Surgical Removal of Ameloblastoma and Keratocystic Odontogenic Tumors in Maxilla and Mandible, a Literature Review on Surgical Techniques and Risk of Recurrence

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ABSTRACT

This literature review examines the literature on surgical management of ameloblastoma and keratocystic odontogenic tumours (KCOT). KCOT represent 3 % - 11 % of all the cystic lesions in the jaws and ameloblastoma 11 % of the odontogenic tumours. Treatment involves removal of the tumours by means of enucleation, curettage, marsupialization or resection. The first three can be combined with each other or with the adjunctive therapies: applications of Carnoy’s solution or cryotherapy. The aim of this literature review is to evaluate the risk of complications correlated to different surgical techniques for removal of KCOT or ameloblastoma.

A search was performed in PubMed based on our keywords (Marsupialization, decompression, fenestration, enukleation, KCOT, OKC, KOT, keratocystic odontogenic tumor, odontogenic keratocyst, ameloblastoma, outcome, follow-up, relapse, prognosis, recurrence). The data was managed with Excel.

Twenty articles met our criteria: 12 articles reported KCOT in 667 patients and 8 articles reported 191 patients concerning Ameloblastoma. The articles almost exclusively presented the risk of recurrence for different treatment modalities. Subsequently the results mainly contain recurrence rates for different surgical techniques.

412 KCOT patients received enucleation alone and 92 recurred, resulting in a recurrence rate of 22.3 %. 91 patients with ameloblastoma received resection and four recurred, resulting in a recurrence rate of 4.4 %.

This review fails to identify any reliable evidence on recurrence rates in relation to treatment modalities for KCOT and ameloblastoma. Further prospective controlled clinical trials are essential to address this important issue.
INTRODUCTION

Keratocystic odontogenic tumours (KCOT)

In 2005 the odontogenic keratocyst was reclassified by the WHO as a benign cystic neoplasm and were given the name “keratocystic odontogenic tumour”. The reason for this reclassification derives from studies by Reichart and Philipsen that show genetic alternations, on a molecular level, as some neoplasms do (Reichart and Philipsen, 2004). WHO approved this reclassification during a consensus conference in Lyon 2003 (Nayak et al., 2013).

KCOT is a unique form of development odontogenic tumour considering its special histopathology and clinical manifestation. KCOT represent 3 % to 11 % of all the cystic lesions in the jaws (Neville et al., 2009). The tumour may grow very large comparing to other odontogenic cysts. Symptoms as pain, swelling with or without bone expansion, or drainage is not uncommon in big tumours. Small tumours are usually asymptomatic (Neville et al., 2009).

KCOT springs from the dental lamina. It has a frail and characteristic fibrous wall, whose inside is coated in a 6-8 cells thick epithelial lining. The basal epithelial layer consists of a palisaded layer of cuboidal or columnar epithelial cells, whereas the luminal surface displays flattened parakeratotic epithelial cells with a wavy appearance. Orthokeratinized odontogenic cysts refer to odontogenic cysts with orthokeratinized epithelial lining. They are associated with considerably lower recurrence rates (Kaczmarzyk et al., 2012), however it is suggested that the risk of malignant transformation is somewhat higher, though the evidence supporting this claim is scarce (Neville et al., 2009). Originally they were considered a subtype of odontogenic keratocyst but now cystic lesions lined by orthokeratinizing epithelium have been excluded by the WHO from the diagnosis of KCOT due to its clinical and pathological differences (Zecha et al., 2010).

KCOT is found in all ages, but reports suggest that 60 % of the cases are found in people between 10 and 40 years of age, with a slightly higher representation in the male population. The most common site for this entity to manifest itself is the posterior parts of the mandible.

In surgical management of KCOT it’s crucial to successfully remove the entire entity. Leaving parts of the epithelium often results in recurrence. Various studies report a
recurrence rate of 5% to 62% (Neville et al., 2009). The wide range can be explained by discrepancy in the number of patients, the length of follow-up and different inclusion and exclusion criteria. Most of the recurrences appear within the first five years after surgery, however a significant amount of cases have been reported to recur 10 years or more after the initial surgery.

The delicate nature of the tumour wall makes it difficult to enucleate from the bone. The high recurrence rate, combined with the difficulty of removing the entity, has resulted in a numerous number of surgical techniques as treatment options. The optimal treatment for KCOT is still debated (Neville et al., 2009).

**Ameloblastoma**

Ameloblastoma is a true neoplasm of odontogenic epithelium and represent about 11% of the odontogenic tumours and 1% of all the odontogenic epithelial tumours. This tumour is characterized by its aggressive, yet benign growth pattern and its persistence (White and Pharoah, 2009).

It origins from the odontogenic epithelium, thus it may arise from the dental lamina, the epithelial lining of a odontogenic cyst, the developing enamel organ or the basal cells of the oral mucosa. (White and Pharoah, 2009).

Ameloblastomas are growing slowly and if untreated they may grow massive, thus disfiguring the patients. Lesions are often characterised by painless swelling and bone expansion. The entity is uncommon in the young population and consequently found in patients over 20 years of age and there is no sex predilection.

The most common site for ameloblastoma is the molar ascending ramus area (Neville et al., 2009).

Ameloblastomas can be divided into three different clinical subtypes based on its clinical and radiographic features: conventional solid or multicystic, unicystic and peripheral (extraosseous).

The tumour often infiltrates the surrounding cancellous bone. However, before the resorption of the mineralised parts of the bone there is no possibility to visualise the tumour resulting in underestimating the size of the tumour when using conventional dental radiology. Similar to KCOT, ameloblastomas are problematic to entirely remove surgically. If the tumours tissue island that has infiltrated the bone is left after treatment, recurrence will most likely occur (Neville et al., 2009).
Treatment alternatives

Enucleation (i.e. cystectomy): Is the procedure where an entity is removed surgically without cutting into or dissecting it.

Curettage (i.e. periphery ostectomy): Is a medical procedure to remove tissue by scraping, scooping or by a round burr. This surgical technique results in loss of 1-2 mm surrounding healthy tissue.

Resection: Removal of either a block of bone or a full segment from the mandible or maxilla due to a tumour. Resection is always associated with loss of healthy tissue i.e. resection with margin.

Marsupialization and decompression: Both techniques involve making a surgical window into the entity, thus exposing its contents to the oral environment. The purpose of this procedure is to decrease the intracystic pressure and promote shrinkage of the cyst or tumour. The reduced pressure allows the surrounding bone a possibility to assimilate the space with new bone formation (Nakamura et al., 2002).

The difference between marsupialization and decompression is how the surgical window is maintained open. Decompression is achieved through a plastic drain, while marsupialization keeps the window open by means of suturing the oral mucosa and the cystic wall together around the periphery of the opening.

Both treatments demand high patient compliance since the cavity needs to be irrigated on a daily basis for several months. When the tumour has decreased in size and bone fill has occurred, secondary treatment by enucleation or/and curettage is often necessary. The objectives of these procedures are to reduce morbidity especially when the lesion is in contact with sensory nerves in the facial skeleton. The procedures also accelerate complete healing of the defect and some studies show histopathological changes in the epithelial lining (Hupp et al., 2014). In this study these two treatment alternatives are considered as one and the same.

Carnoy’s solution (CS): Is a fixative composed of 60 % ethanol with ferric chloride, 30 % chloroform and 10 % glacial acetic acid. CS is used in treatment of bony defects after surgical removal of a tumour or cyst. The purpose of CS is to eliminate epithelial residues from the tumour, thus decreasing the risk of recurrence (Gosau et al., 2010).

Cryotherapy: This method uses freezing to induce tissue necrosis. The aim, as with CS, is to eliminate epithelial residues from the tumour and preventing recurrence. Low temperatures induce tissue necrosis in the bone, while maintaining the inorganic osseous framework (Carneiro et al., 2012).
Complications
Treatments involving surgery always implicate a risk of complications. The literature in this study reports complications such as: recurrence, neurologic damage, fracture and infection.

Recurrence in KCOT and ameloblastoma is thought to mainly be a result of epithelium tissue from the tumour left in the surrounding bone after surgery. Recurrence rates from 5 % to 62 % have been reported in patients with KCOT and usually within five years from the initial treatment. Ameloblastomas treated with curettage exhibit recurrence rates from 50 % to 90 %, and when treated by block resection a recurrence rate of 15 % is presented. If recurrence has not occurred within five years it’s no guarantee that the patient is cured (Neville et al., 2009).

Carnoy’s solution may cause damage to the mandibular nerve when exposed directly (Gosau et al., 2010).

Cryosurgery inflicts cellular necrosis in the bone though maintaining the framework of inorganic mass. The method increases the risk of pathological fracture as a result from the weakened bone (Carneiro et al., 2014).

Aim
The aim of this literature review is to evaluate the risk of complications correlated to different surgical techniques for removal of KCOT or ameloblastomas.

MATERIAL AND METHODS

Search strategy
A search was performed in PubMed based on our keywords (Marsupialization, decompression, fenestration, enucleation, KCOT, OKC, KOT, keratocystic odontogenic tumor, odontogenic keratocyst, ameloblastoma, outcome, follow-up, relapse, prognosis, recurrence) September 13, 2015 (Table 1).

After manually review of the abstracts and articles, studies meeting our inclusion/exclusion criteria were selected (Figure 1).
Inclusion criteria
Published and peer-reviewed human studies in English, which described a surgical management of ameloblastoma and/or keratocystic odontogenic tumours with at least 10 patients and a mean or median post-operative follow-up of five years or more. The studies with less than five years mean follow-up were included if it was possible to trace the results of the individual patients with at least five years follow-up.

Exclusion criteria
Articles that was not digitally accessible through PubMed.

Data extraction
233 of the initial 253 articles did not fulfil the inclusion criteria and were excluded. The remaining 20 articles were reviewed by the two authors independently and both put the extracted data in a database in Excel. The two separate databases were crosschecked and united. The extracted data was obtained from the following variables: Surgical technique, number of patients, gender, mean/median age, recurrence rate, most common position of the tumour and other complications.

Ethical considerations
Since this is a literature review, all data is anonymous. The data for the case report was encrypted by our tutor. There is no risk for individual identification, thus the ethical problems non-existent.

RESULTS

Literature review
12 articles (published 1996 – 2104) presented data concerning surgical treatment of KCOT. From these 12 studies 667 patients, mean age 38.2 years (range 7 – 89), with a male dominance (60 %) were included.
Eight articles (published 1996 – 2014) presented data concerning surgical treatment of ameloblastoma. A total of 191 patients, mean age 29.9 years (range 7 – 87), with a male dominance (54.5 %) were included in the study.
Position of the tumours
For both KCOT and ameloblastoma the most common site of the tumour was the posterior mandible i.e. the ramus, angulus and molar region.

Recurrence rates
By summing up all the patients who received the different types of treatments, the following recurrence rates can be presented in patients with KCOT:
Patients who received enucleation alone had a recurrence rate of 22.3 %. Enucleation followed by curettage had a recurrence rate of 35.3 %. Enucleation with following cryosurgery had a recurrence rate of 22.2 %. Enucleation with additional treatment by Carnoy’s solution had a recurrence rate of 9.1 %. Enucleation followed by curettage and finally supplemented with Carnoy’s solution gave a recurrence rate of 0 %.
Marsupialization as the only treatment had a recurrence rate of 16.0 %. Marsupialization followed by later enucleation had a recurrence rate of 5.4 %. Marsupialization followed by enucleation and additional curettage had a recurrence rate of 26.1 %.
The most aggressive treatment is resection and the patients who received this had a recurrence rate of 0 % (Figure 2 and 3).

Recurrence rates for patients with ameloblastoma is presented below:
Enucleation alone had a recurrence rate of 21.1 %. Enucleation followed by curettage had a recurrence rate of 20.0 %. Enucleation with following cryosurgery had a recurrence rate of 0 %. Enucleation with additional treatment by Carnoy’s solution had a recurrence rate of 18.2 %.
Marsupialization as the only treatment had a recurrence rate of 0 %. Marsupialization followed by enucleation and additional curettage had a recurrence rate of 44.0 %.
The most aggressive treatment is resection and the patients who received this had a recurrence rate of 4.4 % (Figure 2 and 3).

Complications
Half of the articles concerning KCOT and two thirds of the articles regarding ameloblastoma did not consider or report any complications except recurrence rates.
The following complications were seen in patients with KCOT:
Two of 28 patients who received marsupialization alone suffered of infections during the treatment. Paraesthesia was found in two of 17 patients after therapy with enucleation followed by curettage and Carnoy’s solution. Four out of 412 patients that received enucleation alone suffered from postoperative infections, three from hypaesthesia and one suffered of anaesthesia. One of 88 patients treated with enucleation followed by Carnoy’s solution suffered from hypaesthesia and another from anaesthesia.

No complications were found after treatment with enucleation followed by cryotherapy or with patients treated with marsupialization followed by later enucleation and curettage.

Reports regarding complications seen in patients with ameloblastoma were scarce and only two studies discussed the immediate complication of facial deformity and loss of neural input that is associated with resection.

No complications were reported after treatment with enucleation and cryotherapy.

**DISCUSSION**

The aim of this literature review was to critically evaluate the risk of complications correlated to different surgical techniques for removal of KCOT or ameloblastomas.

Most KCOT recur within the first five post-operative years, however cases of recurrence have been reported more than 10 years after surgery (Kaczmarzyk et al., 2012). The same phenomena can be seen with ameloblastoma, where 50 % of all the recurrences occur within five years postoperatively (Reichart et al., 1995). Subsequently a minimum of five years mean or median follow-up time was required of the studies to meet the inclusion criteria in this literature review. A clear majority of studies during the initial data collection were excluded from the review due to lack of follow-up time longer than five years or an incomprehensible way to present that data.

The current microscopic definition of KCOT consists of jaw lesions lined by parakeratinising epithelium. This criterion was stated by WHO 2005, before that the orthokeratinized odontogenic cyst was considered a part in the range of the KCOT.
As a result of this some of the articles before 2005 in this review do not distinguish or report the differences between the parakeratinising and the orthokeratinized type of KCOT. This is a weak point in this study due to the discrepancy of recurrence rates of these two entities. Including orthokeratinized odontogenic cyst resulted in lower recurrence rates than if KCOT alone had been studied. However the orthokeratinized type of KCOT consists of only 7-17 % of all the keratinizing jaw cysts (Neville et al., 2009). Including articles published before 2005 that did not discriminate between these two entities resulted in a larger database.

Ameloblastoma have, as described earlier, different histological subtypes. These diverse types present varying recurrence rates. Unicystic ameloblastomas show the lowest recurrence rate compared with non-unicystic ameloblastomas (Reichert et al., 1995). In this study we did not discriminate between the different types of ameloblastoma and neither did many of the included articles, resulting in a larger database.

The main complication after surgical treatment of KCOT and ameloblastoma is by far a recurrence of the tumour. Other complications that were reviewed were neural damages, infections, fractures and facial deformity. All the reviewed articles focused on recurrence rates in relation to different treatment modalities. Half of the articles regarding KCOT and two thirds of the articles concerning ameloblastoma reported other complications. That fact limits the possibility to conclude the results except for the risk of recurrence. We acknowledged a lack of research on post-operative complications in different treatment modalities vis-à-vis the size of entity, the location of the tumour and age of the patient. The most common place for KCOT and ameloblastoma to appear is in the ramus, angulus and molar region of the mandible. A majority of the studies present this area as the most associated location for a recurrence due to the complicated surgical accessibility and the difficulties of entirely removing the tumour (Kaczmarzyk et al., 2012). A tumour located in the molar, angulus and ramus region of the mandible is in a surgeon’s perspective associated with narrow spaces, the risk of damaging the floor of the mouth and if the tumour involves the inferior alveolar nerve, also the risk of neural damage.

Due to lack of studies in the field, the size of the patient groups treated with different surgical techniques vary widely. This is a statistical bias and we recommend a
cautious mind when reading the different recurrence rates presented in this literature review.

Enucleation alone is considered one of the most conservative treatments and it’s associated with a higher quality of life for the patients. Compared to e.g. decompression in which the technique require a longer treatment, a two-staged procedure, and good patient compliance (Pitak-Arnnop et al., 2010). In this study the recurrence rate of KCOT is 22.3 % (92 of 412) for enucleation alone. This high recurrence rate ought to be a result of not being able to entirely remove epithelium remnants or satellite cysts. We believe this recurrence rate to be the most accurate based on the size of the patient group studied. The recurrence rate of patients treated for ameloblastoma is 21.1 % (4 of 19) when treated with enucleation. This is similar to the rate seen in KCOT patients, however the patient group is considerably smaller.

The risk of leaving epithelium remnants or satellite cysts may be avoided by using secondary techniques with the aim of inflicting a shallow tissue necrosis or mechanically remove the surrounding bone. KCOT enucleation followed by curettage has a recurrence rate of 35.3 % (6 of 17) and ameloblastoma treated in the same fashion has a rate of 20.0 % (4 of 20). These rates contradicts the statement described above, however the size of these four patient groups differ substantially thus making it impossible to make any conclusions. Some classify this surgical technique as conservative, but we find this statement perplexing since the depth of the periphery osteotomy determines the extension of the operation.

Carnoy’s solution as an adjunctive therapy to enucleation has a recurrence rate of 9.1 % (8 of 88) for KCOT and 18.2 % (4 of 22) for ameloblastoma. “Carnoy’s solution is a cauterizing agent with moderate tissue penetration, rapid local fixation, and hemostatic action” (Ribeiro Junior et al., 2012). The usage of Carnoy’s solution poses a risk of neural damages when applied in the vicinity to neural structures and tissue necrosis in the maxillary sinuses (Kaczmarzyk et al., 2012). Some studies uses the original ingredients in Carnoy’s solution, while others use a modified model were chloroform is excluded. We have chosen not to differentiate between the original Carnoy’s solution and the modified ones. It’s possible that these different solutions
vary in potency, thus affecting the recurrence rates in a positive or negative way.

Enucleation followed by cryosurgery generated a recurrence rate of 22.2 % (2 of 9) for KCOT and 0 % (0 of 10) for ameloblastoma. A risk with cryosurgery is the increased risk of pathological fractures (Curiet et al., 1997). No fractures were seen in the study by J.T Carneiro et al. (2014) that was reviewed in this study. A debate concerning different gas combinations and delivered temperatures to the bone suggest that the risk of fracture decreases with higher temperatures.

Patients treated with only decompression/marsupialization had a recurrence rate of 16.0 % (4 of 25) for KCOT and 0 % (0 of 3) for ameloblastoma. This surgical technique is the most conservative and forbearing amongst all treatment modalities. Before treating a patient with decompression it’s important that the patient understands the extent and demands required. Firstly the treatment period is long, varying from months to years. Secondly the patient needs to irrigate the cavity daily with saline water and thirdly, some discomfort may be associated with having a plastic drain intra oral. Other disadvantages with this treatment are the risk of aspiration of the obturator and ulceration of the surrounding mucosa. The advantages with this treatment are that it often saves contiguous structures such as tooth roots, the maxillary sinus, or the inferior alveolar canal from surgical damage. Even if adjuvant treatment such as enucleation or curettage is needed, these advantages are still gained through new bone formation protecting vital structures (Nakamura et al., 2002). If the KCOT or ameloblastoma is large and located in the mandible, a first stage treatment with marsupialization is advocated since enucleation may cause the risk of mandibular fracture (Zhao et al., 2002). The KCOT patients treated with marsupialization followed by enucleation had a recurrence rate of 5.4 % (2 of 37) and in one of the included studies the patients were also treated with curettage and received a recurrence rate of 26.1 % (6 of 23). One of the patient groups treated for ameloblastoma received decompression followed by enucleation and cryotherapy. This group had a recurrence rate of 44.0 % (11 of 25). The discrepancy in recurrence rates between these three groups might be a result of many factors; one of them might be correlated to more or less intractable tumours. KCOT and ameloblastoma might be unicystic or multilocular. The different locus of the tumour might be divided by bony compartments, making surgery more complicated and thus increasing the risk of
recurrence.
KCOT treated with marsupialization is sometimes subject to histologically changes, which makes the entity easier to enucleate. Nakamura et al. (2002) observed: “After marsupialization, substantial histologic changes in the epithelium were observed in many cases. A hyperplastic, stratified, non-keratinizing squamous epithelium and a thick connective tissue wall were the most common features.” The connective tissue wall of KCOT is usually frail which makes it difficult to biopsy or enucleate without it falling apart. The thickened connective tissue wall, as a result of decompression, explains why enucleation is made easier.

Resection is the most radical treatment and is generally believed to present the lowest recurrence rates. This statement is confirmed, since the KCOT patients treated with resection in this study had a recurrence rate of 0 % (0 of 57) and 4.4 % (4 of 91) for ameloblastoma. In a recent study it’s confirmed that the risk of recurrence is 3.15 fold greater when treating multicystic ameloblastoma conservatively, compared to radical treatment e.g. resection (Almeida et al., 2016). Resection involves extraction of teeth and removal of the inferior alveolar nerve, consequently leading to poorer oral function and permanent anaesthesia (Zhao et al., 2002). Resection is highly associated with lower quality of life and morbidity, such as facial disfigurement and loss of jaw continuity (Pitak-Arnnop et al., 2010). We believe resection to be the last resort when others treatments fail e.g. multiple recurrences, when the tumour show aggressive growth patterns and when patient follow-up is impossible. Another aspect is the age of the patient. Because keratocystic odontogenic tumours and ameloblastomas are benign in its nature we believe resection should be avoided, if possible, in children.

**Conclusion**
This literature review fails to identify any reliable evidence on recurrence rates in relation to treatment modalities for KCOT and ameloblastoma. The treatment of choice for KCOT and ameloblastoma is still debatable and further prospective controlled clinical trials are essential to address this important issue. The existing literature is limited and further studies with longer follow-up periods are required to better judge the true recurrence rates of different treatment modalities.
ACKNOWLEDGEMENTS

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REFERENCES


Table 1: Search strategy. A search was made in PubMed and 253 articles came out. 20 articles were selected for complete analysis after manually review of the titles, abstracts and articles.

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Fig. 1: Process of selection. Studies meeting our inclusion/exclusion criteria were selected after manually review of the titles, abstracts and articles. Each step in the figure represents the number of articles selected for further analysis after adding more inclusion and exclusion criteria.
Fig. 2 Recurrence rates for the different surgical techniques. E: Enucleation, C: Curettage, Cryo: Cryotherapy, CS: Carnoy’s solution, M: Marsupialization, R: Resection.

Fig. 3 Recurrence rates for the different surgical techniques. E: Enucleation, C: Curettage, Cryo: Cryotherapy, CS: Carnoy’s solution, M: Marsupialization, R: Resection.
APPENDIX: A CASE REPORT

Clinical findings
A female patient sought medical care for limited ability to open her mouth and a left sided pain. The CBCT and OPG showed an extensive cystic lesion adjacent to the tooth 38, which occupied most of the angle and ramus area of the mandible and stretched towards the mandibular notch and coronoid process (Fig. 4).

Surgical management
The initial treatment consisted of decompression. A window was made into the lesion, three tissue samples were sent to the pathologist and a plastic drain was sutured (Fig. 5). The patient received post-operative information and was instructed to irrigate the cavity with saline once a day.

The histological diagnosis confirmed KCOT and the patient was to irrigate the cavity for six months.

After six months the patient had residing lesions in the base of the coronoid process and another posterior to the lesions peripheral border. These were enucleated along with the tooth 38 in a secondary surgical procedure during narcosis.

Complications
The plastic drain interfered with the occlusion and was lost several times during the six months of irrigation, resulting in additional treatment and adjustments. Other complications were infection, pain, swelling and dizziness.

After secondary surgery the patient has experienced a loss in vertical mandibular movement capacity, a fluctuating pain and loss of sensation in the chin.

Result
Radiological follow-up showed good healing and new bone formation in the periphery of the lesion (Fig 6). The effect of a successful decompression reduced the risk of fracture substantially and perhaps prevented further neural damage.

Follow-up
Since KCOT is associated with the risk of recurrence, the patient will be subject to a 12 months follow-up interval.
Figure 4 and 6 showing the initial appearance of the KCOT and the healing process after approximately six months.
Fig. 5 Image and example of how it can look when a plastic drain is installed. The tube connects the lesion with the oral cavity and is irrigated on a daily basis.