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Review Article

Dentistry Section

Expanding Treatment Horizons with Chemical Agents and Drug Adjuvants in Odontogenic Keratocyst: A Comprehensive Review

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ABSTRACT

Odontogenic Keratocyst (OKC), characterised by its unique histopathological features and propensity for recurrence, presents a clinical challenge in oral and maxillofacial surgery. The present review provides a comprehensive overview of OKC, delving into its aetiology, clinical presentation, and the intricacies of conventional treatment approaches. The significance of addressing OKC lies not only in its distinctive histological nature but also in its potential association with Nevoid Basal Cell Carcinoma Syndrome (NBCCS). The purpose of present review is to synthesise current knowledge on OKC, offering insights into its pathogenesis and emphasising the importance of a holistic understanding for informed clinical decision-making. Conventional treatment modalities, such as surgical excision, decompression techniques, marsupialisation, and enucleation, are explored in detail, highlighting their merits and associated challenges. The high Recurrence Rates (RR), particularly following conservative approaches, underscore the necessity for adjunctive therapies. Additionally, the review navigates recent advances in the treatment landscape, including molecular targeted therapies and immunotherapy, opening avenues for more targeted and effective interventions. The scope of this review extends beyond conventional treatments, addressing the nuances of OKC from molecular and genetic perspectives to the challenges posed by its anatomical location. By providing a comprehensive resource for clinicians, researchers, and dental healthcare professionals, the present review aimed to contribute to the evolving understanding of OKC, guiding future research endeavours and enhancing the clinical management of this intriguing odontogenic lesion.

Keywords: 5-Fluorouracil, Adjunctive therapies, Carnoy's solution, Molecular targets, Recurrence

INTRODUCTION

Odontogenic Keratocyst (OKC) represents a distinctive and intriguing entity within the realm of odontogenic cysts. Historically known as the "Keratocystic Odontogenic Tumour (KOT)" [1], its nomenclature has evolved, reflecting both its biological behaviour and clinical implications. It has undergone a great odyssey, transitioning from a simple cyst to OKC, then to KOT, and back to OKC [2,3]. In 1774, John Hunter used the term "dental cyst," which subsequently underwent terminological and conceptual modification. Philipson in 1956, and Pindborg and Hansen in 1963, described it as "OKC." The World Health Organisation (WHO) officially termed it "Keratocyst" in the 1971 and 1992 classifications [4].

In the following years, due to its aggressive behaviour, high RR, overexpression of the p53 protein, mutations in the p53 and Protein-Patched Homolog (PTCH) genes (the tumour suppressor gene, i.e., the human homologue of the Drosophila polarity Patched gene PTCH), high enzymatic activity with increased Matrix Metalloproteinase (MMP) levels, increased expression of Receptor Activator of Nuclear Factor KB (RANK), RANK Ligand (RANKL), Osteoprotegerin (OPG), and tumour angiogenesis, several investigators have considered OKC as a cystic benign neoplasm. Consequently, in the third edition of WHO 2005, it was reclassified as "KCOT" [5,6]. However, in the fourth edition of WHO 2017, the terminology reverted back to OKC.

Since, numerous studies have demonstrated that PTCH gene mutations can also be identified in non neoplastic lesions like dentigerous cysts, some investigators have hypothesised that the regression of the cyst following marsupialisation does not align with the characteristics of a neoplastic condition. It is essential to clarify that the consensus panel is not asserting that OKCs are definitively non neoplastic; however, they contend that the existing evidence does not adequately support the classification of KOTs as true tumours at this time [7].

This cystic lesion arises from the odontogenic epithelium, most commonly associated with impacted third molars or the mandibular ramus [8]. OKCs predominantly affect the mandible more than the maxilla. In studies, mandibular involvement was reported as follows: Brannon (65%), Browne (79%), and Forssell (78%). In a study by Browne RM in 1970, it was noted that within the mandible, OKCs mostly occur in the ramus-third molar area, followed by the first and second molar areas, and then the anterior mandible. In the maxilla, the third molar area is most commonly affected, followed by the cuspid region. Reported literature reviews state the varied incidences as follows: posterior mandible 49%, anterior mandible 9%, body region 7%, posterior maxilla 20%, anterior maxilla 13%, and mid-maxillary region 2% [9].

The clinical behaviour of OKCs is noteworthy for its locally aggressive nature and high RRs compared to other odontogenic cysts [10]. OKCs are characterised by their unique histopathological features and variants, including orthokeratinised, parakeratinised, and combined forms. Primarily, there is the presence of a parakeratinised stratified squamous epithelium lining the cystic cavity. This lining is often corrugated and may exhibit a palisaded arrangement of basal cells, contributing to the distinctive microscopic appearance of OKCs. Emerging evidence suggests a significant distinction between parakeratinised and orthokeratinised OKCs [11,12]. Parakeratinised OKCs exhibit a high recurrence rate (42.6%), while the orthokeratinised variant rarely recurs (2.2%).

Crowley TE et al., reviewed 449 OKC cases, identifying most as parakeratinised (86.2%). No differences were found among the groups concerning age, race, sex, or symptoms. A histochemical marker (38-kD glycoprotein, gp38) is expressed in parakeratinised

but not orthokeratinised OKCs [13]. Consequently, orthokeratinised OKCs have been proposed to describe the less aggressive variant. Additionally, according to Brannon, the recurrence of parakeratinised OKCs is attributed to the technical challenges of complete surgical excision as well as the aggressive biological behaviour of the cyst; hence, it requires a more aggressive surgical approach compared to other cyst types [13,14].

Recurrence is a hallmark of OKCs, distinguishing them from other odontogenic cysts. This tendency for recurrence poses a significant challenge in managing these lesions. Even after seemingly successful surgical interventions, OKCs may reoccur, necessitating a nuanced approach to treatment and follow-up [10]. The factors contributing to recurrence can include a thin and fragile lining, infiltrative nature, incomplete removal of the cyst lining, retention of satellite or daughter cysts/microcysts, epithelial islands in the wall of the original cyst, the development of new keratocysts from epithelial offshoots of the basal layer of the oral epithelium, and the infiltrative nature of the cyst in inaccessible areas of the jaw bones.

The RRs vary based on treatment modalities. According to Zhao YF et al., resection stands as the only treatment for OKCs that promises consistent results in terms of cure, with RRs close to zero, further emphasising the need for vigilant postoperative monitoring [15,16]. In exploring adjuvant approaches, understanding the recurrence patterns of OKCs becomes pivotal in devising strategies to minimise the likelihood of relapse and enhance long-term treatment success. This knowledge forms the foundation for exploring alternative and supplementary interventions to manage OKCs comprehensively [17].

The significance of addressing OKC extends beyond its histological peculiarities. Given its potential for extensive local tissue involvement and frequent recurrence, OKC poses challenges in managing affected individuals. Moreover, the association between OKC and Nevoid Basal Cell Carcinoma Syndrome (NBCCS) underscores its relevance in the broader context of syndromic conditions and emphasises the need for a comprehensive understanding of its pathogenesis [18].

By synthesising existing literature, this review seeks to offer insights into the complexities of OKC, facilitating a holistic understanding that can inform clinical decision-making and future research endeavours. The scope of this review encompasses various facets of OKC, including its conventional treatment strategies, the role of adjuvant therapies, and emerging therapeutic avenues (chemicals and drugs). By delving into the nuances of OKC, author aimed to provide a comprehensive resource for clinicians, researchers, and dental healthcare professionals grappling with the challenges posed by this intriguing odontogenic lesion.

Treatment Options: Overview

Conventional treatment approaches: Surgical excision is the conventional approach for OKCs. Conservative treatment options include simple enucleation, with or without curettage, and marsupialisation, while more radical treatment options comprise peripheral ostectomy, en bloc resection, and segmental resection [19-22]. Enucleation followed by open packing is an excellent treatment option for OKC, associated with minimal surgical morbidity and a decreased incidence of damage to associated structures such as the inferior alveolar nerve and recurrence [19,20].

Decompression techniques: Decompression, a conservative approach for OKCs, involves creating an opening in the cyst wall and maintaining it with a drain. This method effectively reduces cyst size and recurrence, particularly in cases unsuitable for resection or simple enucleation, such as those involving pediatric patients with nearby developing tooth buds. A two-stage treatment—initial decompression followed by enucleation—has demonstrated lower RRs compared to enucleation alone. A study by D. Stanbouly reported a 22.1% RR for single-stage treatment versus 14.5% for the two-stage approach [23-26].

Marsupialisation: Marsupialisation, or the Partsch procedure, is a conservative treatment for OKCs. It involves creating a 1 cm opening in the cyst wall and suturing it to the mucosa, which reduces intracystic pressure and cyst size, thereby decreasing the risk of recurrence [25].

Indications for marsupialisation include large cysts, significant trauma risk from enucleation, difficult surgical access, aiding tooth eruption, and serving as a conservative option for children and elderly patients. A study by Zhao YF et al., found reduced recurrence rates over 3 to 24 years when marsupialisation was followed by enucleation [16].

Enucleation alone or enucleation with curettage and peripheral ostectomy: Enucleation involves the surgical removal of an OKC in one piece. This procedure, when performed with primary closure, is known as the Partsch II procedure [2]. When combined with marsupialisation, it is referred to as Waldron's procedure. While enucleation is effective with minimal morbidity, OKCs often recur. Thus, enucleation is often supplemented with peripheral ostectomy, where methylene blue stains the cavity and one to two mm of bone is removed with a round bur. Zhao YF et al., evaluated 484 patients and found a higher rate of recurrence at 17.79% when enucleation alone was performed [16]. In contrast, Kolokythas (2007), in a study of 11 patients treated with enucleation followed by peripheral ostectomy, suggested there was the least evidence of recurrence [2,27-29].

Resection: Resection encompasses two types: segmental resection, which involves the resection of the mandible or maxilla without preserving bone continuity, and marginal resection, which entails the surgical removal of a tumour with a margin of uninvolved bone. In this context, marginal resection maintains the continuity of the inferior or posterior borders of the mandible [27,28]. En bloc or marginal resection was utilised in seven studies involving 92 keratocystic odontogenic tumours (KOTs). The weighted RR varied from 3.5% to 18.8%, with an overall weighted RR of 8.4%. According to Stoelinga PJ in 1973, this relatively low RR may be due to the removal of satellite cysts and epithelial remnants within the segmented block of surrounding bone [30]. Although, data have reflected that nearly 100% of recurrent KOTs contain epithelial islands and daughter cysts in the associated mucosa [31,32]. Therefore, to reduce the risk of recurrence, it may be crucial to remove the overlying attached mucosa along with enucleations and resections. Due to the high frequency of recurrence, most surgeons recommend complete removal along with meticulous curettage of the surrounding tissues.

Among the treatments described, resection appears to be the most effective in preventing recurrence, as indicated by five studies reporting a 0% recurrence rate. However, the invasive nature of resection and the subsequent reconstruction of the mandible or maxilla raises concerns, given the benign nature of the disease and the low RRs associated with less invasive procedures [33].

Overview of adjuvant therapies: OKC is a cystic lesion of the jaw that has a high RR. Surgical interventions such as enucleation, curettage, and resection are commonly used to treat OKC. Adjuvant therapies such as cryotherapy, Carnoy's solution, and MCS have also been employed to reduce the RR of OKC. However, the availability of Carnoy's solution has become difficult, leading to the exploration of alternative chemical agents such as 5-Fluorouracil (5-FU) [34-36].

Carnoy's Solution (CS): Carnoy's solution is a fixative composed of 60% ethanol, 30% chloroform, and 10% glacial acetic acid, along with 1 gram of ferric chloride [37]. It is used as an adjuvant therapy in the management of OKC and a few other benign lesions [38]. The main fixative agent in Carnoy's solution is absolute alcohol, which dehydrates exposed cells by drawing out water [39]. Chloroform acts as a lipid solvent.

Carnoy's solution has been used as an adjunct to surgical interventions for OKC, such as enucleation, curettage, and resection, to reduce the recurrence rate of the condition [37,38]. A large systematic review and meta-analysis by Al-Moraissi EA et al., concluded that the weighted RR was 6.8%-18.8% with an average follow-up period of 1-14.6 years when managed by enucleation plus the application of Carnoy's solution [40]. In 2007, Hellstein J compared the effects of using Carnoy's solution with no use among 20 bone connective tissue and mucosal specimens and concluded that chloroform is an unnecessary constituent of Carnoy's solution, as no clinical benefit was seen in the study involving 15 patients. However, according to the 'Report on Carcinogens, Eleventh Edition, 2019', and the 'Food and Drug Administration Compliance Policy Guide, Chapter 4, Subchapter 460, in the year 2013' (FDACPG, USA), the use of chloroform in human beings concerning any therapeutic agent is not advisable because of its carcinogenic hazardous effect [41,42].

Modified Carnoy's Solution (MCS): Due to the carcinogenic effects of chloroform, the Food and Drug Administration (FDA) in 2013 banned the use of Carnoy's solution. Hence, it was modified to create a non chloroform-containing solution. A retrospective cohort study conducted by Anna Naze (2023), spanning 18 years from October 2004 to October 2022, involved 122 patients treated surgically with adjunctive chemical cautery. The patients were divided into two groups: the Carnoy's Solution (CS) group (n=73; median age: 30 years) and the modified Carnoy's solution (MC) group (n=49; median age: 42 years), all treated by a single surgeon. The primary focus was on RRs and the time interval to recurrence, with independent variables including demographics, lesion location, baseline clinical presentation, adjacent tooth extraction, and bone grafting. Males predominated in both groups, and the analysis found no statistically significant differences in RRs between the two solutions [43]. In the CS group, 8.2% experienced recurrences, while 10.2% did in the MC group. Among the 11 recurrences, 10 occurred less than two years post-surgery, with only one occurring in the 7th year of follow-up [36]. Therefore, the findings suggest that when used as adjunctive therapy, the application of MC demonstrates efficiency comparable to CS in lowering the recurrence rates of OKC [41-44].

Other treatment modalities: Sclerosing agents are used in the treatment of various medical conditions, including varicose veins and cysts. In the context of OKC treatment, aside from Carnoy's solution and liquid nitrogen, other sclerosing agents have been explored.

5-Fluorouracil (5-FU): This chemotherapeutic agent has been investigated for its effectiveness as an adjuvant therapy in the management of OKC [38]. 5-Fluorouracil is a novel adjunct for managing OKCs. Genetic mutations in the tumour suppressor gene Protein-Patched Homolog (PTCH) have been implicated in the development of OKCs and Basal Cell Carcinomas (BCCs). Mutations in PTCH1, in particular, activate Smoothened (SMO) and trigger the Sonic Hedgehog (SHh) signaling pathway, ultimately promoting neoplastic proliferation. 5-FU is an anti-metabolite drug that induces cellular apoptosis by inhibiting the SHh signaling pathway. This mechanism underlies its effectiveness in treating several cancers, such as BCCs and hepatocellular carcinomas. Compared to Carnoy's solution, 5-FU is considered advantageous due to its easy availability, ease of application, and improved morbidity when used locally [45-47]. According to Ledderhof NJ et al., in a cohort of 32 cases, 5% 5-Fluorouracil (5-FU) was applied by placing gauze soaked in the solution into the enucleated and curetted cavity of 11 OKC patients for 24 hours. Unlike Carnoy's solution, whether containing chloroform or not, there was no need for protection of the surrounding soft tissues. Their research reported no recurrences, in contrast to the Modified Carnoy's group, which consisted of 21 patients. Additionally, no adverse local or systemic effects were observed, and normal bone healing occurred postoperatively [48]. Caldas ROP et al., also reported similar findings in 2020, although this was based on an isolated case [49]. A systematic review and meta-analysis showed that 5-FU is effective as an adjunct following surgical intervention for OKC [50]. Topical application of 5-FU has also been found to be effective in the management of OKC, with minimal recurrence, low cost, and no functional or cosmetic deformity [51]. A scoping review found that adjuvant therapy using a chemical approach following enucleation is a more effective and beneficial treatment for OKC [35].

Liquid nitrogen cryotherapy: It has been observed that temperatures below -20°C consistently cause mammalian cell death. The principle of cryotherapy damages cells by altering osmotic and electrolyte imbalances. Liquid nitrogen boils at -196°C and forms ice crystals, which are sufficient to cause cell death. In liquid nitrogen cryotherapy, liquid nitrogen is sprayed for one minute over the cyst, followed by a slow thaw of five minutes, resulting in maximum electrolyte imbalance. This process is repeated two to three times to achieve more lethal effects on cells. Afterward, the cystic defect is grafted, and watertight closure is performed. The rationale for the use of liquid nitrogen is to kill the organic content of cysts, including epithelial remnants or satellite cysts, while leaving the inorganic bone matrix intact, which can then be used as a scaffold for bone grafting [45,47].

The use of cryotherapy in OKC as an adjuvant has been documented in studies conducted by Pogrel MA (1993) and Schmidt BL (2001), reporting a relatively low RR of upto 20% [52,53]. There was conflicting data when comparing cryotherapy alone or cases with no adjuvants used after cyst enucleation. A systematic review encompassing 28 studies involving the management of 1,430 odontogenic keratocysts, performed by Tay ZW (2021) [39], notably found that Carnoy's solution exhibited statistically significant differences in outcomes compared to cases with no adjunct therapy. While there was limited evidence supporting the effectiveness of MCS, there was no indication that cryotherapy yielded statistically different outcomes compared to cases without adjunct therapy. In summary, the findings suggest that Carnoy's solution and 5-FU currently stand out as the most effective adjunct therapies. However, the evidence for MCS, cryotherapy, and 5-FU remains inconclusive, emphasising the need for further studies to elucidate their roles in managing OKCs. Additionally, it is challenging to obtain and store liquid nitrogen at the prescribed temperature as it is more technique-sensitive, leading to its being considered outdated in medical practice. Jenson J noted in 1988 that cryotherapy has the potential to compromise bone strength, increasing the likelihood of pathological fractures, with this risk potentially occurring even four weeks following the postoperative period [44,53,54].

Current advances in the treatment of OKC (Molecular targeted therapies): Hedgehog (Hh) pathway inhibitors: Recent studies have explored the potential of molecularly targeted therapies, specifically inhibitors of the Sonic Hedgehog (SHh) pathway, for treating OKC. Vismodegib, an oral medication (150 mg/day for 18 months) that specifically blocks the hedgehog pathway, has been shown to inhibit the growth of BCCs as well as keratocystic odontogenic tumours [47]. Additionally, the SHh inhibitor GDC-0449 has been found to inhibit the growth of OKC cells in-vitro, suggesting its potential as a treatment for OKC. Goldberg et al., proposed a complete resolution of three OKCs in a patient with Basal Cell Nevoid Syndrome (BCNS), who received the Hh pathway inhibitor GDC-0449 as a possible treatment [55].

In certain studies, cyclopamine, a plant-based steroidal alkaloid that blocks the activation of the SHh pathway caused by oncogenic mutations, can effectively treat OKCs. These findings suggest that molecularly targeted therapies, particularly SHh pathway inhibitors, hold potential for the treatment of OKCs. However, further research is needed to determine their efficacy and safety in clinical settings [2].

Radiotherapy: OKCs can transform into intraosseous Squamous Cell Carcinoma (SCC). It has been hypothesised that this malignant transformation could be due to long-standing lesions or remnants of previously treated OKCs. The rate of malignant transformation is quite rare; to date, approximately 250 cases have been reported. The malignant conversion of OKC lining accounts for 14% of all odontogenic cyst malignant transformations [56]. Diagnosing SCC requires careful consideration due to several factors. One significant issue is that clinicians may not be fully aware of the potential for malignant transformation in OKCs, given their rarity. Additionally, both OKCs and SCCs can present with identical complaints, including swelling, pain, chronic infection, and pus discharge. Radiographic examinations may also struggle to differentiate between the two conditions, as both exhibit bony destruction, particularly in the early stages of SCC. According to Bodner L, the duration between a patient's visit and the diagnosis of SCC tends to be significantly longer than for SCC found in other areas of the head and neck region. Limited data are available regarding the treatments and prognosis for SCC. However, prompt diagnosis and appropriate intervention could significantly improve the prognosis for these patients [56].

In a systematic review performed by Kumchai H et al., a total of 679 publications underwent screening, resulting in the inclusion of 37 cases meeting the criteria. The mean age of patients experiencing malignant transformation of OKCs was 45.1 years, with pain (67.5%) and swelling (78.3%) being the predominant symptoms. Malignant transformations were more frequent in the posterior mandible, and larger lesions often spanned over two subunits of the affected jaw. Resection emerged as the definitive treatment in all cases, with 46% employing adjuvant treatments. Variability in patient outcomes and follow-up in the study reduced the ability to determine overall survival. However, reported overall survival rates for malignant transformation of odontogenic cysts range from 62% to 85%, with two-year and five-year survival rates ranging from 30% to 8%, respectively. A total of 14 cases were treated with adjuvant treatments for malignant transformation, of which seven received radiation, two received chemotherapy [57] and five received chemoradiation therapy [Table/Fig-1] [2,37,43,47,48,52].

Particular	Composition	Mode of action	Technique
Carnoy's Solution (CS) [37]	60% ethanol, 30% chloroform, 10% glacial acetic acid, and 1 gram of ferric chloride	- CS is a Fixative - Absolute alcohol, which dehydrates exposed cells by drawing out water - Chloroform acts as a lipid solvent - Induces chemical necrosis, facilitating the eradication of residual epithelial components and satellite microcysts adjacent to the cystic lining	The peanut-shaped cotton is dipped into solution and applied over cystic defect for a period of three minutes and washed off with saline
Modified Carnoy's Solution (MCS) [43]	60% ethanol, 10% glacial acetic acid and 1 gram of ferric chloride	- The absence of chloroform reduces the catchogenass - No significant improvement results were seen	The peanut shaped cotton is dipped into solution and applied over cystic defect for a period of 3 minutes and washed off with saline
Liquid nitrogen cryotherapy [52]	Liquid nitrogen at -196° C	- Damages the cells by altering the osmotic and electrolyte imbalance - Eliminates the organic components of the cyst, such as epithelial remnants and satellite cysts - Preserves the inorganic bone matrix	- Liquid nitrogen is sprayed for one minute over the cyst followed by a slow thaw of five minutes - Repeated two to three times
5-Fluorouracil [48]	5% 5-Fluorouracil solution (an anti-metabolite drug)	Induces cellular apoptosis by inhibiting the Sonic Hedgehog (SHh) signaling pathway	- Placing gauze soaked in the solution into the enucleated and curetted cavity of OKC for 24 hours and removal afterwards
Hedgehog (Hh) pathway inhibitors [47]	Vismodegib	- Specifically, inhibitors of the Sonic Hedgehog (SHh) pathway - Inhibit the growth of OKC cells in-vitro	An oral medication (150 mg/day for 18 months)
Cyclopamine [2,47]	A plant-based steroidal alkaloid	- Blocks activation of the SHh pathway caused by oncogenic mutation	-

[Table/Fig-1]: The action of different agents on OKC [2,37,43,47,48,52].

Outcome assessment and follow-up protocols: The assessment of treatment success in managing OKCs involves a thorough examination of outcomes and adherence to systematic follow-up protocols. Recent studies, including case reports and literature reviews, underscore the efficacy of conservative surgical approaches coupled with multimodal therapeutic interventions, substantiating positive results over a five-year follow-up period. Standard follow-up protocols encompass routine clinical assessments and radiographic examinations, which are essential for monitoring recurrence or complications.

Concurrently, ongoing clinical trials contribute to the advancement of OKC management by evaluating the safety and efficacy of novel treatments. A longitudinal perspective is imperative in evaluating treatment success, as it permits the identification of delayed adverse effects and an extensive assessment of the relative benefits and costs of interventions over an extended duration. The challenges inherent in prolonged follow-up, such as selection bias and attrition risk, underscore the necessity for robust statistical analyses to ensure the validity and reliability of findings. In the context of OKC treatment, long-term follow-up emerges as an indispensable tool for scrutinising the durability of therapeutic responses, elucidating late-onset consequences, and informing decisions regarding the potential necessity for supplementary or salvage therapies.

CONCLUSION(S)

The present review provides a detailed examination of OKCs, highlighting their complex histopathology, clinical challenges, and both conventional and innovative treatment methods. The focus on molecular and genetic factors enhances our understanding of OKC pathogenesis. By emphasising the importance of personalised clinical approaches, it underscores the role of adjuvant therapies in improving traditional treatments. The advent of molecularly targeted therapies, especially those targeting the Hedgehog pathway, marks a shift toward precision medicine. These insights have significant implications for clinical practice, fostering a collaborative future in OKC management.

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