ODONTOGENIC KERATOCYST: FROM CYST TO TUMOR AND BACK: AN EVOLVING PERSPECTIVE

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ABSTRACT

Odontogenic Keratocyst (OKC) is a benign neoplasm of odontogenic origin with the potential for aggressiveness and infiltrative behavior. Philipsen introduced the term 'odontogenic keratocyst' (OKC) in 1956 to describe jaw cysts with keratinized epithelial linings. Studies have reported a male predominance, with a peak occurrence at the age of 30 and a minor occurrence in the fifth to seventh decades of life.[1]. In 2017, it was reclassified as a cyst because numerous studies demonstrated that mutations in the PTCH gene can occur in non-neoplastic conditions, such as dentigerous cysts [4]. Diagnosis of OKC is mostly radiographic, with well-defined radiolucency with scalloped margins, either unilocular or multilocular, with anteroposterior extension. As a result of its aggressive behavior, the management of OKC remains a debatable topic in the literature. Both conservative and surgical methods, or a combination of both, are described as treatment options. These include marsupialization/decompression, enucleation, adjunct therapies like Cornoy's solution, peripheral osteotomy, cryotherapy, 5-Fluorouracil, and marginal/segmental resection. The primary purpose of this review is to give complete insights into changes in nomenclature of OKC terminology, classification, etiopathogenesis, molecular & genetic basis, clinical, radiographical, histopathological features, immunohistochemistry, treatment options, prognosis, recurrence, and malignant transformation of OKC.

Keywords: OKC, 5-Fluorouracil, cryotherapy, marsupialization, decompression, enucleation.

INTRODUCTION:

Odontogenic keratocyst (OKC) is a developmental cyst that arises from remnants of the dental lamina. Many studies have reported a male predominance, with a peak occurrence at the age of 30 and a minor occurrence in the fifth to seventh decade of life.[1]. It can occur in any part of the jawbones, but is most frequently seen in the mandible, especially at the mandibular posterior region extending up to the ascending ramus [2]. Diagnosis of OKC is mostly radiographic, with well-defined radiolucency with scalloped margins, either unilocular or multilocular, with anteroposterior extension. Histologically, variants are classified into two types: Ortho keratinized and Para keratinized [1]. Several researchers have identified specific "keratin expression profiles" that help differentiate OKC from dentigerous cyst. In general, the epithelium that lines the OKC generates low-molecular-weight keratin (i.e., cytokeratins 10 and 11), in contrast to the dentigerous cyst [3]. In 2005, it was classified as a tumour/neoplasm (KCOT) due to its high recurrence rate and aggressive behaviour associated with nevoid basal cell carcinoma syndrome. Mutations in the tumour suppressor gene PTCH1, which triggers the SHH pathway, have been found to cause aberrant and aggressive epithelial proliferation [4]. In 2017, it was reclassified as an odontogenic keratocyst (OKC) because numerous studies had shown that mutations in the PTCH gene can occur in non-neoplastic conditions, such as dentigerous cysts. Additionally, the resolution of the cyst following marsupialization does not align with a neoplastic process.[4].

Management of OKC can be categorized into conservative and surgical methods, or a combination of both. The literature describes procedures such as enucleation, marsupialization/decompression, and resection, as well as adjunct therapies like chemical cauterization, cryotherapy, and 5-Fluorouracil.

CLASSIFICATION & NOMENCLATURE

The term "Odontogenic Keratocyst" was introduced in 1956 by Phillipsen to describe an entity characterized by a keratinized epithelial lining. Pindborg and Hansen described the clinical and pathological features of the cyst in 1963. In 1967, Toller suggested that odontogenic keratocysts could be classified as benign cystic neoplasms due to their aggressive biological nature.

The classification of odontogenic keratocyst (OKC) remains a topic of ongoing debate among dental researchers [6]. In 2005, the WHO Classification of Head and Neck Tumours redefined odontogenic keratocysts as neoplastic lesions, known as "keratocystic odontogenic tumours"

(KCOTs), due to their locally aggressive behaviour and association with PTCH mutations. In 2017, the WHO reclassified it as a developmental odontogenic cyst, while orthokeratinized cysts were categorized separately [4-6]. In 2022, it was again classified as an odontogenic keratocyst (OKC) by the WHO (Fig.1).

Fig.1 – Nomenclature of odontogenic keratocyst over the time period

Histologically, there are two variants based on the epithelial lining

Ortho keratinised- the thin, uniform, orthokeratinized lining epithelium was characterized by onion-skin-like luminal surface keratinization, prominent stratum granulosum, and low cuboidal or flattened basal cell layer with little tendency of nuclear palisading.

Parakeratinized—highly cellular parakeratinized epithelial lining with surface corrugations and a palisaded layer of basal cells [16].

ETIOPATHOGENESIS:

The development of the dental lamina, especially its remnants after the organ has fulfilled its function, is probably associated with the causes of OKC [5]. The frequent occurrence of KCOT behind the third molar area is challenging to rationalize if the dental lamina is considered the primary cause, given the improbable chance of remnants or extensions of this dental lamina being found in the mucosa located behind the last molar. Consequently, it is likely that extensions from the basal layer of the oral mucosa epithelium also play a role in the development of KCOTs. [7-8]. One of the defining characteristics of this lesion is its tendency to spread through the cancellous bone in an anteroposterior direction with minimal expansion of the cortical area.

Numerous theories have been proposed to clarify this regarding the OKC expansion. These include

1) Intraluminal hyperosmolality, active proliferation of epithelial cells [9],
2) Collagenolytic activity in the cyst wall [10] and

3) Production of interleukin one & six by keratinocytes.

Autophagy, a catabolic process that relies on lysosomes, is essential for regulating tumour growth through the degradation of cellular proteins and organelles. Its significance in KCOTs is particularly highlighted, as it is activated during tumour development and is vital for preventing apoptosis and promoting the proliferation of tumour cells [11]. PTCH (Patched), a tumour suppressor gene, is implicated in both Nevoid Basal Cell Carcinoma Syndrome (NBCCS) and sporadic OKCs, and is located on chromosome 9q22.3–q31[12].

Typically, two mutations are necessary to inactivate a tumour suppressor gene. The first one is a mutation in one allele, the second is a loss of the other allele, known as loss of heterozygosity [LOH]. The second allele can be lost in three ways: (a) through deletion; (b) via mitotic nondisjunction; and (c) by mitotic recombination. Tumour growth occurs when both alleles are inactivated. Loss of heterozygosity (LOH) has been observed in basal cell carcinomas (BCCs), odontogenic keratocysts, and medulloblastoma, all of which are characteristics of Nevoid Basal Cell Carcinoma Syndrome (NBCCS) [13-14].

When the PTCH gene binds to SMO, it prevents the transmission of growth signals. This inhibition is removed when SHH connects to PTCH. If PTCH loses its regular function, the growth-stimulating influences of SMO can take effect. Abnormal activation of the SHH signalling pathway in adulthood has been linked to tumour formation [12] **(Figs. 2 & 3).** The neoplastic characteristics and tendency for aggressive recurrence have been linked to a greater prevalence of positive markers for proliferating nuclear antigen Ki-67, p53, and bcl-2 protein [15].

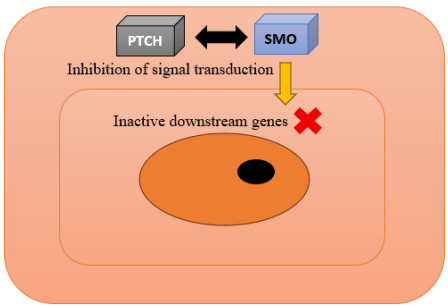

Fig. 2- PTCH (patched)–SMO (smoothened) receptor complex in the cell membrane, which has a suppressor effect on growth signal transduction. Patched (PTCH): transmembrane protein that represses transcription of hedgehog signaling. Smoothened (SMO): transmembrane protein that is inactivated by PTCH. The red cross represents inhibition.

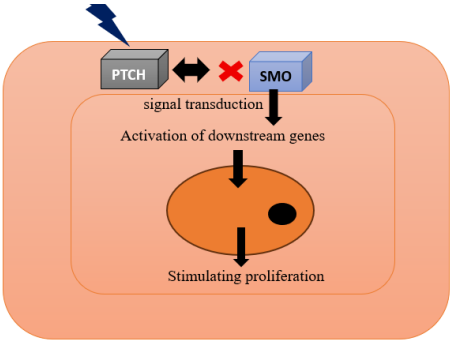

Fig. 3- Mutated PTCH or SHH binding to PTCH; this inhibitory effect is lost, and the proliferative and stimulating effects of SMO outweigh the inhibition. SHH sonic hedgehog ligand: extracellular signalling molecule that acts as a ligand for patched (PTCH). The red cross represents inhibition.

CLINICAL FEATURES:

OKCs induce bone extension due to their propensity to expand through the intramedullary region. Asymptomatic individuals can present with substantial lesions that lead to considerable erosion of the cortical plates and affect nearby structures. Unlike other odontogenic lesions that exhibit similar levels of aggressiveness, such as ameloblastomas, OKCs infrequently cause root resorption of neighbouring teeth [5].

RADIOGRAPHIC FEATURES:

Traditional radiographic techniques (OPG), computed tomography (CT), and CBCT are the most commonly used imaging methods in the examination of odontogenic keratocysts (OKCs).

Three-dimensional radiography, such as CBCT/CT, provides a wide array of lesions from multiple directions (buccal, palatal, lingual cortical plates). Radiographically, it can be unilocular or multilocular with scalloped margins. Unilocular lesions are the most common, whereas multilocular lesions occur in approximately 30% of patients, predominantly in the mandible [5].

HISTOLOGICAL FEATURES:

Histopathologically, an odontogenic keratocyst (OKC) features a cystic lumen lined with six to eight layers of corrugated para-keratinized stratified squamous epithelium of uniform thickness. The lining epithelium is marked by a basal layer of tall columnar cells arranged in a palisade formation of nuclei with reversed polarity. The interface between the epithelium and connective tissue is flat, and the connective tissue wall may include islands of odontogenic epithelium or satellite cysts [17].

In addition to these classical characteristics, there were regions of dystrophic calcification, keratin present in the cystic lumen and in satellite cysts, basal cell growths featuring mitotic

figures, and modifications resulting from inflammation, including epithelial hyperplasia, cholesterol clefts, and inflammatory cells within the connective tissue. Aspiration of cystic fluid reveals keratin flakes with protein levels >4 g/100 ml [17].

MANAGEMENT

The treatment modalities have sparked the most significant debates and controversies due to the potential for tumour recurrence. Management of OKC should focus on selecting the best modality that carries the lowest possible risk of recurrence and minimum morbidity. Management strategies for KCOT generally fall into conservative and radical approaches. Conservative methods, such as marsupialization or decompression, aim to remove the lesion while preserving the bone structure as much as possible. In contrast, more aggressive treatments include enucleation with or without curettage, often combined with additional measures like chemical or cryo-cauterization, or even resection **(Fig. 4).**

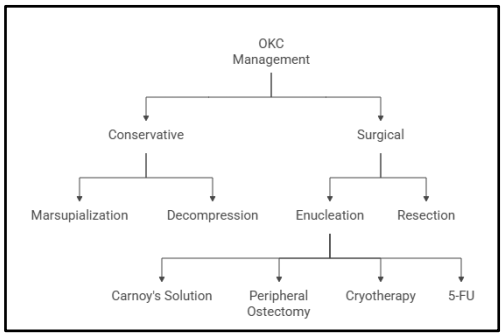

Fig. 4 -Management flowchart of OKC

MARSUPILIZATION:

In German literature, Decompression and marsupialization of cysts in the jaws were first suggested by Partsch, and this procedure is now known as the Partsch 1 procedure. At that time, this method was proposed as a definitive treatment for cysts, primarily involving the removal of the overlying epithelium and bone, along with the deroofing of the cyst [19]. This indicates the formation of a large stoma or opening that can maintain itself [20] **(Fig. 5).** Marsupialization is carried out by excising the overlying mucosa and creating a suitably sized window (at least 1 cm in diameter) into the cystic cavity, followed by suturing the cyst lining to the oral mucosa to form a pouch. Mandibular cysts are marsupialised into the oral cavity, while maxillary cysts may be marsupialised into the oral cavity, the maxillary sinus, or the nasal cavity [18-20].

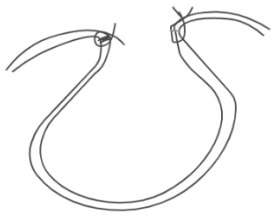

Fig. 5. Diagram showing marsupialization of cyst mucosa sutured to the oral mucosa.

Patients were advised to irrigate the cavity with normal saline twice daily to maintain cleanliness and keep the opening patent. This approach proved effective in cases involving the anterior mandible and the maxilla. However, in the posterior mandible, the cavities tended to close as the buccal mucosa grew over the cyst opening. According to Pogrel et al., the cyst resolves both clinically and radiographically within a relatively short period, with a maximum duration of 19 months.

Fate of cystic epithelium before and after marsupialization [18,21-22]

SL No	Before Marsupialization	After Marsupialization
1.	IHC showed increased levels of IL 1α (inflammatory & multifunctional cytokine)	Significantly reduced after marsupialization.
2	Positive cytokeratin-10 staining is seen.	Negative cytokeratin-10 staining - return to a more normal oral epithelium.
3	Bcl-2, an antiapoptotic protein, showed positive results in the keratocyst lining.	Bcl2 showed negative in the oral mucosa.
4	High mitotic activity	Low mitotic activity
5	A thin, fragile lining with keratinised epithelium is seen	Epithelial lining was thickened with non-keratinised stratified squamous epithelium

TABLE 1: Fate of cystic epithelium pre- and post-decompression

Indications of Marsupialisation [18,21,23]

1. In cases of large cysts, marsupialization helps decrease their size, making enucleation easier and reducing the risk of jaw fractures.
2. Marsupialization helps protect vital structures when the cyst is situated close to them
3. In medically compromised or paediatric patients, conservative therapy is safer and preferable to aggressive surgery.

4. Marsupialization helps to decrease the size of a cyst and allow for the eruption of the affected tooth.

Limitations of Marsupialisation:

1. The use of marsupialization is limited by its long healing period and the discomfort of the patient, especially at the early stages of the marsupialization.
2. In the posterior mandible, there was a tendency for the cavities to seal off due to the buccal mucosa covering the cyst opening.
3. It requires a cooperative patient who will irrigate the cyst regularly and will follow up regularly [19].

DECOMPRESSION

Decompression refers to any method used to reduce the pressure within a cyst that leads to its enlargement. This is achieved by creating an opening in the cyst wall to insert a drain, thereby keeping the cyst cavity open (Fig. 6). Decompression decreases the size of the cystic lumen. It increases the thickness of the epithelial wall, facilitating enucleation [25]. It can also be inferred that decompression can alter oxygen levels, reducing hypoxia and positively affecting the microenvironment, ultimately hindering the progression of OKCs [24].

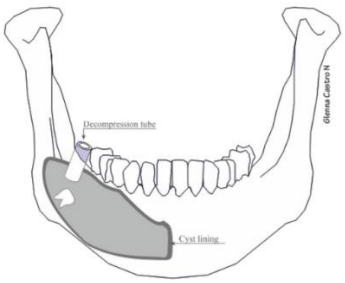

Fig.6 shows placing a tube in a cystic lesion

Tolstunov [27] proposed five ideal features for decompression devices:

1) Prevents the tube from falling into the cystic cavity
2) It should not interfere with daily mastication;
3) It can be easily fixed to the soft tissue through sutures.
4) easy to clean the cystic cavity daily by the patient or doctor
5) should not accumulate food particles over the time of its function

Different materials used for decompression of cysts: Various decompression devices and securing methods for cystic lesions in the jaw have been documented in the literature

Reference	Material	Fixation Method	Tissue
Marker et al, 1996 [28]	Polyethylene tubes	Suture	Mucosa
Enislidis et al,2004[33]	Shortened Polyethylene tubes	Suture	Mucosa
Pogrel and Jordan, 2004 Shakib et al 2010[37]	Nasopharyngeal tube	Suture	Mucosa
Tolstunov, 2008[27]	Shortened Nasal Oxygen Cannulas	Suture	Mucosa
Kolokythas et al, 2011[35]	Polyethylene intravenous tube	Ligature wire	Teeth (at CEJ)
Swantek et al, 2012[36]	Suction tubing plastic connector	Two screws, 1.2-mm suture	Bone, Mucosa
Catunda et al, 2013[34]	Luer syringe	Two self-tapping screws, 1.2- or 1.5-mm suture	Bone, Mucosa
Jung et al 2014[26]	Stainless steel tube	Suture	Adjacent teeth
Coasta et al 2014[29]	Polyethylene tube	Orthodontic ligature wire	Composite resin to the adjacent tooth
Bayar GR et al, 2015[32]	Plastic syringe	suture	mucosa
Zhu et al 2017 [30]	universal polyethylene intravenous infusion tube	Orthodontic ligature wire	brackets attached to an adjacent tooth
Kimura et al 2019[31]	Silicon tube with radio-opaque line (used in Abdominal surgeries)	0.4mm stainless steel wire	To adjacent teeth

TABLE 2: Various materials used for decompression in the literature

Many authors used polyethylene tubes, nasopharyngeal airways, silicon tubes, plastic syringes, stainless steel tubes, IV catheters, which have their own advantages and limitations [28,33,27,35,36,37,29,20,31]

ENUCLEATION: Marsupialization or Decompression alone results in a higher chance of recurrence. Parsch describes enucleation & primary closure (cystectomy) as the Parsch II procedure [18,19]. As the OKC has a thin, fragile lining, enucleation and curettage alone are reported with a recurrence rate of 62%. Adjuvant treatments like chemical cauterization, cryotherapy, peripheral ostectomy, & 5FU to minimise the recurrence rate [20].

CARNOY'S SOLUTION: Cutler and Zollinger were the first to employ Carnoy's solution as a surgical medicament in 1933. It is an effective fixative, haemostatic, and cauterization agent. It effectively removes remaining cystic lining cells by penetrating cancellous bone, with an average penetration depth of 1.54 mm after five minutes [38].

Composition of Carnoy's solution by Cutler and Zollinger [38] Numerous studies have indicated that chloroform has carcinogenic properties, leading to its elimination from Carnoy's solution, which is now referred to as modified Carnoy's solution.

SL NO	VARIENTS	COMPOSITION
1	**COMPOSITION -I** Ecker et al [40]	Ethyl alcohol 96%: 3 mL; Glacial acetic acid: 1 mL
2	**COMPOSITION -II** Madhu Laxmi et al [39]	Chloroform: 3 ML, Glacial acetic acid: 1 mL; Ethyl alcohol 96%: 6 mL
3	**COMPOSITION-III** Ecker et al [40]	Ferric chloride: 1 g, Glacial acetic acid: 1 mL, Ethyl alcohol 96%: 6 mL

TABLE 3 Different Compositions of Canoy's solutions

Effects of exposure to Carnoy's solution on the artery and vein vascular walls in rats [41]

SL NO	Time of exposure of Carnoy's solution on the blood vessel wall	Effect
1	2min	Hyalinization of the vascular wall, absence of complete Damage to the vascular wall, 5 min, absence of clot formation, 10 min
2	5min	
3	10min	Damage to the wall and irreversible vasculopathy, fibrosis, and clot formation

TABLE 4 Effects of Carnoy's solution on blood vessels.

Effects of Exposure to Carnoy's solution on the rabbit inferior alveolar nerve [42]

Sl.No	Time of exposure to Carnoy's solution on the inferior alveolar nerve	Effect
1	30s	The involved area is the external nerve sheath: epi and perineurium
2	1min	
3	2min	
4	3min	The involved area is the epineurium and perineurium, as well as the endoneurium, without damage to the nerve tissue architecture.
5	5min	Complete and irreversible damage to the nervous tissue architecture
6	10min	

TABLE 5 Effects of Carnoy's solution on Nerves

PERIPHERAL OSTECTOMY. It is defined as mechanically removing a thin layer (typically 1.5–2 mm) of peripheral bone at the margins of the cyst cavity using a rotary instrument after enucleation. The main goal is to eliminate the epithelial remnants and satellite cysts that may be present in the adjacent bone, which are frequent sources of recurrence in OKC [48].

CRYOTHERAPY: Robert Boyle is credited with reporting, more than 300 years ago, that freezing could be used to destroy cells. Since that time, cryosurgery has been widely used for various types of pathological lesions. Cryosurgery involves more than just freezing the tissue. Cryosurgery aims to kill and destroy the cells. This surgical procedure relies on controlled freezing and thawing to achieve various cryobiological effects [44].

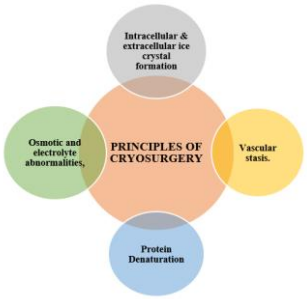

Fig 7 Principles of cryosurgery

Principles of cryosurgery: Cryosurgery induces cell and tissue death by several mechanisms,

1) Intracellular & extracellular ice crystal formation, Osmotic and electrolyte abnormalities, Protein denaturation, and Vascular stasis.

The precise temperature required to kill mammalian cells effectively is a source of debate. Tissues freeze at around -2.2°C, while temperatures below -20°C are thought to trigger cell death constantly [44].

RESPONSE OF ORAL TISSUES TO CRYOTHERAPY

ORAL MUCOSA: When liquid nitrogen comes into contact with any oral mucosa, it becomes necrotic. After 12-24 hours, tissues become discoloured and edematous. Within 72 hours, the oral mucosa undergoes necrosis and ulceration, resulting in the formation of a pseudo

membrane and subsequent healing. After 12 days, there was no sign of a pseudo-membrane, and by 16 days, complete re-epithelialization had occurred [42].

BONE: Cellular elements within the bone undergo necrosis by 48-72 hours. The osseous structure remains intact, and within two to three weeks, cellular elements repopulate the bone. Wound dehiscence exposes devitalized bone to the oral cavity, leading to the development of superficial sequestra [44]. Many authors stated that cryotherapy weakens the bone, leading to a pathological fracture. Fisher et al studied the effect of cryosurgery on bone strength in rat mandibles. The authors observed a substantial decrease in mechanical strength after eight weeks of cryosurgery. Surgeons at the University of California, San Francisco, use bone grafts following cryotherapy for most lesions, regardless of size. They suggest a soft diet for eight to ten weeks. Pogrel et al, who found that liquid nitrogen spray produced a mean depth of bone necrosis of 0.82 mm in the mandible [43-44] .

TEETH: Cryotherapy has had varying effects on adult human teeth, including persistent inflammation and spontaneous healing. In 1995, Pogrel studied the use of liquid nitrogen cryotherapy in 48 patients with advanced bone lesions over 11 years. The study involved 14 teeth in the area treated with liquid nitrogen cryotherapy. Only two teeth regained vitality after electrical pulp testing, indicating that cryotherapy may cause degenerative pulpal changes. Root canal therapy is recommended preoperatively before application of cryotherapy [44].

INFERIOR ALVEOLAR NERVE: Animal studies revealed that cellular damage is evident within the first 24 hours. Nerve revitalization occurred around 12 days following injury, with the sheath's connective tissue forming a collagenous tube. Normal nerve architecture had been restored within 25-30 days. Schmidt and Pogrel observed that the average period for sensation return or improvement was 91 days (range, 6-235 days), with an average follow-up period of 2.6 years.

The cryotherapy treatment involves quickly freezing tissues with liquid nitrogen spraying for 1 minute to maximize ice crystal formation, followed by a gradual thaw of 5 minutes to minimize electrolyte imbalance. This process is repeated two or three times to optimize the lethal effects on cells. The rationale for the use of cryotherapy to manage OKC is that liquid

nitrogen can destroy epithelial remnants or satellite cysts while leaving the inorganic bone matrix intact as a scaffolding for osteogenesis [44,45]

Carnoy's solution has the same rationale as cryosurgery. Both methods aim to eliminate epithelial remnants and the dental lamina within the osseous margin. Liquid nitrogen preserves bone architecture, allowing for new bone formation. Patients also reported considerable sensory return after applying liquid nitrogen to the inferior alveolar nerve [44]. Some surgeons have tried using different refrigerants, such as a mixture of propane, butane, and isobutene, which is used in endodontic testing, as a substitute for liquid nitrogen. According to reports, this mixture can reach a temperature of -50 °C, which is more than sufficient to kill cells [45].

5-FLOROURACIL (5-FU):

Nowadays, a targeted strategy based on the molecular understanding of the OKC has led to the use of 5-fluorouracil. Like BCCs, OKCs are known to arise from mutations in the PTCH gene. Smoothened (SMO) activation and Sonic Hedgehog (SHH) signalling are caused by mutations in PTCH1, which lead to tumour growth [47]. This suggests that antagonism of the SHH signaling pathway may be an effective strategy for molecularly targeting OKCs through SMO inhibition and reduction of SHH transcription factors [46].

5-FU is an antimetabolite that has been widely used as a chemotherapeutic agent for various neoplasms. It targets the DNA synthesis in rapidly growing cells, triggering cell apoptosis [48]. Ledderhof et al. introduced 5-FU as an adjuvant therapy in the management of OKC [46]. 5-FU is converted to fluorodeoxyuridine by thymidine phosphorylase (TP), which initiates the cytotoxic action of 5-FU. Thymidine kinase transforms fluorodeoxyuridine to fluorodeoxyuridine monophosphate, an active metabolite of 5-FU that inhibits thymidylate synthase **(Fig.10).**

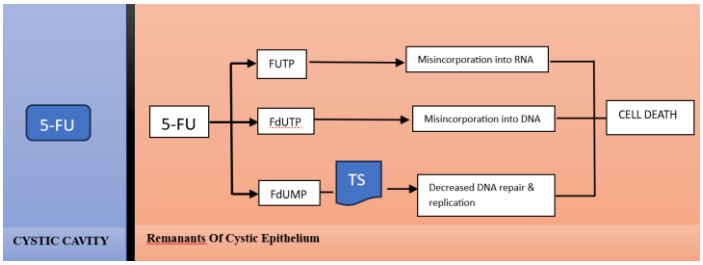

Fig 10-Mechanism of 5-FU on cystic epithelium

After the enucleation and peripheral ostectomy, a sterile radiopaque quarter-inch ribbon gauze, coated with 5% 5-FU cream, was packed into the surgical wound. The wound was subsequently closed using the standard technique, with a small distal portion (about 1 cm) of gauze left exposed for removal 24 hours after the operation [46]. According to Caminiti et al, 5-FU is effective at reducing the recurrence rate of OKCs when applied topically. Topical 5-FU may be an effective alternative for treating OKCs, especially when compared to the high recurrence rates associated with MCS, which can reach up to 35%. 5-FU may be more ideal due to its ready availability, technical ease, shorter operating time, and reduced morbidity compared to MCS [47].

RESECTION: Resection can be segmental or marginal, and is commonly performed on the mandible. Segmental resection removes a portion of bone, resulting in loss of continuity, while marginal resection preserves the inferior or posterior borders, maintaining continuity of the mandible [53]. Resection is an aggressive approach that may minimize the chance of recurrence; however, the management of OKC by radical resection remains highly controversial in the literature. Jackson et al. suggested radical resection as the preferred treatment for OKC lesions with soft-tissue involvement. According to a comprehensive study and meta-analysis by Al-Moraissi et al, resections should only be used for multiple recurring lesions or syndromic conditions.

INDICATIONS FOR RADICAL RESECTION [50]

1. Aggressive primary OKC affecting the mandible's basal bone with less than 1 cm of normal bone.
2. OKC involving the maxillary sinus, with bony perforation and affecting the pterygoid musculature or skull base.
3. Large cysts (>5cm) with multilocular, i.e., involving the mandibular posterior region
4. Multiple recurrent OKCs with or without cortical perforation, with previous procedures that failed to manage the disease.
5. Malignant transformation of the lesion.

According to clinical guidelines given by Bushabu, et al, Smaller OKCs (size <5 cm) can be managed with simple enucleation/curettage with adjuvant therapies (chemical cautery, peripheral ostectomy, cryotherapy 5-FU etc.) and with multilocular, larger OKC with or without cortical perforation, primary, that extends beyond the inferior border of the

mandible or into pterygoid muscles and malignant transformation [50]. Despite its success in lowering recurrence rates, resection should not be the first-line treatment in non-syndromic patients [55].

REASONS FOR RECURRENCE

1. Thin and fragile epithelial lining
2. Presence of satellite cysts/daughter cysts
3. Incomplete removal of lining
4. Epithelial rests/microcysts are often present in the overlying oral mucosa
5. High mitotic activity

The molecular and genetic alterations associated with KCOTs may predict individual biological behaviour[51]. Vered et al. suggest that the immunological profile of Sonic hedgehog (SHH)-related proteins and the SHH-induced bcl-2 oncoprotein can determine an individual's KCOT phenotype and biological behaviour. In 2009, Pan and Li observed that KCOTs with PTCH1-truncation mutations exhibited increased Ki-67 labelling and proliferative activity, possibly indicating a higher recurrence potential [51].

Stoelinga observed a high concentration of OKCs in the retromolar/ramus area. He discovered epithelial islands in the mucosa of 50% of the OKCs in the area. The author suggests that recurring keratocysts in this area could be caused by epithelial islands in the mucosa or remains of the original cyst lining. Stoelinga's protocol involved removing the cyst from the mucosa and using Carnoy's solution. If there were lingual perforations, electrocautery was recommended to remove epithelial remains and prevent soft tissue recurrence [2].

RECURRENCE RATES OF OKCs IN THE LITERATURE

Blanas N et al [58].	**Kaczmarzyk et al** [53].	**Nigel R. Johnson et al** [54].	**Al Morraissi et al** [55].	**Lebedev et al** [38].	**Al Morraissi et al** [56].
Oral Surgery, Oral Medicine, Oral Pathology,	International Journal of Oral &	Oral Surgery, Oral	Journal Of Cranio-	Moscow University	International Journal of Oral &

Oral Radiology, And Endodontology, 2000	Maxillofacial Surgery 2012	Medicine, Oral Radiology, Oral Pathology Journal Systematic Review 2012	Maxillofacial Surgery- A Systematic Review & Meta-Analysis 2016	Biological Science Bulletin 2019	Maxillofacial Surgery A Meta-Analysis 2023
MARSUPULISATION- 24.8%	MARSUPULISATION- 40%	MARSUPULISATION + ADJUVANT MEASURES 15.8%	MARSUPULISATION32.3%	MARSUPULISATION ALONE 24.8%	MARSUPULISATION ALONE 19.6%
ENUCLEATION- 17-56%	ENUCLEATION- 26.09%	ENUCLEATION 25.6%	ENUCLEATION- 23.1%	ENUCLEATION- 23.3%	MARSUPULISATION+2E+PO 15.5%
DECOMPRESSION/ CARNOYS SOLUTION- 1- 8.7%	ENUCLEATION +CS 50%	ENUCLEATION +CS 7.9%	ENUCLEATION+ LIQUID N2- 14.5%	ENUCLEATION+ LIQUID N2- 23.1%	ENUCLEATION ALONE 22.1%
	ENUCLEATION + PERIPHERAL OSTECTOMY- 18.18%	ENUCLEATION+ ADJUVANT MEASURES	ENUCLEATION+ CURETTAGE- 17.4%	ENUCLEATION + PO 20%	ENUCLEATION +PO/CURETTAGE 14.3%

	ENUCLEATION +PO +CS -0%	(OTHER THAN CARNOYS) 30.3%	DECOMPRESSION+ CYSTECTOMY-14.4%	MARSUPULISATION+ ENUCLEATION- 14.7%	ENUCLEATION +PO+CS 8.8%
	RESECTION-	RESECTION-	ENUCLEATION+CS 11.5%	ENUCLEATION+CS 6.6%	ENUCLEATION+PO+ MCS 24.7%
RESECTION- 0 %	0%	6.3%	SEGMENTAL RESECTION- 8.4%	MARGINAL/ SEGMENTAL RESECTION 2.5%	ENUCLEATION+PO+ 5-FU 0 %
	OVERALL RECURRENCE 23.15%		OVERALL RECURRENCE 16.6%		ENUCLEATION+ CRYOTHERAPY 22.1%
					RESECTION 2.3%

TABLE 6: Recurrence rates of OKC With Different Treatment Modalities In Literature

ABBREVIATIONS: Peripheral Ostectomy (PO), Carnoys Solution (CS), Secondary enucleation (2E)

CONCLUSION:

In conclusion, the odontogenic keratocyst remains one of the most significant and challenging lesions in the maxillofacial region due to its unique biological behaviour, high recurrence potential, and association with syndromic conditions. A thorough understanding of its histopathology, clinical presentation, and radiographic features is essential for accurate diagnosis and tailored treatment planning. While conservative approaches aim to preserve surrounding structures, more aggressive methods may be necessary in cases of recurrence or extensive damage. With the aid of modern imaging, adjunctive therapies, and long-term follow-up, clinicians can achieve improved outcomes and minimize the recurrence of disease.

Ultimately, successful management of OKC requires a balance between eliminating pathology and maintaining function, underscoring the importance of individualized, evidence-based care.

REFERENCES

1) Dioguardi, M., Quarta, C., Sovereto, D. *et al.* Factors and management techniques in odontogenic keratocysts: a systematic review. *Eur J Med Res* **29**, 287 (2024). https://doi.org/10.1186/s40001-024-01854-z

2) Stoelinga PJ. Long-term follow-up on keratocysts treated according to a defined protocol. Int J Oral Maxillofac Surg. 2001;30:14–25. https:// doi.org/ 10. 1054/ ijom. 2000. 0027.

3) August M, Faquin WC, Troulis MJ, Kaban LB. Dedifferentiation of odontogenic keratocyst epithelium after cyst decompression. J Oral Maxillofac Surg. 2003 Jun;61(6):678-83; discussion 683-4. doi: 10.1053/joms.2003.50137

4) Soluk-Tekkeşin M, Wright JM. The World Health Organization Classification of Odontogenic Lesions: A Summary of the Changes of the 2017 (4th) Edition. Turk Patoloji Derg. 2018;34(1). doi: 10.5146/tjpath.2017.01410.

5) Sharma S, Kamarthi N, Malik S, Goel S, Gupta S, Sharma A. OKC- an update on etiopathogenesis, clinical & radiological features [Internet]. J Oral Med Oral Surg Oral Pathol Oral Radiol. 2022 [cited 2025 Sep 09];8(2):55-60. Available from: https://doi.org/10.18231/j.jooo.2022.012

6) Soluk-Tekkesin M, Wright JM. The World Health Organization classification of odontogenic lesions: A summary of the changes of the 2022 (5th) edition Turk Patoloji Derg. 2022;38:168–84

7) Stoelinga PJW, Peters JH (1973) A note on the origin of keratocysts of the jaws. Int J Oral Surg 2:37

8) Stoelinga PJW (1976) Studies on the dental lamina as related to its role in the aetiology of cysts and tumours. J Oral Pathol 5:65

9) Toller P. Origin and growth of cysts of the jaws. Ann R Coll Surg Engl. 1967;40(5):30636.

10) Ahlfors E, Larsson A, Sjogren S. The odontogenic keratocyst: a benign cystic tumor? J Oral Maxillofac Surg. 1984;42(1):10–9

11) Lia RF, Chena G, Zhaoa Y, Zhaoa YF, Liua B. Increased expression of autophagy-related proteins in keratocystic odontogenic tumors: its possible association with growth potential. Br J Oral Maxillofac Surg. 2014;52(6):551–6

12) M. Michael; Jr. Cohen. (1999). Nevoid basal cell carcinoma syndrome: molecular biology and new hypotheses. , 28(3), 216–223.

13). GAILANI MR, BALE AE. Review. Developmental genes and cancer: role of Patched in basal cell carcinoma of the skin. J Natl Cancer Inst 1997: 89: 1103– 7

14)LAVENAT S, GORLIN RJ, FALLET S, et al. A two-hit model for developmental defects in Gorlin syndrome. Nat Genet 1996: 12: 85–7

15) Menon S. Keratocystic Odontogenic Tumours: Etiology, Pathogenesis and Treatment Revisited. J Maxillofac Oral Surg. 2015 Sep;14(3):541-7. doi: 10.1007/s12663-014-0734-5

16) Ravi J, Wadhwan V, Gotur SP. Orthokeratinized versus parakeratinized odontogenic keratocyst: Our institutional experience. J Oral Maxillofac Pathol. 2022 Jan-Mar;26(1):60-64. doi: 10.4103/jomfp.jomfp_498_20

17) Athira C P, Niveditha, Sundaram I T S, Thampy LM, Sadasivan S, Raj S. Odontogenic Keratocyst with Diverse Histopathological Features. Oral Maxillofac Pathol J 2023; 14(2)

18) Pogrel MA, Jordan RC. Marsupialization as a definitive treatment for the odontogenic keratocyst. J Oral Maxillofac Surg. 2004 Jun;62(6):651-5; discussion 655-6. doi: 10.1016/j.joms.2003.08.029. Erratum in: J Oral Maxillofac Surg. 2007 Feb;65(2):362-3.

19) Pogrel MA. Decompression and marsupialization as a treatment for the odontogenic keratocyst. Oral Maxillofac Surg Clin North Am. 2003 Aug;15(3):415-27.

20) Bhargava D, Deshpande A, Pogrel MA. Keratocystic odontogenic tumour (KCOT)--a cyst to a tumour. Oral Maxillofac Surg. 2012 Jun;16(2):163-70

21) Rahpeyma A, Khajehahmadi S. Marsupialization for treatment of jaw cysts: indications and limitations. Journal of International Oral Health. 2016 Feb 1;8(2):158-62.

22) Ninomiya T, Kubota Y, Koji T, Shirasuna K. Marsupialization inhibits interleukin-1alpha expression and epithelial cell proliferation in odontogenic keratocysts. J Oral Pathol Med. 2002;31:526-33

23) Briki S, Elleuch W, Karray F, Abdelmoula M, Tanoubi I. Cysts and tumors of the jaws treated by marsupialization: A description of 4 clinical cases. J Clin Exp Dent. 2019;11(6):e565-9

24) Muret M, Malthiéry E, Casenave T, Costes-Martineau V, Torres JH. Decompression: a first-intention treatment for “large” non-syndromic odontogenic keratocysts. Journal of Oral Medicine and Oral Surgery. 2021;27(2):29.

25) Oh J-S, You J-S, Kim S-G. Clinical and histomorphometric evaluation of decompression followed by enucleation in the treatment of odontogenic keratocyst. J Dent Sci. 2018;13:329–333.

26) Jung EJ, Baek JA, Leem DH. Decompression Device Using a Stainless Steel Tube and Wire for Treatment of Odontogenic Cystic Lesions: A Technical Report. Maxillofacial Plastic and Reconstructive Surgery. 2014 Nov 12;36(6):308.

27) Tolstunov L. Marsupialization catheter. J Oral Maxillofac Surg 2008;66:1077-9.

28) Marker P, Brøndum N, Pr P, Bastian HL. Treatment of large odontogenic keratocysts by decompression and later cystectomy: a long-term follow-up and a histologic study of 23 cases. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 1996 Aug 1;82(2):122-31.

29) Costa FW, Carvalho FS, Chaves FN, Soares EC. A suitable device for cystic lesions close to the tooth-bearing areas of the jaws. Journal of Oral and Maxillofacial Surgery. 2014 Jan 1;72(1):96-8.

30) Zhu F, Huang S, Chen Z, Li W, Zhang D. New method to secure cyst decompression tube in tooth-bearing areas. British Journal of Oral and Maxillofacial Surgery. 2017 Feb 1;55(2):200-1.

31) M. Kimura, K. Ishibashi, A. Shibata et al.. A new decompression device for treating odontogenic cysts using a silicone tube. *Br J Oral Maxillofac Surg* (2019),

32) Bayar GR. Using a plastic dental syringe for decompression and marsupialization of jaw cysts: A technical note. Journal of Dental Sciences. 2015;1(10):109-10.

33) Enislidis G, Fock N, Sulzbacher I, et al: Conservative treatment of large cystic lesions of the mandible: A prospective study of the effect of decompression. Br J Oral Maxillofac Surg 42:546, 2004

34) Catunda IS, Catunda RB, Vasconcelos BC, et al: Decompression device for cavitary bone lesions using Luer syringe. J Oral Maxillofac Surg 71:723, 2012

35) Kolokythas A, Schlieve T, Miloro M. Simple method for securing a decom-pression tube for odontogenic cysts and tumors: a technical note. *J OralMaxillofac Surg* 2011;**69**:2392–5.

36) Swantek JJ, Reyes MI, Grannum RI, et al. A technique for long term decom-pression of large mandibular cysts. *J Oral Maxillofac Surg* 2012;**70**:856–9.4.

37) Shakib K, Heliotis M, Gilhooly M. The nasopharyngeal airway: reliable and effective tool for marsupialisation. British Journal of Oral and Maxillofacial Surgery. 2010 Jul 1;48(5):386-7.

38) Lebedev VV, Butsan SB. The use of Carnoy's solution and its modifications for reducing the number of recurrences after surgical removal of keratocystic odontogenic tumors and ameloblastomas: a systematic review. Moscow University Biological Sciences Bulletin. 2019 Apr;74(2):108-16.

39) Madhulaxmi, M. and Abdul Wahab, P.U., Carnoys solution as a surgical medicament in the treatment of KCOT, *Int. J. Pharma Bio Sci.,* 2014, vol. 5, no. 1,pp. 492–495.

40). Ecker, J., ter Horst, R., and Koslovsky, D., Current role of Carnoy's solution in treating keratocystic odontogenic tumors, *J. Oral Maxillofac. Surg.,* 2016, vol. 74,no. 2, pp. 278–282.

41) Saulacic, N., Stajcic, Z., Stajcic, L.S., Piattelli, A.,Iizuka, T., and Lombardi, T., Effects of Carnoy's solution on blood vessels of the axillary fossa of rats, *Int. J. Oral Maxillofac. Surg.,* 2009, vol. 38, no. 8, pp. 876– 879.

41. Frerich, B., Cornelius, C.P., and Wietholter, H., Critical time of exposure of the rabbit inferior alveolar nerve to Carnoy's solution, *J. Oral Maxillofac. Surg.,* 1994, vol. 52, no. 6, pp. 599–606.

42) Poswillo DE. A comparative study of the effects of electrosurgery and cryosurgery in the management of benign oral lesions. Br J Oral Surg 1971;9(1):1–7.

43) Schmidt BL, Pogrel MA. The use of enucleation and liquid nitrogen cryotherapy in the management of odontogenic keratocysts. J Oral Maxillofac Surg 2001; 59(7):720– 5.

44) Schmidt BL. The use of liquid nitrogen cryotherapy in the management of the odontogenic keratocyst. Oral and Maxillofacial Surgery Clinics. 2003 Aug 1;15(3):393-405.

45) de Souza Cruz EL, da Silva Tabosa AK, Falcao AS, et al. Use of refrigerant spray of a propane/butane/isobutane gas mixture in the management of keratocystic odontogenic tumors: a preliminary study. Oral Maxillofac Surg 2017;21:21–6.

46) Ledderhof NJ, Caminiti MF, Bradley G, Lam DK, Topical 5-Fluorouracil is a Novel Targeted Therapy for the Keratocystic Odontogenic Tumor, *Journal of Oral and Maxillofacial Surgery* (2016).

47) Caminiti MF, El-Rabbany M, Jeon J, Bradley G. 5-Fluorouracil is associated with a decreased recurrence risk in odontogenic keratocyst management: a retrospective cohort study. Journal of Oral and Maxillofacial Surgery. 2021 Apr 1;79(4):814-21.

48) Singh AK, Khanal N, Chaulagain R, Bhujel N, Singh RP. How effective is 5-Fluorouracil as an adjuvant in the management of odontogenic keratocyst? A systematic review and meta-analysis. British Journal of Oral and Maxillofacial Surgery. 2022 Jul 1;60(6):746-54.

49) Khalil A, Albash Z, Sleman N, Sayegh W. Marsupialization and peripheral ostectomy for the management of large odontogenic keratocyst: a case report. Journal of surgical case reports. 2023 Mar;2023(3):rjad119.

50) Bushabu FN, Titinchi F, Bing L, Davda L. Clinical indications for radical resection of odontogenic keratocyst: A systematic review. Natl J Maxillofac Surg. 2023 May-Aug;14(2):177-184. doi: 10.4103/njms.njms_90_22. Epub 2023 Jul 13. PMID: 37661990; PMCID: PMC10474539.

51) Warburton G, Shihabi A, Ord RA. Keratocystic odontogenic tumor (KCOT/OKC)—clinical guidelines for resection. Journal of maxillofacial and oral surgery. 2015 Sep;14(3):558-64.

52) Moellmann HL, Parviz A, Goldmann-Kirn M, Rana M, Rana M. Comparison of five different treatment approaches of mandibular keratocystic odontogenic keratocyst (OKC): a retrospective recurrence analysis of clinical and radiographic parameters. Journal of Maxillofacial and Oral Surgery. 2024 Feb;23(1):145-51.

53) Kaczmarzyk T, Mojsa I, Stypulkowska J. A systematic review of the recurrence rate for keratocystic odontogenic tumour in relation to treatment modalities. International journal of oral and maxillofacial surgery. 2012 Jun 1;41(6):756-67.

54) Johnson NR, Batstone MD, Savage NW. Management and recurrence of keratocystic odontogenic tumor: a systematic review. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2013 Oct 1;116(4):e271-6.

55) Al-Moraissi EA, Dahan AA, Alwadeai MS, Oginni FO, Al-Jamali JM, Alkhutari AS, Al-Tairi NH, Almaweri AA, Al-Sanabani JS. What surgical treatment has the lowest recurrence rate following the management of keratocystic odontogenic tumor?: A large systematic review and meta-analysis. Journal of Cranio-Maxillofacial Surgery. 2017 Jan 1;45(1):131-44.

56) Al-Moraissi EA, Kaur A, Gomez RS, Ellis III E. Effectiveness of different treatments for odontogenic keratocyst: a network meta-analysis. International Journal of Oral and Maxillofacial Surgery. 2023 Jan 1;52(1):32-43.

57) CP A, TS IS, Thampy LM, Sadasivan S, Raj S. Odontogenic Keratocyst with Diverse Histopathological Features. Oral & Maxillofacial Pathology Journal. 2023 Jul 1;14(2).

58) Blanas N, Freund B, Schwartz M, Furst IM. Systematic review of the treatment and prognosis of the odontogenic keratocyst. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2000 Nov 1;90(5):553-8.