CURRENT TRENDS IN MANAGEMENT OF ODONTOGENIC KERATOCYSTS

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INTRODUCTION

The odontogenic keratocyst (OKC) is a relatively common benign pathological entity found in the gnathic bones. OKC is one many odontogenic related cysts, however, special attention is warranted because of its known locally aggressive behavior and increased tendency to recur. OKCs are developmental and arise from the remnants of odontogenic epithelium known as the dental lamina, and comprise 5-15% of all odontogenic cysts. Due to its rapid growth potential and locally destructive nature, OKC was classified as a benign neoplasm by the World Health Organization in 2005. More recently though, the World Health Organization reclassified it as an odontogenic cyst due to insufficient evidence to define the lesion as a neoplasm.

The purpose of this article is to review the current management of OKCs, with the primary goal of treatment strategies aimed at reduction of recurrence rate of the lesion as well as to assist the surgeon when a more radical procedure may have historically been indicated due to tumor size or association with adjacent structures.

CLINICAL STUDIES

Histologically, the OKC is characterized by a lining of parakeratinized stratified squamous epithelium. **Figure 1** demonstrates histological features of OKC.

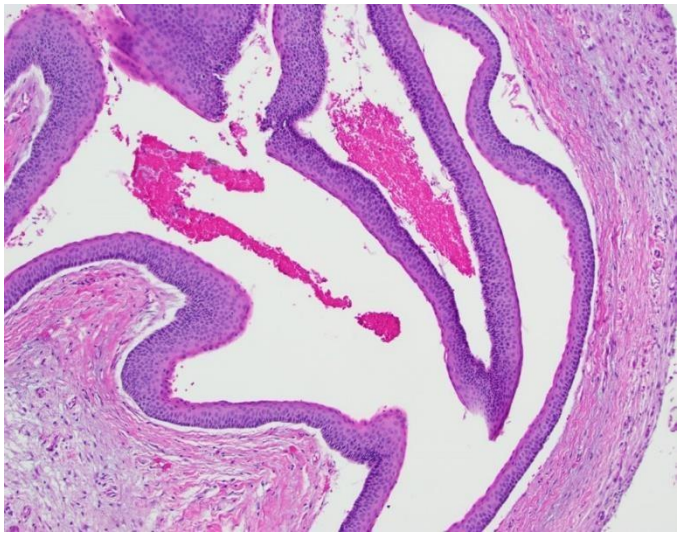
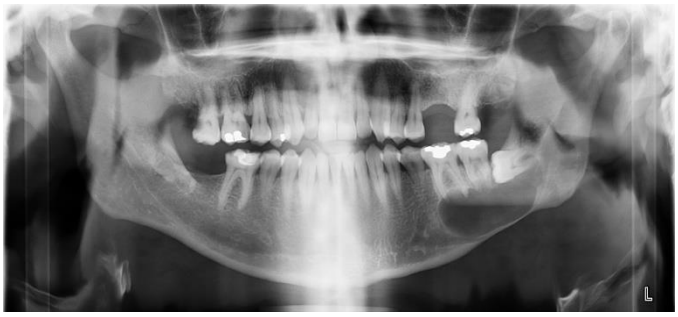


***Figure 1**: Histological features of OKC characterized by a lining of parakeratinized stratified squamous epithelium.*

OKCs can occur in the maxilla or mandible, but has a higher propensity to occur in the mandible.[1] It has also been shown to have higher prevalence in males. The peak incidence tends to be between the second and third decades of life.[2] Radiographic features of OKC include a well-defined unilocular or multilocular radiolucent lesion, cortical bone destruction, association with

an impacted tooth, tooth displacement, and/or root resorption.

Various treatment modalities have been used throughout the years including simple enucleation and curettage, peripheral ostectomy, decompression, marsupialization, cryosurgery, chemical destruction, radical resection, or a combination of these modalities.**Figure 2** demonstrates a representative example of treatment of OKC with enucleation and curettage with peripheral ostectomy and no additional adjunct therapy with acceptable results three years post-operatively. Literature does demonstrate unsatisfactorily high recurrence rates associated with simple enucleation ranging from 25 to 60%.[3]



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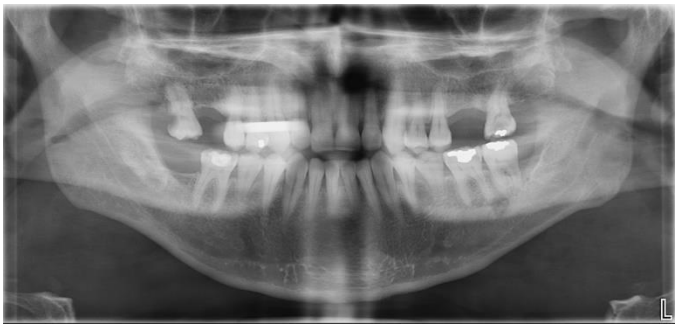

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Figure 2: ***A****, Panoramic radiograph of a 46M with biopsy proven OKC treated with extraction of tooth #17, enucleation and curettage and peripheral ostectomy.* ***B****, Three year follow up demonstrating osseous fill of previous bony lesion.*

Carnoy's solution (CS) has long been the gold standard to be used as a treatment adjunct in OKC. The solution is composed of 1 g of ferric chloride dissolved in 6 mL of absolute alcohol, 3 mL of chloroform, 1 mL of glacial acetic acid.[4] It was traditionally used as a tissue fixative but is effective in treatment of odontogenic keratocysts by the fact that it penetrates bone to a depth of 1.54 mm, thus, able to remove cystic evaginations in bone. Its use in live patients was banned by the FDA in 2013 due to its inclusion of chloroform. Chloroform has been shown to be carcinogenic in animals after oral exposure, resulting in an increase in kidney and liver tumors.[6] When the FDA ban on CS was initiated, many surgeons began to search for treatment alternatives.

Thus, modified Carnoy's solution (MCS) began to be used. It has the same formulation as CS, minus the chloroform, and is now being widely used. Recently there has been skepticism to MCS true efficacy. A study by Donnelly *et. al.*[5] entitled *"Modified Carnoy's Compared to Carnoy's Solution Is Equally Effective in Preventing Recurrence of Odontogenic Keratocysts"* discusses chemical treatment of OKC. MCS contains absolute ethanol, glacial acetic acid and ferric chloride without chloroform found in CS. This is a retrospective cohort study evaluating patients treated by a single surgeon with enucleation and currettage, peripheral ostectomy, and application of either MCS or CS to prevent recurrence. As with the previous studies, the primary outcome is recurrence of OKC and time to recurrence. This study looked at 77 patients with 36 patients in the CS and 41 in the MCS group, from 2004 to 2019.

In this, the procedure was performed with enucleation and curettage of the cystic lesion, peripheral ostectomy, and then

application of CS or MCS on Kittner sponges to bony cavity for five minutes with subsequent irrigation. The recurrence rate was 13.9% in the CS group and 14.6% in the MCS group. Median time to recurrence for both groups was 24 months. There was no statistical difference in recurrence for OKC based on treatment by CS or MCS. Both chemical cautery agents appear to be effective in reducing the recurrence rate of OKCs, however recurrence still persists despite these treatment modalities.

A recent study performed by SiguaRodriguez et. al.[7] entitled "*Is Surgical Treatment Based on a 1-Step or 2-Step Protocol Effective in Managing the Odontogenic Keratocyst?*" was published in the Journal of Oral and Maxillofacial Surgery. The study compares the effectiveness of enucleation and curettage with peripheral ostectomy with a 2-step protocol of decompression followed by enucleation and curettage with peripheral ostectomy at a later date. It is a retrospective cohort study viewing patients from 1991 to 2008 diagnosed with OKC treated with one of these two modalities. In the 1-step protocol, 13 patients were included in the study. Fifty-nine patients received the 2-step protocol. If the cystic lesion was greater than 3 cm, the patient was placed into the 2-step protocol for decompression initially. Decompression of the cyst involves opening a window into the cyst and suturing a device such as a nasal trumpet to the periphery. This allows the ability to irrigate the cystic cavity with potential reduction in size of the cyst over time. In addition, the cystic cavity becomes thicker and can be removed easier during surgery at later date.[8] The authors of this study suggest that both groups demonstrated appropriate responses to treatment with decreased recurrence rate. They conceded that decompression is not a definitive treatment and will require frequent follow up which can lead to high attrition rate. However, it can be effective in reduction of larger lesions if the patient follows up regularly.

With the lingering doubts about the usefulness of MCS as adjunct treatment, 5-FU, a topical chemotherapeutic medication has been employed as a treatment alternative. In an article by Caminiti et al.[9] entitled "5Fluorouracil is Associated With a Decreased Recurrence Risk in Odontogenic Keratocyst Management: A Retrospective Cohort
Study," the authors discuss the use of 5-FU for management of patients with OKC after enucleation and curettage. The article is a retrospective cohort study in which 70 patients were included. The treatment group consisted of 34 patients in which 5% topical 5-FU cream was used in comparison to 36 patients managed with modified Carnoy's solution (MCS). The ingredients for the 5-FU cream (Efudex) contains 5% fluorouracil in a vanishing cream base consisting of methylparaben, polysorbate 60, propylene glycol, propylparaben, purified water, stearyl alcohol, and white petrolatum.[10] Its proposed mechanism of action is that 5-FU targets thymidine kinase and thymidylate phosphorylase in the cystic lining of an OKC. The primary study outcome was to look at the time to recurrence of the OKC with secondary variable of postoperative paresthesia. The mechanism of action of 5-Fluorouracil (5FU) occurs by its metabolites being incorporated into RNA and DNA along with competitive inhibition of thymidylate synthetase, which leads to decreased DNA repair and replication due to a lack of thymidine. The use of topical 5-FU has been shown to be successful in treatment of basal cell

carcinomas. The 34 patients treated with 5-FU initially had enucleation and peripheral ostectomy completed prior to application. Subsequently, they had placement of sterile radiopaque quarter-inch ribbon gauze packed into the cystic cavity with approximately 1 cm of gauze exposed for removal 24 hours postoperatively. The 36 patients in the comparison group were treated after enucleation and peripheral ostectomy with application of MCS-soaked gauze to all surfaces of the lesion for three minutes. The surrounding tissue was protected with Petroleum gauze. The results demonstrate that no recurrences occurred in the 5-FU group with median follow up time of 22 months. Nine recurrences occurred in the patients treated with MCS with median follow up time of 27 months. No statistically significant findings were found between 5-FU and MCS treatment groups regarding nerve paresthesia. The results of this study are promising in regards to the use of 5-FU for treatment of OKCs. The concern with this study is followup time is short in relation to the timeline for recurrence for OKCs. Recurrence could occur between 5-10 years postoperatively. However, the difficulty in following patients for that long, and not being lost to follow up is inherently difficult and should not discount the results found in this study. 5FU is readily available and should be considered for treatment of OKCs.

The next study by Casino et. al.[11] entitled "Refined Topical 5-Fluorouracil Technique for the Targeted Treatment of Odontogenic Keratocysts" furthers the research completed by Caminiti at the University of Toronto. This is a retrospective case series in which the authors at Stony Brook University studied the efficacy of applying a 5-FU coated absorbable gelatin sponge to the cavity created by the cystic lesion rather than ribbon gauze used by Caminiti. The primary outcome again is OKC recurrence and secondary outcome is nerve injury after treatment. In this study, 13 patients were included. After enucleation and peripheral ostectomy was completed, topical 5% 5-FU was directly applied to the bony cavity with cotton swab and then packed with an absorbable gelatin sponge coated in 5-FU. The authors found no recurrences with a median follow up time of 28.5 months. The patients involved in the study presented with no adverse events. A benefit of using absorbable gelatin is that the patient does not have to return 24 hours postoperatively for packing removal. In addition, the absorbable gelatin can be better contoured in comparison to traditional ribbon gauze to a bony cavity allowing increased 5-FU contact to the cavity walls. Also, it takes approximately 46 weeks for the sponge to completely resorb which may allow for prolonged 5-FU contact to retained satellite cysts or microcysts. The authors go on to discuss that the amount of 5-FU absorbed systemically from packing a cystic cavity is negligible compared to lethal dose in rats. One caveat to this is patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency may develop adverse reactions to 5-FU including pancytopenia and GI toxicities, which is generally only seen in systemic administration of the drug. This study expands on previous studies on topical 5-FU and demonstrates its potential applicability in treating OKCs.

CONCLUSION

There are several treatment techniques that can be used for the management of OKCs and while surgical intervention remains the mainstay in treatment, clinical experience and surgical acumen remain the key factors in treatment selection and decision making. Since the ban of Carnoy's solution, many surgeons have been at a loss for how to definitively treat these lesions especially when vital structures such as teeth and the inferior alveolar nerve are involved and a more radical surgery would result in significant post op morbidity. These studies show that MCS has a recurrence rate similar to the previously thought gold standard of CS. More recently, topical application of 5FU has become a viable treatment option but questions exist as to whether it has similar utility to CS as well as what side effects this topical chemotherapeutic drug may carry. The studies by Caminiti and Casino show that 5-FU is a safe and viable alternative to CS/MCS. As of now, research continues to progress into the most effective management that are to both minimize the chance of recurrence as well as carry minimal morbidity to the patient.

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