *Carnoy's* solution and resection.

Discussion and conclusions: Treatment by enucleation, in combination with adjunctive measures, is associated with minor recurrence rates when compared with enucleation alone. The small number of KCOT that were treated with en bloc resection did not obtain statistically relevant results. Therefore, more studies with well-established criteria are necessary to enable an adequate analysis of recurrence rates associated with each treatment modality.

Introduction

In 2005, WHO reclassified the intraosseous parakeratinised variant of the odontogenic keratocyst. The keratocystic odontogenic tumour (KCOT) is actually defined as a benign intraosseous odontogenic tumour, uni or multicystic, with a regular parakeratinised stratified squamous epithelial lining, and a potentially infiltrative behaviour[1–7]. The KCOT morphological code in the International Classification of Diseases for Oncology (ICD-O) is 9270/0[1].

This reclassification reflected the necessity to distinguish this lesion from all other keratinised odontogenic cysts due to its particular characteristics: aggressive nature, increased epithelial proliferative capacity and propensity to recur after

treatment[2,3,5,7–9]. A difference in genetic and molecular mechanisms, when compared to other cystic lesions of the jaws, also suggests a distinct biological origin of this entity[7,10].

The KCOT may be associated with Gorlin–Goltz syndrome patients[2,3,5,6]. Keratinised lesions, both orthokeratinised and parakeratinised, peripheral and solid variants, do not form part of a KCOT's spectrum[4,7,11].

Treatment modalities

A wide variety of surgical approaches are presently suggested for the treatment of KCOT, ranging according to the size, extension and clinical and/or radiographic appearance[10,12–14].

Marsupialization and decompression are considered distinct surgical techniques, despite having the same purpose[15]. Both methods allow a decrease of the intraluminal lumen[15]. The majority of authors currently reviews them as inadequate and non-definitive therapies in KCOT treatment, given the fact that the odontogenic epithelium remains *in situ* in the KCOT cavity[16], allowing the continuity of epithelial proliferation and enabling future recurrences[15,17,18].

Marsupialization was first mentioned by Partsch in 1892 and is described as the surgical removal of a wall in the KCOT's body followed by the suture of the tumour's boundaries to the adjacent mucosa. A surgical window that communicates with the oral cavity is created, allowing for regular irrigation by the patient[5,8,19–21]. Decompression involves any method that allows a decrease in intracystic pressure, based on the fact that this pressure is responsible for the KCOT expansion[14,15]. This surgical approach may be conducted through an opening made in the lesion cavity. It is then kept in touch with the oral cavity through a drain[15,22,23]. Two-stage surgical procedures (marsupialization and/or decompression precede tumour enucleation) are the primary indication for these two methods, by reducing volume and size in extensive KCOT, enabling the preservation of vital structures, such as teeth[16,24,25].

Enucleation or simple enucleation is composed by the complete removal of KCOT from the bone cavity without any macroscopic remnants of the lesion[20,21,26]. The KCOT excision with or without bone perforation in one surgical piece is difficult due to the thin and friable epithelial lining[12,15,21,27].

Radical enucleation involves the excision of KCOT together with the removal of the overlaying mucosa followed by extensive curettage and reduction of the adjacent bone cavity. It aims to remove tumour epithelial islands and/or microcysts[21,27,28].

Enucleation and *Carnoy*'s solution consists of a chemical cauterisation agent with rapid local fixation and haemostatic action and a penetration capacity of 1.54 mm in the cystic locus, after enucleation of the KCOT[5,15,29,30]. The original composition of the solution consisted of 3 ml of chloroform, 6 ml of absolute alcohol (95%), 1 ml of glacial acetic acid and 1 g of ferric chloride. Chloroform is currently not a component of this solution, due to the fact of being a carcinogenic agent[5,15,30,31]. Carnoy's solution must be applied to the bone defect for 3 min after the tumour's enucleation, preventing any axonal damages and optimising the elimination of any possible remaining tumour cells[5,26,32]. The main purpose of the application of this solution is to eliminate possible viable tumour epithelial cells remaining in the bone cavity[2,11,15,33–35].

Enucleation and cryotherapy with liquid nitrogen is a surgical method highly recommended by some authors[8,15,27,36–40]. Liquid nitrogen presents the ability to eliminate the organic component in the lesion locus, keeping the inorganic architecture of the bone intact[8,19,38,39,41]. The cryotherapy technique should be applied after enucleation of KCOT and consists in the vaporisation of the bone defect with liquid nitrogen for 1 min, one or two times, with an interval of 5 min between applications[8,15,40].

Enucleation and peripheral ostectomy are similar to a simple enucleation. However, it is followed by the removal of 1.5–2 mm of bone with a handpiece in KCOT margins[8,20].

Enucleation, peripheral ostectomy and Carnoy's solution consist of the surgical excision of the tumour followed by peripheral ostectomy with a handpiece and posterior application of Carnoy's solution[20]. The combination of adjunctive techniques is used due to the fact that simple enucleation presents high recurrence rates (25–50%), whereby the use of adjuvant therapies will reduce these recurrences in 10%, optimising the treatment[8,26,30,34,42–45].

En bloc resection may be realised by two different methods: marginal or segmental resection. The surgical en bloc excision of KCOT is made together with the extraction of 1 cm of healthy bone beyond the tumour's margins[15,42].

Marginal resection is based on the surgical removal of KCOT, leaving a portion of the non-involved bone with the conservation of its continuity. Segmental resection involves mandibular or maxilary section removal without maintenance of bone continuity[20,21,26].

Materials and methods

Following the PICO model (*Problem, Intervention, Comparison, Outcome*), the research was structured with the aim of answering the following question: "In the treatment of keratocystic odontogenic tumours, what is the best suited therapeutic method for minimising the short- and long-term recurrence rates associated with this lesion?".

Primary and secondary databases (Cochrane; EMBASE e MEDLINE) were searched with the *keratocyst*, *odontogenic*, *tumor*, *KCOT*, *treatment* keywords and the following search filter: species – humans.

Out of the 756 articles displayed, 153[3,6–8,11–13,16–18,21–26,31,33,35–169] were pre-selected based on the title and abstract. To avoid data analysis bias, articles with reference in the title and/or abstract to extraosseous or solid variants of these cysts, along with cases associated with the Gorlin–Goltz syndrome, were not considered. No time restrictions were applied, and languages included English, French, Portuguese and Spanish. Two independent investigators assessed the articles. Instead of performing a formal quality and sensitivity assessment of the selected studies, stringent inclusion and exclusion criteria were formulated, as seen in Fig. 1. From the final 153 studies considered for the analysis presented in Table 1, only three articles were included in the final statistical analysis of this study.

The data were submitted to statistical analysis using the *Comprehensive Meta-analysis™ software*, version 2.0. Recurrence rates were meta-analytically calculated for a confidence interval of 95% according to the treatment modalities. The treatment data were grouped into:

1 KCOT submitted to any combination of adjuvant therapies (categories 2b, 2c, 2e or 1 + 2e) as seen in Fig. 2;

2 KCOT submitted to simple therapies (categories 1 and 2).

Results are also presented in Tables 2 and 3.

Results

Three retrospective studies fulfilled the inclusion criteria and were submitted to statistical analysis[5,30,170]. One hundred and nineteen patients (73 males and 46 females) with a histological diagnosis of KCOT and age from 11 to 81 years (mean 38.55) were included in the analysis. Males were more affected than females in two studies, with a ratio of 1.7:1. Each patient presented only a single lesion of KCOT. Twenty-nine tumours were located in the maxilla: 9 in the anterior region (between the upper canines) and 20 in the posterior region (between the first upper premolar and the third upper molar). Ninety-one lesions were found in the mandible: 8 in the anterior region (between the lower canines), 61 in the posterior region (between the first lower premolar and the third lower molar) and 48 in the mandibular ramus region (posterior to the third lower molar). The radiographic appearance was only referred in one study, with the unilocular aspect (sevencases) being more prevalent than the multilocular (four cases) one. The symptomatology was only referred in one study, with 23 symptomatic lesions (swelling, pain, drainage and infection) and 17 asymptomatic. Treatment modalities were classified in three categories:

Category 1 comprises all KCOT treated with marsupialization/decompression. Ten patients were treated with this surgical approach, with a mean follow-up of 5.4 years and four associated recurrences. Category 2 consists of all cases dealt with by simple enucleation (69 patients, with a mean follow-up of 5.35 years and 18 recurrences); Category 2a: radical enucleation (with excision of the overlaying mucosa). None of the studies entered in the final analysis have been subjected to this treatment method; Category 2b: enucleation followed by the use of Carnoy's solution (two patients with a mean follow-up of 5.3 years and one recurrence); Category 2c: enucleation and peripheral ostectomy (11 lesions, with a mean follow-up of 5.3 years and two associated recurrences); Category 2d: enucleation followed by cryotherapy with liquid nitrogen, with zero patients treated with this method included in the final analysis; Category 2e: enucleation followed by peripheral ostectomy and use of Carnoy's solution (22 patients, with a mean follow-up of 4.4 years and 0 recurrences). Category 3 covered all KCOT treated with segmental or marginal en bloc resections (three tumours, with a mean follow-up of 5.3 years and no recurrences). Furthermore, two patients were handled in a two-stage surgical treatment. The patients were submitted to the marsupialization/decompression techniques and posterior enucleation followed by peripheral ostectomy and the use of Carnoy's solution (1 + 2e), with a mean follow-up of 3.5 years and zero recurrences.

Recurrences were considered as the presence of radiolucent lesions in imaging exams in areas previously submitted to surgical treatment.

This statistical analysis verified that techniques associated with adjunctive therapies (categories 2b, 2c, 2e or 1 + 2e), presented a recurrence rate of 9.9

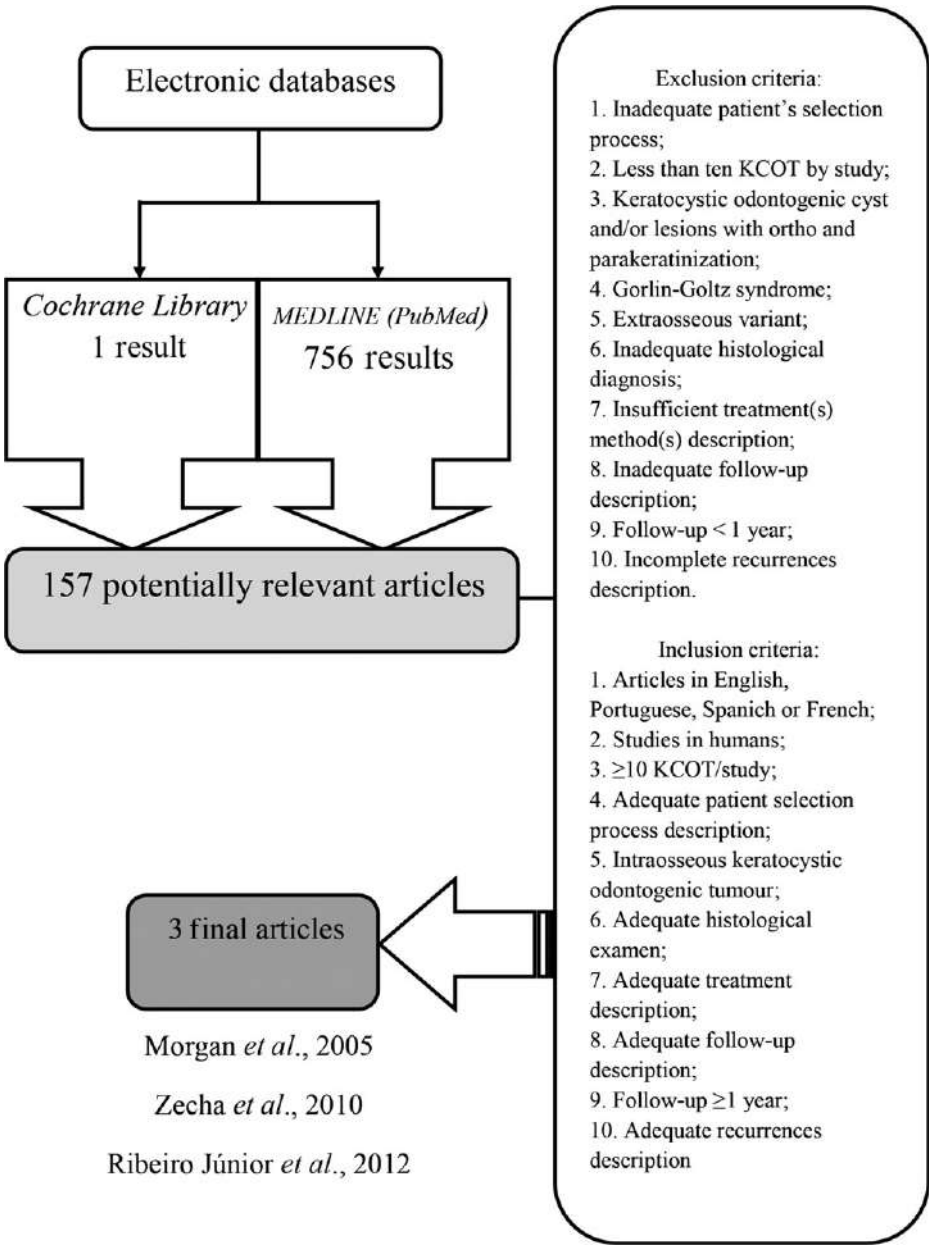

Figure 1 Methodology applied for obtention of the final articles for analysis.

(interval ranging from 3.5% to 24.9%) calculated for a confidence interval (CI) of 95%.

KCOT's treated with a surgical method without any adjunctive therapy (categories 1 or 2) presented a recurrence rate of 26.8% (interval ranging from 17.3% to 39.1%) calculated for a confidence interval (CI) of 95%, as seen in Fig. 2.

Despite the various recurrence rates, there was no statistical significance among the two analysed groups, probably due to the small number of cases included in each sub-group that made into the final analysis.

Discussion

The main objective of this study was to analyse KCOT recurrence rates due to treatment modalities used in all studies available until the present day. An important point observed during the study derived from the fact that from the 756 obtained

Table 1 Articles excluded from the final analysis and exclusion criteria applied.

Author and publication year	Title	Exclusion criteria applied
Pindborg & Hansen, 1963	Studies on odontogenic cyst epithelium. II. Clinical and roentgenologic aspects of odontogenic keratocysts	6
Fickling, 1965	Cysts of the jaw: a long-term survey of types and treatment	6
Bramley, 1967	Recurring odontogenic cysts	6
Toller, 1967	Origin and growth of cysts of the jaws	6
Panders & Haddlers, 1969	Solitary keratocysts of the jaws	6
Rud & Pindborg, 1969	Odontogenic keratocysts: a follow-up study of 21 cases	6
Browne, 1970	The odontogenic keratocyst: clinical aspects	6
Bramley, 1971	Treatment of cysts of the jaws	6
Browne, 1971	The odontogenic keratocyst. Histological features and their correlation with clinical behaviour	6
Donoff *et al.* 1972	Keratocysts of the jaws	6
McIvor, 1972	The radiological features of odontogenic keratocysts	6
Payne, 1972	An analysis of the clinical and histopathologic parameters of the odontogenic keratocyst	6
Radden & Reade, 1973	Odontogenic keratocysts	6
Bramley, 1974	The odontogenic keratocyst: an approach to treatment	6
Forssell *et al.* 1974	A clinical and radiographic study of odontogenic keratocysts in jaws	6
Bradley & Fisher, 1975	The cryosurgery of bone. An experimental and clinical assessment.	6
Eversole *et al.* 1975	Aggressive growth and neoplastic potential of odontogenic cysts: with special reference to central epidermoid and mucoepidermoid carcinomas	6
Brannon, 1976	The odontogenic keratocyst. A clinicopathologic study of 312 cases. Part I. Clinical features	4,6
Brannon, 1977	The odontogenic keratocyst. A clinicopathological study of 312 cases. Part II. Histological features	4,6
Gryfe & Gryfe, 1977	Isolated odontogenic keratocyst	6
Hodgkinson *et al.* 1978	Keratocysts of the jaw: clinicopathological study of 79 patients	6
Rittersma & van Gool, 1979	Surgical access to multicystic lesions by sagittal splitting of the lower jaw	2,6,7
Vedtofte & Prætorius, 1979	Recurrence of the odontogenic keratocyst in relation to clinical and histological features. A 20 year follow-up study of 72 patients	6,9
Forssell *et al.* 1980	The primordial cyst. A clinical and radiographic study	6
Anniko *et al.* 1981	Jaw cysts with special regard to keratocyst recurrence. A long-term follow-up	6
Voorsmit *et al.* 1981	The management of keratocysts	6
Altini & Cohen, 1982	The follicular primordial cyst—odontogenic keratocyst	6
Chuong *et al.* 1982	The odontogenic keratocyst	6
Farmand & Makek, 1983	Late results following the Brosch-procedure for treating large mandibular ramus cyts	4,6
Wetmore *et al.* 1983	Odontogenic keratocyst: diagnosis and treatment	6
Ahlfors *et al.* 1984	The odontogenic keratocyst: a benign cystic tumor?	4,6
Arafat & Lunin, 1984	Odontogenic keratocysts	6
Webb & Brockbank, 1984	Treatment of the odontogenic keratocyst by combined enucleation and cryosurgery	2,6
Eyre & Zakrzewska, 1985	The conservative management of large odontogenic keratocysts	6
Irvine & Bowerman, 1985	Mandibular keratocysts: surgical management	6
Zachariades *et al.* 1985	Odontogenic keratocysts: review of the literature and report of 16 cases	4,6
Swanson, 1986	The recalcitrant keratocyst	2,6
Partridge & Towers, 1987	The primordial cyst (odontogenic keratocyst): its tumour-like characteristics and behaviour	6
Woolgar *et al.* 1987b	A comparative study of the clinical and histological features of recurrent and non-recurrent odontogenic keratocysts	6
Wong, 1987	Odontogenic keratocysts: patient followup key to preventing cyst recurrence	6
Forssell *et al.* 1988	Recurrence of keratocysts: a long term follow-up study	4,6
Jensen *et al.* 1988	A comparative study of treatment of keratocysts by enucleation or enucleation combined with cryotherapy	6,8
Köndell & Wiberg, 1988	Odontogenic keratocyst. A follow-up study of 29 cases	6

Table 1 (*Continued*)

Author and publication year	Title	Exclusion criteria applied
Stoelinga & Bronkhorst, 1988	The incidence, multiple presentation and recurrence of aggressive cysts of the jaws	6
Oikarinen, 1990	Keratocyst recurrences at intervals of more than 10 years: case reports	2,6,7
Brøndum & Jensen, 1991	Recurrence of keratocysts and decompression treatment. A long-term follow-up of fourty-four cases	1,6
Crowley *et al.* 1992	Odontogenic keratocyst: a clinical and histologic comparison of the parakeratin and orthokeratin variants	7,8,10
MacDonald-Jankowski, 1992	The involvement of the maxillary antrum by odontogenic keratocysts	6
Thomas *et al.* 1992	The incredible odontogenic keratocyst	6
Jackson *et al.* 1993	Penetration of the skull base by dissecting keratocyst	2,6
Pogrel, 1993	The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions	6
Browne, 1994	Per[cyst]ent growth: the odontogenic keratocyst 40 years on	6
Cranin *et al.* 1994	Novel method of treating large cysts of jaws in children	6
Meiselman, 1994	Surgical management of the odontogenic keratocyst: conservative approach	6
Anand *et al.* 1995	Odontogenic keratocysts: a study of 50 patients	3,6
Nakamura *et al.* 1995	A study of cysts in the oral region. Cysts of the jaw	6
Pogrel, 1995	The management of lesion of the jaws with liquid nitrogen cryotherapy	6
Salmassy & Pogrel, 1995	Liquid nitrogen cryosurgery and immediate bone grafting in the management of aggressive primary jaw lesions	6,9
El-Hajj & Anneroth, 1996	Odontogenic keratocysts – a retrospective clinical and histologic study	1,3,4,6,7
Marker *et al.* 1996	Treatment of large odontogenic keratocysts by descompression and later cystectomy.	6,8
Meara *et al.* 1996	Odontogenic keratocysts in the pediatric population	4,6
Dammer *et al.* 1997	Conservative or radical treatment of keratocysts: a retrospective review	4,6,7,8,10
Moody *et al.* 1997	Odontogenic keratocyst	2,6
Bataineh & Al Qudah, 1998	Treatment of mandibular odontogenic keratocysts	6,8,10
Blanchaert & Ord, 1998	Vertical ramus compartment resection of the mandible for deeply invasive tumor	2,6
Chow, 1998	Odontogenic keratocyst. A clinical experience in Singapore	1,6,8
Garlock *et al.* 1998	The odontogenic keratocyst: a potential endodontic misdiagnosis	6,7
Hsun-Tau, 1998	A clinical experience in Singapore	6,7,8
Meara *et al.* 1998	The odontogenic keratocyst: a 20-year clinicopathologic review	4,6
Blanas *et al.* 2000	Systematic review of the treatment and prognosis of the odontogenic keratocyst	4,6,9
Lam & Chan, 2000	Odontogenic keratocysts: a clinicopathological study in Hong Kong	1,3,7,8,9,10
Oda *et al.* 2000	Odontogenic keratocyst: the Northwestern USA experience	6
Myoung *et al.* 2001	Odontogenic keratocyst: Review of 256 cases for recurrence and clinicopathologic parameters	6,7,8
Schmidt & Pogrel, 2001	The use of liquid nitrogen cryotherapy in the management of odontogenic keratocysts	1,6
Stoelinga, 2001	Long-term follow-up according to a defined protocol	4,6
Bsoul *et al.* 2002	Odontogenic keratocyst	6
Nakamura *et al.* 2002	Marsupialization for odontogenic keratocyst: long-term follow-up analysis of the effects and changes in growth characteristics	1,4,6
Sortino & Buscemi, 2002	Clinical-statistic survey regarding odontogenic keratocysts in a sample of population in Eastern Sicily	6
Zhao *et al.* 2002	Treatment of odontogenic keratocyst: a follow-up of 255 Chinese patients	6
August *et al.* 2003	Dedifferentiation of odontogenic keratocyst epithelium after cyst decompression	6
Bell & Dierks, 2003	Treatment options for the recurrent odontogenic keratocyst	6
Ghali & Connor, 2003	Surgical management of the odontogenic keratocyst	6
Pogrel, 2003	Decompression and marsupialization as a treatment for the odontogenic keratocyst	6
Stoelinga, 2003	Excision of the overlying, attached mucosa, in conjunction with cyst enucleation and treatment of the bony defect with *Carnoy* solution	6
Chapelle *et al.* 2004	Rational approach to diagnosis and treatment of ameloblastomas and odontogenic keratocysts	1,6,8

Table 1 (*Continued*)

Author and publication year	Title	Exclusion criteria applied
Enislidis *et al.* 2004	Conservative treatment of large cystic lesions of the mandible: a prospective study of the effect of decompression.	1,6,9
Kerr *et al.* 2004	Midline maxillary odontogenic keratocyst	2,6
Lipovec & Hren, 2004	Keratocysts in the jaws	6
Pippi & Vitolo, 2004	A clinical radiographic and histologic revaluation of a 10 years sample of surgically treated cysts of the jaws, with special emphasis on keratocysts	6,8
Pogrel & Jordan, 2004	Marsupialization as a definitive treatment for the odontogenic keratocyst	1,6,8,10
Vicente-Barrero *et al.* 2004	Cartilage in the walls of odontogenic keratocyst.	2,6,7,8,10
Boyne *et al.* 2005	The multifocal nature of odontogenic keratocysts	2,6
Jung *et al.* 2005	Decompression of large odontogenic keratocysts of the mandible.	2,6
Auluck & Pai, 2006	Treatment of recurrent odontogenic keratocyst: a known but forgotten point	6
Chaisuparat *et al.* 2006	Primary intraosseous odontogenic carcinoma arising in an odontogenic cyst or de novo: a clinicopathologic study of six new cases	6
Chirapathomsakul *et al.* 2006	A review of odontogenic keratocyst and the behaviour of recurrences	1,6,7,8,9
Giuliani *et al.* 2006	Conservative management of a large odontogenic keratocyst: report of a case and review of the literature.	2
Maurette *et al.* 2006	Conservative treatment protoc of odontogenic keratocyst: a preliminary study	1,6
Meningaud *et al.* 2006	Odontogenic cysts: a clinical study of 695 cases	3,4,6,7,9,10
Vencio *et al.* 2006	Odontogenic keratocyst in maxillary sinus with invasive behaviour	2,6,7,8,10
Habibi *et al.* 2007	Keratocystic odontogenic tumor: a 10-year retrospective study of 83 cases in an Iranian population	4,7,8,9,10
Kolokythas *et al.* 2007	Odontogenic keratocyst: to decompress or not to decompress? A comparative study of decompression and enucleation versus resection/peripheral ostectomy	6,8
Mozaffari *et al.* 2007	Odontogenic keratocyst with a misleading clinical and radiologic appearance	2,6
Shirani *et al.* 2007	Immediate reconstruction of a large mandibular defect of locally invasive benign lesions (a new method)	1,2,6
Tan *et al.* 2007	Effects of mandibular odontogenic keratocyst surgery and removable partial prostheses on masticatory performance	1,6,7,8,10
González-Alva *et al.* 2008	Keratocystic odontogenic tumor: a retrospective study of 183 cases	7,8,10
Madras & Lapointe, 2008	Keratocystic odontogenic tumour: reclassification of the odontogenic keratocyst from cyst to tumour.	1,7,8,9
Tolstunov & Treasure, 2008	Surgical treatment algorithm for odontogenic keratocyst: combined treatment of odontogenic keratocyst and mandibular defect with marsupialization, enucleation, iliac crest bone graft, and dental implants	2
Yagyuu *et al.* 2008	Recurrence of keratocystic odontogenic tumor: clinicopathological features and immunohistochemical study of the Hedgehog signaling pathway	6
Eryilmaz *et al.* 2009	Odontogenic keratocyst: an unusual location and review of the literature	2,6
Godhi & Kukreja, 2009	Keratocystic odontogenic tumor: a review	6
Kuroyanagi *et al.* 2009	Prognostic factors for keratocystic odontogenic tumor (odontogenic keratocyst): analysis of clinico-pathologic and immunohistochemical findings in cysts treated by enucleation	6
Almeida *et al.* 2010	Conservative approach to the treatment of keratocystic odontogenic tumor.	2
Bande *et al.* 2010	Prevalence, treatment and recurrence of odontogenic keratocyst in Central India	6,7
Boffano *et al.* 2010	Keratocystic odontogenic tumor (odontogenic keratocyst): preliminary retrospective review of epidemiologic, clinical, and radiologic features of 261 lesions from University of Turin.	6,7,8,10
Gosau *et al.* 2010	Two modifications in the treatment of keratocystic odontogenic tumors (KCOT) and the use of *Carnoy*'s solution (CS)—a retrospective study lasting between 2 and 10 years.	6,9
Pitak-Arnnop *et al.* 2010a	Enucleation of keratocystic odontogenic tumours: study interpretation, technical refinement and future research	6
Pitak-Arnnop *et al.* 2010b	Management of odontogenic keratocysts ofthe jaws: a tenyear experience with 120 consecutive lesions.	3,6,7,10
Semi *et al.* 2010	Surgical management of recurrent odontogenic keratocyst.	2,6

Table 1 (*Continued*)

Author and publication year	Title	Exclusion criteria applied
Zhao *et al.* 2010	Computed densitometry of panoramic radiographs in evaluation of bone healing after enucleation of mandibular odontogenic keratocysts.	7,8
Anavi *et al.* 2011	Decompression of odontogenic cystic lesions: clinical long-term study of 73 cases.	4,6,8,10
Apajalahti *et al.* 2011	Computerised tomography findings and recurrence of keratocystic odontogenic tumor of the mandible and maxillofacial region in a series of 46 patients.	1,6,7
Houpis *et al.* 2011	Unusual odontogenic keratocyst of the maxillary sinus.	2,6
Iwai *et al.* 2011	Use of methylene blue for precise peripheral ostectomy of keratocystic odontogenic tumour.	2
Jattan *et al.* 2011	A case series of odontogenic keratocysts from a New Zealand population over a 20-year period.	6
Leite *et al.* 2011	Odontogenic keratocystic tumor: A clinical and Histopathologic Retrospective Study Based on the New WHO Classification.	4,7,8,10
MacDonald-Jankowski,2011	Keratocystic odontogenic tumour: systematic review.	7,8,10
Mello *et al.* 2011	Keratocyst odontogenic tumour: an experience in the Northeast of Brazil	4,7
Nishikawa *et al.* 2011	Orthodontic treatment of deep impacted teeth in multiple keratocystic odontogenic tumor.	2
O'Neill & Al-Hezaimi, 2011	Identification of an odontogenic keratocyst and treatment with guided tissue regeneration: case report.	2,6
Schussel *et al.* 2011	Retrospective study of 25 cases of keratocystic odontogenic tumor: epidemiology and treatment.	6,7
Tonietto *et al.* 2011	Enucleation and Liquid Nitrogen Cryotherapy in the Treatment of Keratocystic Odontogenic Tumors: A Case Series.	1,2,6
Yang *et al.* 2011	A retrospective study of 220 cases of keratocystic odontogenic tumor (KCOT) in 181 patients.	4,6,7,8
Zhao *et al.* 2011	Changes in bone density and cyst volume after marsupialization of mandibular odontogenic keratocysts (keratocystic odontogenic tumors)	4,10
Koçak-Berberoğlu *et al.* 2012	Three-dimensional cone-beam computed tomography for diagnosis of keratocystic odontogenic tumours; Evaluation of four cases.	1,6,7,8
Kubota *et al.* 2012	Effects of the patient's age and the size of the primary lesion on the speed of shrinkage after marsupialisation of keratocystic odontogenic tumours, dentigerous cysts, and radicular cysts.	6,7,8,10
Lizio *et al.* 2012	Volume reduction of cystic lesions after surgical decompression: a computerised three-dimensional computed tomographic evaluation.	1,6,7,8,10
Manor *et al.* 2012	Cystic lesions of the jaws – A clinicopathological study of 322 cases and review of the literature.	1,6,7
Rossi *et al.* 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.	2
Scartezini *et al.* 2012	Diagnostic and treatment features of keratocystic odontogenic tumors.	2,6
Selvi *et al.* 2012	Keratocystic odontogenic tumors: predictive factors of recurrence by Ki-67 and AgNOR labelling.	1,7,10
Shudou, 2012	Marsupialisation for keratocystic odontogenic tumours in the mandible: longitudinal image analysis of tumour size using 3D visualized CT scans.	6
Sinvanmalai *et al.* 2012	*Carnoy*'s solution in the management of odontogenic keratocyst	2
Tabrizi *et al.* 2012	Marsupialization as a treatment option for the odontogenic keratocyst.	6
Titinchi & Nortje, 2012	Keratocystic odontogenic tumor: a recurrence analysis of clinical and radiographic parameters.	1,4,6,7
Zhao *et al.* 2012	Changes in Bone Density and Cyst Volume After Marsupialization of Mandibular Odontogenic Keratocysts (Keratocystic Odontogenic Tumors).	7
Zhou, 2012	Secondary Healing After Removal of Large Keratocystic Odontogenic Tumor in the Mandible: Enucleation Followed by Open Packing of Iodoform Gauze.	6
Finkelstein *et al.* 2013	Keratocystic odontogenic tumor: a retrospective analysis of genetic, immunohistochemical and therapeutic features. Proposal of a multicenter clinical survey tool	7,8

Table 1 (*Continued*)

Author and publication year	Title	Exclusion criteria applied
Johnson *et al.* 2013	Management and recurrence of keratocystic odontogenic tumor: a systematic review.	4,6,7
Matsuzaki *et al.* 2013	Case series: conditions inhibiting eruption of permanent first molars.	6,7,8
Sansare *et al.* 2013	Keratocystic odontogenic tumor: systematic review with analysis of 72 additional cases from Mumbai, India.	4,7,8
Simiyu *et al.* 2013	Keratocystic odontogenic tumours of the jaws and associated pathologies: a 10-year clinicopathologic audit in a referral teaching hospital in Kenya.	4,6,8
Singh *et al.* 2013	Are all Odontogenic Keratocysts Keratocystic Odontogenic Tumors? Correlation between Imaging Features and Epithelial Cell Proliferation	6

Exclusion criteria: 1. Inadequate patient's selection process; 2. Less than ten KCOT by study; 3. Keratocystic odontogenic cyst and/or lesions with ortho and parakeratinisation; 4. Gorlin–Goltz syndrome; 5. Extraosseous variant; 6. Inadequate histological diagnosis; 7. Insufficient treatment(s) method(s) description; 8. Inadequate follow-up description; 9. Follow-up <1 year; 10. Incomplete recurrences description.

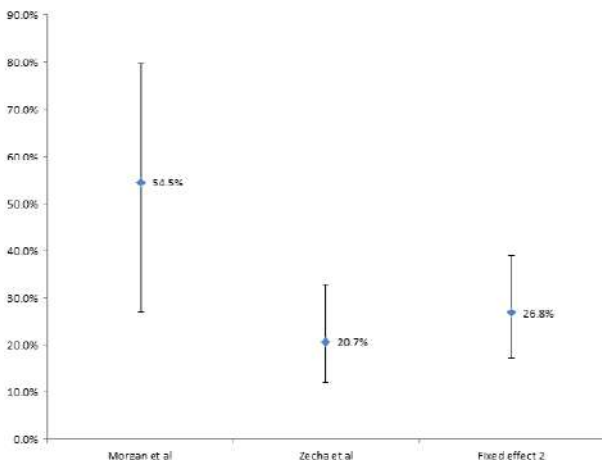

Figure 2 Recurrence rate for KCOT treated without any adjunctive therapy.

results, only three were eligible in the final statistical analysis. None of the results about KCOT treatment were randomised clinical trials (RCT) or controlled clinical trials (CCT). This demonstrates the lack of information in this particular topic, consequently compromising the achievement of any possible practical results and hindering the establishment of guidelines for clinical practice. The evaluation of recurrence rates introduces some inherent difficulties due to the inclusion of only three studies in the final analysis, limiting the number of KCOT cases included, and the acquisition of statistically relevant results. The number of patients who have undergone different methods vary widely among the different surgical approaches, creating the aforementioned underlying impediments.

Regarding recurrence rates associated with therapeutic modalities, it was possible to verify that the methods that featured a higher recurrence rate were the ones that belonged to the simple therapies group (marsupialization or simple enucleation), with a recurrence rate of 26.8% (confidence interval of 95%), in a mean follow-up period of 5.35 years. This statistical result is consistent with that observed in most of the available literature, which admits that these values may reach or exceed recurrence rates of 56%[171].

Myoung *et al.* after the treatment of 256 lesions using simple enucleation or marsupialization, had a recurrence rate of 58.3% over a mean follow-up period of 29 months[160]. In 2007, Habibi *et al.* presented six lesions treated by marsupialization with a recurrence rate of 33.3% at a mean period of 32.5 months[125]. Kaczmarzyk *et al.* (2010) presented a recurrence rate of 26.09% and 40% in lesions treated with simple enucleation and marsupialization respectively[20]. This rate is similar to the one observed in the present analysis, which reached 26.8%.

The KCOT sub-group treated with various adjuvant therapeutic modalities presented recurrence rates of 9.9% (CI of 95%), with a mean follow-up period of 4.4 years. This value was substantially lower (2.9) when compared to the group of tumours whose methodology was surgical marsupialization or enucleation. The obtained value is indicative that the association with adjuvant methods may be favourable for the prognosis of these lesions, namely with reduced recurrence rates, which is in agreement with the evidence present in the literature[26,30,35,172,173].

In 2005, Morgan *et al.* found that KCOT treatment with enucleation followed by peripheral ostectomy was associated to a decrease in recurrence rates[30]. In

Table 2 Analysis between Morgan et al. e Zecha et al. studies

Model	Study name	Subgroup within study	Statistics for each study					Events/total
			Event rate	Lower limit	Upper limit	*Z*-value	*P*-value	
Morgan *et al.*[30]			0.545	0.268	0.797	0.301	0.763	6/11
Zecha *et al.*[172]			0.207	0.121	0.330	−4.145	0.000	12/58
Fixed			0.268	0.173	0.391	−3.513	0.000	

Table 3 Statistic analysis between Morgan et al and Ribeiro Junior et al groups

Model	Study name	Subgroup within study	Statistics for each study					Events/total
			Event rate	Lower limit	Upper limit	*Z*-value	*P*-value	
Morgan *et al.*[30]			0.111	0.036	0.293	−3.396	0.001	3/26
Ribeiro Júnior *et al.*[5]			0.050	0.003	0.475	−4.145	0.042	0/9
Fixed			0.099	0.035	0.249	−3.918	0.000	
Random			0.099	0.035	0.249	−3.918	0.000	

2007, Kolokythas *et al.* presented six lesions with a parakeratinised epithelium and a recurrence rate of 0% over a period of 1.5–9 years with that treatment modality[45]. In 2010, Gosau *et al.* obtained an estimated cumulative risk of recurrence of 30% during the third year after treatment in cases where excision was not followed up by adjuvant therapeutic measures. This cumulative risk decreased to 15% in the third year when the enucleation was followed by the application of Carnoy's solution[35]. In this study, 14 patients with KCOT were treated with the enucleation of the lesion followed by the use of Carnoy's solution, with a recurrence rate of 3.14% in an average period of 3.8 years.

In 2002, Zhao *et al.* reported a recurrence rate of 6.7% in 29 patients treated with this method in a follow-up period of 3–29 years[42]. The effectiveness of the combination of enucleation with Carnoy's solution was also considered by Morgan *et al.* in 2005, which had a null recurrence rate in patients treated with this surgical method[30].

In 2001, Stoelinga reported three recurrences in 82 lesions treated with enucleation, removal of the overlying mucosa and use of Carnoy's solution, with a recurrence rate of 7.8% over a period of follow-up ranged from 1 to 25 years[33].

In 2001, Schmidt and Pogrel reported one of the studies with the largest number of lesions treated with liquid nitrogen, with a recurrence rate of 11.5% in a follow-up period of 3.5 years[40].

Tonietto *et al.* (2011) presented a series of nine patients who underwent enucleation and the subsequent use of liquid nitrogen. No recurrences were recorded during the follow-up period of 9 years[149].

In this study, it was not possible to evaluate patients that undergone cryotherapy with liquid nitrogen. Therefore, studies with a considerable number of samples are required to obtain evidence of the effectiveness of this therapeutic modality in the treatment of KCOT.

The combination of Carnoy's solution with peripheral ostectomy after enucleation also demonstrated positive results, with low recurrence rates associated with lesions treated with these methods[5,30].

In patients whose treatment was en bloc resection, it was not observed any recurrence of KCOT. Nevertheless, this therapy was not considered for statistical analysis due to the unsatisfactory number of samples ($n = 3$) and insufficient information, making it difficult to obtain valid results. As mentioned above, this method is associated with a high success rate, but it usually compromises the patient's quality of life. The treatment of choice is usually a more conservative one[31]. In the study by Zhao *et al.* in 2002, 76 patients were submitted to this method with no recurrences observed after a follow-up period ranging between 3 and 11 years[42]. In 1998, Bataineh and al Qudah verified that in a sample of 31 KCOT treated with marginal resection, no tumour recurrences were described[17].

The major fault in the majority of studies about this topic is that they do not consider the current histopathological definition of KCOT, according to the WHO classification, although it was reclassified 8 years ago[1]. Thus, many authors continue to refer to KCOT as an odontogenic keratocyst (OKC) according to the 1992 WHO's classification.

Several authors also consider the orthokeratinised and parakeratinised variants as being the same

pathology, which limits the validity of results, as the orthokeratinised variant presents lower recurrence rates, causing bias of those studies.

Some authors also base their parakeratinised and orthokeratinised diagnosis on radiographic features, with the multilocular appearance being considered as parakeratinised and the multilocular image being considered as orthokeratinised, compromising a proper final diagnosis.

Therefore, it is essential to clarify that these two entities have not only microscopic differences but also distinct biopathology origins. The parakeratinised variant (or keratocystic odontogenic tumour) exhibits a much more aggressive behaviour locally and recurrence rates that can reach 56%, while the orthokeratinised counterpart (or odontogenic cyst) has recurrence rates of 2.2%[20]. This difference should be highlighted in studies including the parakeratinised and orthokeratinised variant.

The short follow-up periods found in most studies will, unfortunately, lead to the occurrence of unreliable results. Although the majority of recurrences occur within the first 5 years after treatment, there are reports of cases in which recurrences took place in a period of 10, 23 and even 41 years after the initial treatment, thus creating uncertain findings[11,35,42,86,113]. Besides, there are also studies with a non-standardised follow-up period.

In the future, a minimum follow-up period should be considered to ensure the validity of results, and the information relative to patients whose follow-up was lost should be excluded from the analysis.

Many studies also consider patients with Gorlin–Goltz syndrome without segmentation of data, which will also interfere with the analysis of results as it is known that these lesions occur in an inferior age and are more likely to present multiple recurrent lesions when associated with the syndrome[174].

Conclusions

Since it was first reported almost 60 years ago, the keratocystic odontogenic tumour still remains a controversial theme among dentists, maxillofacial surgeons and pathologists. Available literature does not currently present any consensus about the most appropriate surgical method(s) for KCOT treatment, as treatment methods range from more conservative ones, such as marsupialization and enucleation, up to more aggressive techniques, as en bloc resection. Due to the inconsistency and variability of criteria in the study of this lesion, it is not possible to discern a homogeneous analysis of present cases in the literature.

Currently, it is not possible to enlighten the therapeutic method with better and more predictable long-term results.

Nevertheless, it was possible to demonstrate by this study that the combination of surgical methods and the use of adjunctive therapies, such as Carnoy's solution, peripheral ostectomy or liquid nitrogen, may present more favourable results than the ones verified with a simple enucleation or marsupialization.

The reclassification of this lesion by the World Health Organization is not unanimous. Thus, the question regarding the nature of the KCOT remains inconclusive: will this be classified as a benign cystic neoplasm or a cyst with high aggressive potential? It is paramount to clarify the most appropriate definition to standardise the diagnosis and treatment criteria. This homogenous classification is crucial to establish studies with well-defined analysis variables and obtain clinically relevant results in the treatment of KCOT.

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