Suzanne Baromand Rad
V course Group 13

Evaluation of the Keratocystic Odontogenic Tumor (KCOT) recurrence after different treatment modalities
A systematic review

Tadas Keizeris

Kaunas, 2017
Evaluation of the Keratocystic Odontogenic Tumor (KCOT) recurrence after different treatment modalities.
TABLE OF CONTENTS

Summary
1. Introduction
2. Materials and method
   2.1. Literature search strategy
   2.2. Study eligibility
      2.2.1. Inclusion Criteria
      2.2.2. Exclusion Criteria
   2.3. Data extraction process
   2.4. Literature search
      2.4.1. Results of Search strategy
   2.5. Risk of bias in individual studies
3. Results
   3.1. Results of variable outcome
      3.1.1. Different types of treatment methods
         3.1.1.1. Conservative treatment methods
            3.1.1.1.1. Simple Enucleation
            3.1.1.1.2. Marsupialization, Decompression and secondary excisions
         3.1.1.2. Aggressive treatment methods
            3.1.1.2.1. Enucleation with adjunctive treatment modalities
               3.1.1.2.1.1. Cryotherapy
               3.1.1.2.1.2. Carnoy’s solution
               3.1.1.2.1.3. Modified Carnoy’s solution (MC)
               3.1.1.2.1.4. Peripheral ostectomy (with rotary instruments)
            3.1.1.2.2. Resection and marginal resection
         3.1.1.3. Excision of adhered mucosa
         3.1.1.4. Application of Topical 5-Fluorouracil
      3.1.2. Recurrence of the Keratocystic Odontogenic Tumor (KCOT)
      3.1.3. Nevoid basal cell carcinoma and its interrelation with KCOT and children
      3.1.4. Risk of bias across studies
4. Discussion
5. Conclusion
6. References
Summary

**Purpose:** To understand the correlation between the recurrence rates of the Keratocystic odontogenic tumors (KCOT) with different treatment modalities used to treat the lesion.

**Materials and Method:** A systematic review. Items for Systematic reviews PRISMA guidelines were performed. An extensive search in a major university search motor Chalmers, including major databases such as Science Direct and PubMed, was performed to include all articles of relevance. Articles selected were adapted using the PICOS components the following inclusion criteria: Published studies, cohort studies, prospective randomized controlled clinical trials, prospective or retrospective clinical studies, prospective and retrospective reviews, case series with regard to various treatment modalities and recurrence rate.

**Results:**
Resection is the only treatment modality that has displayed a 0% recurrence rate (RR) and also the treatment modality correlated with the highest morbidity. Cryotherapy and Carnoy’s solution in combination with enucleation has proven to have similar effects as resection and has displayed a decrease in RR to 2%. Potential reasons for recurrence; epithelial remnants left postoperatively, involvement of surrounding vital structures and size and location has shown heterogeneity in their significance to cause recurrence.

**Conclusion:** Keratocystic odontogenic tumour is a very aggressive cyst and is widely recognized for its high recurrence rate. A definitive and optimal treatment method is still not agreed upon nor is there an agreement upon all aspects that may contribute to the recurrence of the KCOT. There is a clear lack of published evidence in this matter.

**Key words:** Odontogenic Keratocyst (KCOT), Treatment method, Marsupialization, Enucleation, Keratocyst recurrence.
1. Introduction

In 1956 Phillipsen inaugurated the word odontogenic keratocyst (OKC). [1-4] In 2005 the World Health Organization (WHO) designated the name keratocystic odontogenic tumor (KCOT) to better describe the cysts potential for aggressive and infiltrative behaviour. [1-10] The KCOT is believed to originate from residues of the dental lamina or extensions of the basal cell overlying the oral epithelium. [1,3,5,6,8,10] The cysts are most commonly found accidentally during examinations where X-rays are used.

The patients are usually asymptomatic however if symptomatic; swelling, pain, infection, drainage or paraesthesia of the inferior alveolar nerve may be present depending on the size of the cystic lesion. KCOT frequently appears in the posterior mandible 60-80% of the cases, the most usual location is the ramus and angle of mandible. Third molar involvement is commonly found in greater cystic lesions. [1-6, 8] KCOT is recognized to have a male predilection of a 2:1 ratio. [2,3,6,8,11] The KCOT stands for approximately 11% of the developmental cysts of the jaw. [2,12] The age of patients with KCOT covers a wide range from 7-83 years with two peaks. First peak is at 25-34 years and the second peak at 55-64 years. [1,8]

The KCOT have been observed to grow in anterio-posterior direction rather than from a buccal to lingual direction within the medullary cavity of the bone. This type of growth may occur without obvious bone expansion. [1,6,12] Displacement and resorption of teeth adjacent to the cyst occur; however it should be noted that displacement occurs more frequently than resorption. [1,8] Radiographically a unilocular or multiocular radiolucency may be present. Scalloped well-defined smooth and commonly corticated margin. [1,2,8,12] The KCOT are usually discovered and diagnosed by mishap during conventional X-ray examinations. [12,13]

Histologically the cyst is recognized by, its thin 8-10 cell layer, of stratified squamous epithelium. The lining may either be orthokeratinized, parakeratinized and least frequently it is mixed. [1,2,8,13] Cases of Nevoid basal cell carcinoma syndrome (NBCCS) are associated with the parakeratinized lining of the cyst and has shown higher recurrence rate (RR). [1,2,10] KCOTs are notorious for their high recurrence rate following treatment and their locally aggressive behaviour. [12]
Throughout the years different surgical modalities have been introduced for treating KCOTs, in broad terms conservative and aggressive treatment methods. Included into the conservative treatment methods are; enucleation, with or without adjunctive treatment options, marsupialization and decompression with or without secondary adjunctive treatment. The aggressive treatment modalities include Carnoy’s solution, cryotherapy, electrocautery, and marginal resection and block resection. However, among all the treatment options, what is the optimal or appropriate treatment modality is still contentious.

There is not one specific treatment method that is correlated with 0 RR. The different treatment modalities either lower the possible morbidity or reduce the recurrence rate. The aim of this systematic review is: to determine the most optimal treatment method when treating KCOT and pinpoint the potential factors that contribute to the high RR. Study objectives are the following:

1. Review current treatment methods and their potential cause for recurrence.
2. Look closer at the contributing factors that cause recurrence and how and if they can be prevented.
3. Analyse all types of KCOTs and classifications of their severity. [4,14] The hypothesis of this study is that the RR is dependant on treatment modality and that the clinician can affect factors that contribute to the recurrence.

2. Materials and Methods

This Systemic review was conducted in accordance with the regulations of master thesis integrated study program of odontology, approved by the board of the faculty of odontology, Lithuanian university of health sciences and preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement.

2.1 Literature search strategy

Extensive electronic online search with date and language restriction to English was conducted, using specific keywords according to PICOS criteria in a major university search motor Chalmers, including major databases such as Science Direct and PubMed, was performed to include all articles of relevance published with date restrictions from inception to December 2016. Articles collected from inception of search until December 2016. Keywords; Odontogenic keratocyst (KCOT), Treatment method, Marsupialization, Enucleation, Keratocyst recurrence.
2.2. Study eligibility

2.2.1 Inclusion criteria

The inclusion criteria were adapted using the PICOS components. Population (P), Intervention (I), Comparator (C), Outcome (O), Study design (S).

(P): Adults, children, elderly, syndrome patients, parakeratinized, orthokeratinized, initial lesions and recurrent lesions.

(I): All published studies including at least one or more different surgical modalities for the KCOT. Enucleation as definitive treatment and with adjunctive treatments (peripheral ostectomy Carnoy’s solution, Modified Carnoy’s solution, cryotherapy, topical 5-Fluorouracil), marsupialization and decompression with or without secondary surgery and adjunctive therapy (cystectomy), and resection.

(C): Not applicable. (O): Optimal treatment methods for KCOT, potential recurrence rates in correlation with each surgical treatment method. Reasons behind the high recurrence rates in KCOTs. (S): Published studies, cohort studies, prospective randomized controlled clinical trials, prospective or retrospective clinical studies, prospective and retrospective reviews, case series with regard to various treatment modalities and recurrence rate.

2.2.2 Exclusion criteria

Following exclusion criteria were used; Articles with animal studies or in vitro studies, articles in other languages than English, articles older than 10 years (with exception 18).

2.2 Data extraction process

One independent reviewer reviewed the articles and evaluated what to be included by following the inclusion and exclusion criteria. Any insecurity over articles was resolved by confiding in reviewer’s supervisor.

2.3 Clinical appraisal of individual studies

Because of intermixture of articles included, quality assessment was not performed.
2.4 Literature search

2.4.1 Results of Search strategy

An independent reviewer using the Cochrane Collaboration tools assessed the methodological quality in the individual studies. Articles were not excluded due to their risk of bias. Articles were assessed using four quality criteria: Random sequence generation, blinding of outcome assessment, incomplete outcome data and reporting bias. Allocation concealment and performance bias was excluded from the quality assessment, as withholding information from the patients about any surgical procedure they are about to undergo is unethical and impractical. The studies were classified into three criteria: Low risk, intermediate and high risk of bias. Low risk; if all criteria were positive or 2 of the variables are unclear/missing. Intermediate; if all criteria were positive or 3 of the variables are unclear/missing. High risk; if all criteria were positive and 3/more of the variables are missing.
3. Results

3.1. Results of variable outcome

3.1.1. Different types of treatment methods

The treatment goal is to establish an optimal treatment method that will reduce or eliminate possible causes of recurrence and minimalize postoperative morbidity in the patients being treated. [15]

Over the years different surgical treatment modalities have been introduced and used to manage the KCOT. Some of these treatment modalities include enucleation, marsupialization, curettage and resection. [7,14,16] The treatment of choice may vary from what each surgeon prefers to perform depending on various factors such as; size of the lesion, location, adjacency of vital structures, including inferior alveolar nerve, teeth, bony landmarks, maxillary sinus and nasal cavity. [2,16,17]

The treatment options have in broad terms been divided into conservative and aggressive treatment modalities. [11,13,14,17,18] Some clinicians advocate a conservative treatment modality while others advocate a more aggressive treatment modality. What is included in each category varies from each surgeon/author and this regards mainly if curettage (mechanical, physical and chemical) is to be placed within the conservative or aggressive category of treatment modalities when used in conjunction with enucleation. [4,14,18]

Depending on the treatment method being used it will determine a complete or incomplete removal of the cyst. High RR can widely be associated with what treatment modality that the surgeon has chosen to utilize. [11,17]

Postsurgical morbidity is a major factor to take into consideration when planning an optimal treatment plan for each patient [12]

Small and accessible lesions may be treated with one procedure alone while the larger and less accessible lesions might require a primary procedure followed by a secondary procedure. [16,17] Small cysts are on a regular basis enucleated while larger are treated with marsupialization. Follow up should be made periodically due to its high recurrence rate and aggressive behaviour. [16,20]

The treatment goal should involve a minimal distortion, morbidity and maintaining vitality of surrounding tissues. It should also involve eradication the potential factors promoting the high RR of KCOTs. [16]
3.1.1.1. Conservative treatment methods

Conservative treatment refers to treatments such as decompression, marsupialization and enucleation. These treatment modalities have proved to reduce the RR of KCOTs. [4,11,12,13]

3.1.1.1.1. Enucleation

Enucleation is when the surgeon removes the cyst from its bony envelope. [11,13,18] Enucleation can be performed with or without adjunctive therapies. According Ledderhof et al. there is a 56% recurrence rate when enucleation is performed alone as a definitive treatment option. [15,19] Adjunctive therapies include treatments such as peripheral ostectomy, cryotherapy, Carnoy’s solution (CS) and modified Carnoy’s solution (MC). [15] This procedure is not always easy considering that the lining of the cyst is thin, fragile and difficult to achieve access to; however, the competence and experience of the surgeon plays an important role. Getting full access during enucleation and removing the hole lining in one intact piece may be particularly difficult is cysts that are multilocular and when there is perforation of the cortical bone. Many authors stress a remarkable difference in RR when the epithelial lining was removed in one piece versus several pieces. [4] If it is possible to remove the cyst in one piece also depends on the surgeons desire to preserve surrounding vital structures. Enucleation may be the optimal treatment modality in cases where the adjacent vital structures can be preserved. The vital structures that's are involved depend mainly on the size of the cyst and location, structures such as maxillary sinus, mandibular canal, vessels and nerves, nasal cavity, teeth and bony landmarks are common sites of involvement. [16] When performing an enucleation a standard disinfection and draping is performed, later the KCOT is disclosed by a mucoperiosteal flap and bone removal. Adjacent soft tissues can be protected using gauze. [12] Enucleation alone has the highest recurrence rate due to the presence of satellite cysts or daughter cells in the bone surrounding the cyst. [4,11,13] In theory many authors believe it is ideal to have adjunctive modalities subsequent to enucleation. [4]

3.1.1.1.2. Marsupialization, Decompression and secondary excisions

Marsupialization and decompression are conservative methods and are being used more regularly as a treatment modality for KCOT. These treatment methods decrease the size of the cyst hence
minimizing the morbidity. The significant success rate in both marsupialization and decompression as primary or definitive treatment of large KCOTs have been wildly recognized. [16,17,21] Marsupialization is not to be confused with decompression. Decompression is defined as an operation that is made to relief pressure in a body chamber [18,21] Decompression is simply making a small opening in the cystic lesion and to maintain the opening in order for the cyst to be able to keep on draining. The opening and constant drainage is maintained by a cannula or other equipment that is sutured in situ.

Decompression is subsequently followed by cystectomy when the size of the cyst has decreased; this is to be assessed radiographically. Decompression might be considered an easier procedure to perform and due to its simplicity is indicated in children. [4,21] According Lizio et al. parents accept decompression better than marsupialization even though decompression requires equipment being left in the mouth and constant irrigation to avoid possible infections and closure of the wound. [21] Another factor that should be considered regarding decompression is that it is not a definitive treatment modality and additional surgical intervention is required for the complete removal of the KCOT. [16,17] Marsupialization is defined as the formation of a pocket of a cyst by making a incision of the anterior epithelial lining of the cyst and suturing the lining of the remaining cyst to the surrounding oral mucosa hence forming a pouch of the before enclosed cyst. The pouch is subsequently irrigated on a regular basis.

Marsupialization also relives the intracystic pressure and aims to expose the cystic lining to the oral environment by creating a window between the two epithelia. This allows the cyst to slowly decrease in size due to the decreased intra cystic pressure and the surrounding bone to regenerate thus preventing permanent damage to surrounding vital structures. Significant bone formation and reconstruction of anatomical landmarks, such as the mandibular foramen and cortical bone can be observed after a period of 3 months. Marsupialization allows the surgeon to maintain vitality of involved teeth, inferior alveolar nerve, the periodontal stability close to the lesion and maxillary sinuses. If teeth around the lesion are under development they can be preserved. This treatment modality also prevents pathological bone fractures. [16,21]

The surgeon may choose to excise the epithelium in a secondary procedure or to leave the epithelium. If the surgeon prefers to not excise the epithelium, marsupialization may be considered as a definitive treatment modality. [4,7,16,17,18, 21]
This treatment method requires a cooperative patient that will irrigate and follow up on a regular basis. [4]

However, if marsupialization is to be considered as a definitive treatment method or should be followed by enucleation, still remains to be topic of controversy. [21]

That marsupialization can be followed by enucleation was suggested by Parsch and later supported by Killey and Kay according to Chacko et al., studies have shown that the recurrence of cysts treated by marsupialization as a definitive treatment modality has a RR ranging between 11% - 18%.

The surgeons use radiographs to follow up in order to detect bone regeneration and healing of osseous defect they may also use an operative approach. Bone regeneration in radiographs is observed when there is increase of radiopacity. The increase of radiopacity is to be evaluated after every follow up appointment. [16]

Advantage of decompression and marsupialization is that local anaesthesia is usually sufficient. If tooth involvement is present, vitality of these teeth may be maintained when marsupialization is the treatment of choice. [4]

Some say marsupialization is indicated in larger cysts to decrease morbidity of patient and is more conservative however, when the surgery should be performed it is fated by the morphological changes around the cystic area. [16]

There are still many aspects of these treatment methods that need to be resolved. There are no guidelines regarding the assessment of volume reduction of the cystic lesion, therefore the relationship between percentage and decline in volume remains uncertain.

There are other possible influential elements that might effect the outcome of these types of treatment and have not been investigated such as; period of decompression, sex of the patient, age of patient, histological considerations to the type of epithelium of the cyst, location and size of the cyst.

A study by Lizio et al. demonstrated that only the duration of decompression was significantly associated with volume reduction and no other significant associations were found. A digital postoperative analysis by Chacko et al. showed that the mean value of reduction size of a residual cavity is 25.85% after 6 months, 57.13% after 9 months, 81.03% after one year and 100% after 2 years. Maximum cyst pathology size in this study was 150.40 mm, the minimum was 14.73 mm and the average cyst size among the 44 patients was 58.16mm. All the cysts were evaluated with radiographic examinations (digital orthopantomogram) every 6,9,12 and 24 months. [22]
Furthermore, osseous replacement should be, as previously mentioned, radiographically investigated. A computerized three-dimensional (3D) tomography (CT) is more dependable than accurate than a two-dimensional radiograph. This is due to the fact that a three-dimensional image can give us a more proper understanding of the cysts borders and positioning to surrounding vital structures. A 3D image also shows the integrity of the cortical bone, tooth displacement adjacent to cyst, proximity of essential anatomical structures. [21]

3.1.1.2. Aggressive treatment methods
3.1.1.2.1. Enucleation with adjunctive treatment modalities

Mechanical, physical and chemical curettage procedure in combination to enunciations obtains better results.
Curettage is defined as the removal of material and growth from cavity wall. [4,14,18]
Mechanical curettage physically eradicates the epithelial islands – suspected source of recurrence. [12,17]
Degree of ostectomy or curettage varies depending on adjacent vital structures. [12]

3.1.1.2.1.2. Cryotherapy

When bone is perforated and exposed to the covering mucosa, cryotherapy as an adjunctive treatment to enucleation has proven to have similar effects as complete eradication of residual satellite cysts. [4,12] However, in a study by Ledderhof et al. cryotherapy has shown similar recurrence rates as Carnoy’s solution. [19]
Liquid nitrogen (−70°C) as well as Carnoy’s solution has shown necrotizing effects on cellular components of bone, mucosal lining of the maxillary sinuses and reported effect on the inferior alveolar nerve. [4,13,19] Some authors (due to potential of pathological fracture) recommend immediate bone grafting after application of liquid nitrogen. [4]

3.1.1.2.1.2. Carnoy’s solution

Carnoy’s solution (CS) is a chemical fixative cauterizing agent that is characterized by its rapid local fixation, moderate penetration of the cancellous bone spaces and also its exceptional haemostatic ability. [4,11,17,19]
Carnoy’s solution has proven to reduce the RR when used as an adjunctive therapy method to enucleation. [19] The solution may be used inside the cyst or directly over the bone after cyst removal.

If used inside the cyst Carnoy’s solution induces a total obliteration of the cystic membrane. When used upon the bony bed after enucleation the solution eliminates remnants of epithelium still left within the bone and decreases the likelihood of recurrence. Originally the solution was intended to be used in the cyst however, most clinicians apply it after. [11]

Better results have been achieved with Carnoy’s solution is used in combination with enucleation. [11,13,17,23] This reduces the recurrence rate to 2 %. Some studies even state that enucleation together with Carnoy’s solution has the lowest RR out of the conservative treatment methods. [23]

Usage of Carnoy’s solution should be restricted to the mandible, in the maxilla the solution may lead to necrosis of the mucosal lining of the nasal cavity and the maxillary sinus.

Carnoy’s solution is a mixture consisting of 6 ml of absolute alcohol, 3 ml of chloroform, 1 ml of glacial acetic acid and 1 g of ferric chloride. [4,13,19,17,23]

In areas that are difficult to access and excise the overlaying mucosa of the fenestrated cyst some authors believe that Carnoy’s solution may help to eradicate any satellite cysts and epithelial remnants that are left after enucleation. [4,12]

Duration of application time varies in different publications from 3 minutes [12] 5 minutes [17] 10-15 minutes [11]. If nerve is exposed (inferior alveolar nerve) not more than 3 minutes of application is indicated. Exceeding 3 minutes has shown damage to the nerve fibers and cells. [4,11,12,19]

According Ledderhof et al. after CS is applied surgeons should rinse with regular saline. Soft tissues surrounding the lesion should be covered with sufficient amount of sterile neuropatties and dressed with petroleum jelly. [19]

Double or triple application of Carnoy’s solution in larger or longer lesions have been discussed and needs further research. In order to remove all attached residual satellite cysts and epithelial remnants. [12]

Complication in combination with the use of cryotherapy and Carnoy’s solution is neurosensory hypoesthesia this is because nerve is close to the lesion. [4,12] In majority of cases it is transient. However it is not possible to determine if the neurosensory deficit is due to the solution being used or the mechanical manipulation at the area at hand. [12]
3.1.1.2.1.3. Modified Carnoy’s solution

Modified Carnoy’s solution (MC) is without chloroform. This was introduced after the prohibition of using chloroform in several countries such as the USA. The chloroform was excluded from the solution after the discovery of the carcinogenicity of the substance. Study by Dashow et al. showed a significant higher recurrence rate in patients treated with modified Carnoy’s solution rather than regular Carnoy’s solution. [12,17,19,23] In this study it showed a 10 % recurrence rate with CS and 35 % with MC however there is not enough evidence regarding the efficiency of MC. [17,23]

3.1.1.2.1.4. Peripheral ostectomy (with rotary instruments)

Peripheral ostectomy after performing enucleation is considered to be an adjunctive treatment modality and is indicated when resection could be avoided. The method involves removing the required quantity of bone to secure the eradication of the residual epithelial lining. Some studies compare the recurrence rate of this treatment modality with resection. [4]
A study has shown that the combination of peripheral ostectomy and application of Carnoy’s solution demonstrated a promising low recurrence rate. [4]

3.1.1.2.2. Resection and marginal resection

Resection removes the cyst in a block and the adjacent normal tissues and is the treatment modality associated with the highest morbidity. [2,17]
Not accepted as a routine treatment considering that resection is the most aggressive and also has significant local morbidity. [2,4,10,12] Many clinicians argue that the most severe cases should be treated with resection. Cysts that have perforated the cortical plate and specially cysts that are recurrent are considered severe. Cysts that only have trabecular bone involvement and no thinning of the cortical plate should be treated with a less aggressive treatment modality than resection. [4]
Resecting a lesion, more specifically small lesions, can cause severe morbidity in patients. [15]
There has been evidence of recurrences despite resection and marginal resection however, majority of studies show 0% recurrence rate. The low recurrence rate can be explained by total removal of satellite cysts and epithelial residues and that resection is indicated when the goal is to totally eliminate any residues. [2,4,11,12,14,15,13] Resection provides the lowest recurrence rate overall however it also causes the highest morbidity therefore may not be the most effective treatment at hand. [11,12,17,23]
Resection with an approximate 5 mm margin of healthy bone is without a doubt the treatment method associated with the lowest recurrence rate. [17] After resection there is no presence of micro cysts in the bony surroundings. [24]

3.1.1.3 Excision of adhered mucosa

According Al-Moraissi et al. studies have shown that approximately 100% of cysts that recur had epithelial islands and satellite cysts in the mucosa overlying areas of cortical perforation, therefore many surgeons highly recommend excising the mucosa overlying an area where the cortical bone has been perforated. [4,14,24]

3.1.14. Application of Topical 5-Fluorouracil

There is a well-known correlation between the development of KCOTs and the protein patched homolog tumour suppressor gene (PTCH). Mutations in the PTCH1 gene cause smoothened (SMO) activation and it also causes sonic hedgehog (SHH) signalling which induces a neoplastic growth to occur. 5-fluorouracil (5-FU), an antimetabolic drug, induces apoptosis through inhibiting the SHH. 5-FU can be administered in many different ways in different malignant diseases. When applying 5-FU to basal cell carcinomas (BCCs), it is applied topically.

The application of 5-FU is performed after the KCOT has been enucleated and peripheral ostectomy has been performed at the site of the lesion. When 5-FU is to be applied to treat KCOT, 5% 5-FU is applied generously with a sterile ribbon gauze and placed into the wound, covering the entire surface area. The wound is not completely closed; a small opening estimated to be around a 1 cm should be left distally, exposing the gauze. 24 hours postoperatively the gauze is to be removed. No other irrigation, lavage or rinse is performed at the surgical site postoperatively.

A study by Ledderhof et al. compared the recurrence time for patients treated with MC and 5-FU. Lesions treated with 5-FU had 0 % recurrences while 19 % of the patients treated with MC showed recurrent lesions. The mean recurrence time for the MC group was 26.3 ± 1.8 months and for 5-FU group 41.31 ± 1.8 months. All the 5-FU-treated patients also displayed normal bone healing. [19]
3.1.2. Recurrence of the Keratocystic Odontogenic Tumor (KCOT)

Recurrences of the KCOT have been reported for more than a decade. There are many different factors that play potential roles in the recurrence of the KCOT. Factors such as site of involvement, histology, age of patient and accessibility all play an essential role in the recurrence of a lesion. However, there are also other contributing factors such as epithelial remnants from the lining of the cyst, satellite and or daughter cysts and microcysts and remnants left in the overlaying mucosa. [24]

Recurrence may be dependent on treatment modality according. [4,12,17,24] There has been numerous attempts to reduce the high recurrence rate by improving especially the surgical techniques. [7]

With regard to the factors that might contribute to the recurrence of KCOTs, it was found that younger age, multilocular KCOTs, larger KCOT size, and greater length in anterior-posterior dimension of the KCOT were risk factors for recurrence. [12]

There are authors that did not find a correlation between the recurrence of the cystic lesion and the size, location or if the cyst was treated by extirpation or fenestration. [4,10]

The local index for aggressiveness is characterized by the status of the cortical plate comparatively to the size of the cyst. In many cases these circumstances are overlooked and treatment modality is based solely on the size of the cyst. This may be an explanation to the persistent recurrence of the cyst despite treatment modality being used. Taking these contributing factors into consideration not only does the treatment modality play a role in the recurrence but also the clinical nature of the lesion itself. [4]

Satellite cysts and epithelial remnants are still being preserved in the bone after surgical procedures such as enucleation. [11,17,18]

A primary cyst formation in same area as former cyst may be interpreted as a recurrence. [11]

KCOT lining is very thin and are easily ruptured especially in larger cystic lesions, therefor they are significantly more difficult to remove than and cyst with thicker cystic lining. If the cyst is incompletely removed it may give rise to the origin of recurrence. [4,10,12] In the pursuit of saving vital teeth and nerves adjacent to cyst may lead to incomplete removal and thus increasing likelihood of recurrence. [10] One of the main characteristics of KCOTs is its special tendency to recur after surgical treatment. [10,12,17,18]
Scalloped margined also known as multilocular cysts are more difficult to remove in one piece this may be an explanation to the higher recurrence rate than the cysts with uniform contour. [4,10,12] The location of the cyst and its correlation with recurrence is also discussed, it has been a majority of incidences when cysts in the molar region is more likely to recur while some authors didn't find any correlation between size and recurrence. Difficulty in removing KCOT from the mandibular ramus is extensively recognized. [4]

Generally cysts present in the maxilla are detected earlier than the mandible due to thinner bone in the maxilla and the presence of the sinuses.[4]

Some authors have presented strong evidence that the KCOT may originate from proliferations of basal cells of the oral mucosa also known as basal cell hamartia.

When the cyst perforates the overlying bone a strong interrelation has frequently been observed between the cyst and the overlying oral mucosa.

In these cases the overlying mucosa should be excised along with the cyst to prevent recurrence. Some areas may be difficult to reach and therefore difficult to excise the overlying mucosa where the cyst has been fenestrated. [10,12,18]

Both dental lamina and basal cell hamartia originate from the stomodeal ectoderm and are altered by ectomesenchyme. This makes it more equitable to contemplate that the basal cells of the mucosa could be influenced by the same genetic influence as the dental lamina.

Possible reason for recurrence may also be the presence of satellite cysts are more common in syndrome cases than non-syndrome cases. Satellite cysts have also been found frequently in the cystic walls in recurrent cases than non-recurrent cases.

Early family detection and genetic counselling is critical in syndromic cases.

Proliferation of epithelial remnants occurs more frequently in patients with NBCCS than solitary KCOTs. 85% recurrence in syndrome cases. [10]

Clinicians that come across cases with multiple or recurrent cysts are obliged to cater patient with extensive dental care in addition to carried out diagnostic testing for NBCCS.

KCOTs that are associated with NBCCS that occur earlier in life have greater potential to recur and also become more aggressive than the usual KCOTs. [10,18]

There have been reports that the KCOTs transform into more aggressive neoplasms such as ameloblastomas and squamous cell carcinoma.

A mutation of the tumor suppressor gene (PTCH) has been associated with KCOT in syndromic cases. [10]
3.1.3. Nevoid basal cell carcinoma and its interrelation with KCOT and children

Multiple KCOTs commonly occur in association with nevoid basal cell carcinoma (NBCCS). This syndrome is also referred to as Gorlin-Goltz syndrome, multiple nevoid basal cell epithelioma, jaw cyst bifid rib syndrome. [20]

NBCCS is an inherited syndrome with autosomal dominant characteristics of chromosome 9 or mutations of the human patched gene; in some cases even the loss of the gene is a contributing factor. [10,13,20,25]

Biologically the behaviour of the KCOTs is correlation with NBCCS is more aggressive in nature and has an 82% higher recurrence rate than a sporadically occurring KCOT. [25,26]

Histologically Odonotogenic keratocysts me be either parakeratinized or orthokeratinized. The first mentioned has a significantly higher recurrence rate than then second mentioned. The parakeratinized are also more commonly seen in NBCCS syndrome. [1,2,4,10]

Odontogenic keratocysts most commonly peek in the 2:nd to 3:rd decades in life and also in the 5:th to 6:th decades in life. Rare cases have been reported as early as the first decade to the ninth decade of life. In conclusion to this sporadic odonotogenic keratocysts have very low prevalence in children, especially under the age of 10. Case studies have been reported among children below the age of 10.

Nevertheless it should be noted that children under the age of 10 that are diagnosed with KCOTs should be taken into special consideration. Due to the presence of KCOTs in children under 10 is acknowledged as a main indicator for NBCCS syndrome [1,8,25]

In NBCCS cases the cyst tends to be multiple in number and vary in numbers between 1-30 with an average number of 5 cystic lesions. Non syndromic cases display isolated lesions. [10,25]

While diagnosing, presence of disease among family members is an important tool for proper diagnosis however 20-40% of cases result form a de novo mutation. [13]

NBCCS syndrome is not a very commonly occurring syndrome and is conveyed in variable ways. Has equal male and female predilection. Main features include KCOT, Palmar and plantar pits (30-65% involve children under 10 years). [10,13,20]

Skeletal abnormalities such as vertebral and rib anomalies and intracranial calcifications.

Multiple basal cell carcinomas (BCCs) are also considered a main characteristic along side a list of other developmental disturbances. BCCs appear in early childhood or adolescence. [10,13,20,25]
The most significant pathology that is present is the odontogenic keratocyst, lesion occurs in 90% of patients above age 40 and is considered to be the first indication for NBCCS in children less than 10 years of age. [13,20,25]

3.1.4. Risk of bias across studies

<table>
<thead>
<tr>
<th>Citation</th>
<th>Selection Bias</th>
<th>Blinding of Outcome Assessment (Detection Bias)</th>
<th>Incomplete Outcome Data (Attrition Bias)</th>
<th>Reporting Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Morassi EA, Pogrel MA, Ellis 3, Edward (2016)</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Kinard BE, Chuang S, August M, Dodson TB (2013)</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Ledderhof NJ, Caminiti MF, Bradley G, Lam DK (2016)</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Authors</td>
<td>Year</td>
<td>Grade</td>
<td>Evidence</td>
<td>Data Source</td>
</tr>
<tr>
<td>---------</td>
<td>---------------</td>
<td>-------</td>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Leung YY, Lau SL, Tsoi KYY, Ma HL, Ng CL</td>
<td>2016</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Belenguer AD, Torres AS, Gay- Escoda C</td>
<td>2016</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Kiwilsza M, Sporniak-Tutak K</td>
<td>2012</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Rao K, Kumar S</td>
<td>2014</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Bhargava D, Deshpande A, Pogrel MA</td>
<td>2012</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Tarakji B, Baroudi K, Hanouneh S et al.</td>
<td>2013</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>
Discussion

The aim of this study was to determine evaluate the Keratocystic Odontogenic Tumor (KCOT) tendency to recur after different treatment modalities.

The treatment goal when treating any KCOT is to completely eliminate any cyst remains and this should be performed in the best possible manner in order to prevent recurrence of the cyst while also choosing a treatment modality that gives the least postoperative morbidity. A primary cyst formation in same area as former cyst may be interpreted as a recurrence. Many different surgical techniques have been introduced in order to manage the KCOT in a better manner. When choosing
appropriate treatment method it is important to take into consideration adjacent anatomical and vital structures (mandibular continuity, vitality of teeth, inferior alveolar nerve, nasal cavity and maxillary sinuses, bony landmarks, vessels) to provide the patient with the most optimal treatment with least morbidity, to preserve as much function as possible and should also involve eradication the potential factors promoting recurrence of the KCOT. [2,7,11,14,16,17,22]

All the factors that may contribute to the recurrence of the KCOT should be well understood by the surgeon, there are many authors stating that RR of the KCOT is depending on the treatment modality that each surgeon chooses to perform. Some of the studies do not characterise the treatment used in detail and use vague terms such as conservative or aggressive surgery. Not only is it, what technique or treatment modality is utilized but also the accessibility to lesion when operating is important. [4,12,17,24] Furthermore, the cyst has a very fragile lining that is easily raptured during surgery, especially larger in cysts. There has been a remarkable difference in RR between cysts that have been removed with an intact epithelial lining and those that have failed to be removed in as an intact unit. Patients with intact lining showed lowered RR. Due to the epitheliums brittle nature in KCOTs it is remarkably difficult to remove without rapturing the epithelium of the cyst in compassion to other cyst with thicker lining.

Therefore, the removal of the cyst requires a skilled surgeon if the goal at hand is to remove the cyst in one piece for instance in procedures like enucleation. It is particularly difficult to remove the cyst in one piece when the cyst is multilocular with scalloped margins, the path of access is not optimal and when the cortical bone is perforated. This considered being an explanation to the higher RR in multiocellular cysts compared to the uniform cysts. [4,10,12] The surgeons desire to preserve the vital structures play an important role and this has to be taken into consideration, when removing the cyst as a unit, if the vital structures will be compromised and what we can do cause minimal damage.

Enucleation can be performed with adjunctive therapies that are meant to decrease the RR. [4,10,12]

Cryotherapy has been proven to have the same effect as complete eradication of residual satellite cells, even when the cortical bone was perforated and there was a clear connection between cyst and over lying mucosa. [4,12] In a study by Ledderhof et al. cryotherapy has shown similar recurrence rates as Carnoy’s solution in conclusion to this there is not a clear unity between authors regarding the RR when using cryotherapy. However, there is clear agreement regarding the negative effects of
liquid nitrogen (-70°C) and Carnoy’s solution, it has been proven that both of these adjunctive treatment methods have demonstrated a necrotizing effect upon the cellular components of bone, mucosal lining of the maxillary sinuses and there has also been reported effect upon the inferior alveolar nerve. There is also a clear agreement on the positive effects of Carnoy’s solutions ability to achieve rapid local fixation, moderate penetration of cancellous bone spaces and its exceptional haemostatic ability. Duration of application also varies depending on site and if mucosal lining or nerves are exposed in after removal of the cyst, duration varies from 3-15 minutes. If these vital structures are exposed application of Carnoy’s solution or Liquid nitrogen for more than 3 minutes have shown damage to nerve fibers and cells further complications is hypoesthesia that in majority of cases is transient, nevertheless it is impossible to determine if the nerve deficit is due to the solution or due to the mechanical manipulation in the area. [12] What should also be further discussed and is not elaborated in most articles is the number of application that is performed after the removal of the cyst. Carnoy’s solution can be applied 1-3 times and is believed to make a difference in the RR. [4,11,12,17,19,13] In regard to a study by Jason et al. showed a 10 % recurrence rate with CS and 35% with MC however there is not enough evidence regarding the efficiency of MC.

When using enucleation alone as a definitive treatment studies have shown a RR of 56 %. [15,19] 56% RR may be unacceptably high, resulting in multiple episodes of care during the patient’s life. In the pursuit of saving vital teeth and nerves adjacent to cyst may lead to incomplete removal and thus increasing likelihood of recurrence because of the presence of satellite cysts in the surrounding bone and tissues. Studies have shown that cysts in the molar region are more likely to recur and also to perform a complete removal from the mandibular ramus is well recognized. [4,8,11,13]

In order to decrease the RR when using enucleation as treatment modality there are several adjunctive treatment modalities that are utilized to remove material or growth from cavity wall simultaneously to the removal of the cystic lesion. It is considered ideal to use adjunctive treatment together with enucleation rather than enucleation alone. [4,18] Enucleation is a standard treatment modality when managing KCOTs, whether or not to fill the defect with bone substitutes after enucleating is a topic of controversy, especially in larger KCOTs. A study by Chacko et al. shows 100% bone regeneration after a period of 2 years examined by radiographic examinations (digital Orthopantomogram) image. The automatic bone regeneration can happen after the removal of KCOTs in the jaw without placing any graft or bone substitute in the defected area, even if the defect is as large as 150.40mm. This makes the surgical procedure less
expensive and easier. Furthermore, avoiding using graft material decreases the risk of postoperative complications commonly correlated with graft material. [22]

There are also other contributing factors besides the treatment modalities that should have some light shed on them such as; sight of involvement, age and histology [4,12,17,24] Patients that demonstrated scalloped/multiocular lesions, were younger in age or lesions that were longer in anterior-posterior dimension were at greater risk for the KCOT to recur. [12] However, the size of the cyst is not the way to assess the status of the KCOT, clinicians should utilize the local index for aggressiveness, an index determining amount of cortical bone destruction rather than just assessing the size.

What is the preferred treatment method depending on the size of the KCOT also varies between authors. Small and accessible lesions may be treated with on primary and definitive treatment modality such as enucleation, while larger lesions might need a primary and should be followed up with a secondary procedure for instance marsupialization. [16,17,20]

The local index for aggressiveness in rarely mentioned and usually overlooked by many surgeons, explaining why there are significant amount of recurrences despite the countless efforts of perfecting the treatment methods being used for the KCOT. Therefore, it is not safe to say that the recurrence is solely dependant on the treatment modality being used but also the clinical nature of the lesion itself. (4) When the KCOT has perforated the overlaying bone there has been a strong interrelation between the cyst and the oral mucosa had been observed and in these cases to prevent recurrence of the cyst it is recommended to excise the overlying mucosa. [10,12,18]

Remnants of the epithelial lining, satellite cysts and micro cysts left in the overlying mucosa are all factors that have been proven to contribute to increased RR of the cyst. [1,2,4,10] Satellite cysts and epithelium remnants also referred to as basal cell hamartia may be preserved in the proximal bone after surgical modalities. [10,11,12,17,18]

The parakeratinized has significantly higher recurrence rate when compared to the orthokeratinized. The parakeratinized cyst is more commonly seen in patients with NBCCS [1,2,4,10]

The behaviour of KCOT in NBBCS patients is biologically more aggressive and has a 82% higher recurrence rate compared with sporadic KCOT. These factors should play a major role when determining the course of treatment; a treatment modality specifically aimed at removing the epithelial lining is of essence. Satellite cysts have also been found frequently in the cystic walls in recurrent cases than non-recurrent cases. Proliferation of these satellite cells or epithelial remnants
occurs in 85% of syndrome cases. In most of the articles it is impossible to retrieve information regarding the exact type of KCOT.

Follow up should be made periodically due to its high recurrence rate and aggressive behaviour. However, follow periods are not specified in many studies and may affect the reliability of the studies and what treatment modality has the lowest RR.

Postsurgical morbidity is a major factor to take into consideration when planning an optimal treatment plan for each patient. Resection has in majority of studies demonstrated a 0% RR. When weighing between alternative treatment methods resecting a lesion, specifically a small lesion, it can cause more morbidity and damage rather than the cyst itself. Resection is the treatment modality presenting the highest morbidity in the patients postoperatively and should be used with caution because it not only resects the cyst but some surgeons also resect with a 5 cm margin around the cyst and excises adjacent soft tissues to ensure complete eradication of the KCOT, satellite cysts and daughter cysts. Due to the high morbidity rate in patients it is not accepted as a routine treatment modality. Many clinicians argue that resection should only be used in the most severe cases. What is considered the most aggressive or most severe cases is not agreed upon and gives rise to a discussion. Some studies include cysts that have perforated the cortical bone as severe others consider recurrent cysts as the most aggressive. Cysts that are confined to the trabecular bone are less aggressive according Kaczmarsyrek et al. However cysts that are small despite cortical involvement should be considered for a less invasive treatment modality.

Another more conservative new study by Ledderhof et al. discovered that the application of 5-FU had 0% RR, these results are confined to a single study and more studies should be performed.

Cysts that have recurred have shown a staggering presence of epithelial islands and satellite cysts in the mucosa overlying areas of cortical perforation in 100% of the cases, overlying should always be excised when the cortical bone is perforated. [4,14,24]

Marsupialisation and decompression are widely used techniques for primary or definitive treatment of extended odontogenic cysts, preventing damage to important anatomical structures and reducing the surgical trauma with no necessity for grafting. This is particularly useful in younger, elderly or high-risk patients with local or general diseases [3, 20, 29] or who are undergoing pharmacological
5. Conclusion

To briefly conclude this systematic review the Keratocystic odontogenic tumour is a very aggressive cyst and is widely recognized for its high recurrence rate. A definitive and optimal treatment method is still not agreed upon is a clear lack of published evidence in this matter. Authors do not agree on all aspects that may contribute to the recurrence of the KCOT and how they can be prevented, some factors are widely recognized such as epithelial remnants from the cyst that are left in the surrounding bone and oral epithelium postoperatively, patients with NBCCS also are more genetically predisposed to have recurrent KCOTs.

While reviewing the current treatment methods and what clinicians can to prevent recurrences resection has proven to be the treatment method that carries the lowest risks for the KCOT to recur. However, this treatment method also has the highest morbidity among patients and should be exercised with caution and should be utilized in the most aggressive, recurrent KCOTs and possibly syndrome cases. In order to minimize the RR in KCOTs, enucleation with Carnoy’s solution or cryotherapy is an option in the first line of treatment for primary KCOTs, in addition to this marsupialization followed by secondary cystectomy has shown reduced recurrence. Clinicians should be aware of the their ability to influence the recurrences that are related to the treatment modality and how they can prevent it in the best possible manner.

Some authors do not take the type of epithelial lining (types of KCOTs) into consideration in articles, hence both types are included to this studies leading to what the more optimal treatment method being dependant also on type of lining sense the parakeratinized is more likely to recur in comparison to the orthokeratinized KCOT. Proper means for determining the severity of the KCOT should be clarified; in what cases the cyst should be treated with conservative treatment or more aggressive measures. Different authors present different means for determining severity of the lesions.

Follow up time for recurrence is not always evaluated and needs to be taken into consideration. Many articles do not have an adequate follow up time, which makes the recurrence rate that is reported untrustworthy.
6. References


