

ODONTOGENIC KERATOCYST: A COMPREHENSIVE REVIEW

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Abstract

Odontogenic keratocyst (OKC) is a distinctive developmental odontogenic cyst characterized by a unique parakeratinized epithelial lining, considerable proliferative potential, locally aggressive behavior, and a clinically significant tendency for recurrence. First described by Philipsen in 1956, OKC has generated considerable controversy regarding its biological nature because of its characteristic histopathology, molecular alterations, aggressive growth pattern, and association with nevoid basal cell carcinoma syndrome (NBCCS). The 2005 World Health Organization (WHO) classification temporarily designated the lesion as a keratocystic odontogenic tumor; however, subsequent evidence and the 2017 WHO classification returned to the term odontogenic keratocyst and recognized it as an odontogenic cyst. [1,2] Molecular studies have demonstrated alterations involving the Sonic Hedgehog signaling pathway, particularly the PTCH1 gene, providing important insights into the biological behavior of the lesion. [3,4] Clinically, OKCs most commonly involve the posterior mandible and ascending ramus and may remain asymptomatic despite extensive intraosseous growth. Radiographically, they generally appear as well-defined unilocular or multilocular radiolucencies and may mimic dentigerous cysts and ameloblastomas. [5,6] Histopathologically, the classic lesion demonstrates a thin and relatively uniform parakeratinized stratified squamous epithelial lining with a corrugated luminal surface and palisaded hyperchromatic basal cells. [2,7] Treatment ranges from conservative approaches such as decompression and marsupialization to enucleation with adjunctive procedures and, in selected aggressive or recurrent lesions, surgical resection. Long-term surveillance is essential because recurrence may occur several years after treatment. [8–10]

Keywords: Odontogenic keratocyst; parakeratinized epithelium; PTCH1; Sonic Hedgehog pathway; histopathology; recurrence; Carnoy's solution; decompression; odontogenic cyst.

Introduction

Odontogenic keratocyst is one of the most distinctive developmental cysts encountered in the jaws and remains an important lesion in oral and maxillofacial pathology because of its characteristic histopathological appearance and locally aggressive biological behavior. The lesion was first

described by Philipsen in 1956 and subsequently became the subject of extensive clinical, radiographic, histopathological, molecular, and therapeutic investigations. [1,5] Unlike many other odontogenic cysts, OKC may grow extensively within cancellous bone while producing comparatively limited buccolingual expansion. This characteristic growth pattern allows lesions to attain considerable dimensions before producing obvious clinical manifestations. Consequently, many OKCs are discovered incidentally during routine radiographic examinations. [5,6]

The biological nature of OKC has been debated for several decades. The 2005 WHO classification introduced the term “keratocystic odontogenic tumor” and classified the lesion as a benign odontogenic tumor because of its aggressive growth, high recurrence potential, epithelial proliferative activity, and molecular alterations. [11] However, subsequent studies questioned whether these findings were sufficient to establish all OKCs as true neoplasms. The 2017 WHO classification therefore reinstated the term odontogenic keratocyst and placed it among odontogenic cysts. [2] This classification history emphasizes the complex biological behavior of OKC and the importance of integrating clinical, radiographic, histopathological, and molecular findings.

Etiology and Origin

The precise origin of odontogenic keratocyst has not been completely established; however, the lesion is generally considered to arise from remnants of the dental lamina or other odontogenic epithelial remnants within the jaws. [2,7] During normal odontogenesis, remnants of the dental lamina may persist within the developing jaw and subsequently undergo proliferation and cystic transformation. These epithelial remnants provide a plausible cellular source for the development of OKC.

Two broad biological settings are recognized. Sporadic OKCs account for the majority of lesions and occur without an identifiable inherited syndrome, whereas syndromic OKCs occur particularly in individuals with NBCCS. In syndromic cases, multiple and recurrent OKCs are strongly associated with germline abnormalities involving PTCH1. [3,4,13] Although inflammation can significantly modify the microscopic appearance of an existing OKC, it is not considered the primary etiological mechanism of the typical lesion. [7]

Molecular Pathogenesis

One of the most important advances in understanding OKC has been the recognition of abnormalities involving the Sonic Hedgehog signaling pathway. The PTCH1 gene encodes the Patched-1 receptor, an important regulator of Hedgehog signaling. Under physiological conditions, PTCH1 suppresses Smoothened (SMO) signaling in the absence of Hedgehog ligand. Activation of the pathway results in downstream signaling through GLI transcription factors and regulation of genes involved in cellular proliferation, differentiation, and survival. [3,4]

Loss-of-function alterations involving PTCH1 may result in inappropriate activation of Hedgehog signaling. Somatic PTCH1 mutations have been identified in a subset of sporadic OKCs, while germline PTCH1 abnormalities are characteristic of many patients with NBCCS. [3,4,13] Barreto et al. demonstrated PTCH mutations in sporadic as well as NBCCS-associated OKCs, supporting a role for PTCH abnormalities in the pathogenesis of at least a subset of these lesions. [3]

Further molecular studies have identified alterations involving PTCH1 and SMO and have investigated the potential therapeutic relevance of Hedgehog pathway inhibition. [4,14] However, these genetic alterations are not currently considered diagnostic in isolation. The diagnosis of OKC remains primarily morphological, with molecular findings providing important biological and pathogenetic support. [2,15]

Epidemiology

Odontogenic keratocyst can occur over a wide age range but is particularly common among young and middle-aged adults. Several large clinical series have demonstrated a peak incidence during the second and third decades of life, with additional cases occurring in later decades. [5,12] A slight male predilection has been reported in several populations, although the magnitude varies among individual studies.

The mandible is considerably more commonly affected than the maxilla, with a marked preference for the posterior body, angle, and ascending ramus. Maxillary OKCs occur less frequently but may be clinically significant because of the close anatomical relationships of the maxilla with the maxillary sinus, nasal cavity, orbit, and skull base. [5,6] The reported proportion of OKCs among odontogenic cysts varies considerably between studies because of differences in population characteristics, geographical distribution, diagnostic criteria, and historical classification systems. [6,12]

Clinical Features & Radiographic

OKCs are frequently asymptomatic during their early stages and are often discovered incidentally on panoramic radiographs obtained for unrelated dental conditions. Their ability to extend extensively through cancellous bone with relatively limited cortical expansion permits lesions to reach considerable dimensions before becoming clinically apparent. [5,6]

When symptoms occur, they may include painless or painful swelling, cortical expansion, secondary infection, drainage, tooth displacement, tooth mobility, delayed eruption, trismus, and, rarely, pathological fracture. Neurological manifestations such as paresthesia may occur when the lesion involves or compresses the inferior alveolar nerve. [5,7] Mandibular OKCs may extend along the posterior body and ramus, whereas maxillary lesions can involve the maxillary sinus, nasal cavity, orbit, or other adjacent anatomical spaces.

Radiographically, OKCs usually appear as well-defined radiolucent lesions with a corticated or sclerotic margin. The internal architecture may be unilocular or multilocular depending on the size and extent of the lesion. Small lesions are frequently unilocular, whereas larger lesions may demonstrate multilocularity and internal septations. Scalloped margins are also characteristic and reflect the tendency of the lesion to grow through cancellous bone. [5,6]

A proportion of OKCs are associated with impacted teeth and may closely mimic dentigerous cysts. The radiolucency may surround the crown of an unerupted tooth or extend beyond the cemento-enamel junction. Other findings include displacement of adjacent teeth, cortical thinning, cortical perforation, displacement of the inferior alveolar canal, and extension into adjacent anatomical spaces. [5,6] Because of the considerable radiographic overlap with other odontogenic lesions, radiographic appearance alone is insufficient for definitive diagnosis.

Histopathological Features

Histopathological examination remains the cornerstone of definitive diagnosis. The classic OKC demonstrates a thin, relatively uniform stratified squamous epithelial lining, commonly approximately 5–8 cell layers thick. The luminal surface is characteristically parakeratinized and exhibits a corrugated or wavy appearance. The basal cell layer is composed of cuboidal or

columnar cells that frequently show hyperchromatic nuclei and a characteristic palisaded arrangement. [2,7,15]

The basal cells are generally oriented perpendicular to the basement membrane and produce the classical “picket-fence” or “tombstone” appearance. The epithelial-connective tissue interface is generally relatively flat, with minimal development of rete ridges in the classic lesion. The combination of a thin parakeratinized epithelium, corrugated surface, and palisaded basal cells represents one of the most characteristic microscopic patterns of OKC. [7,15]

The connective tissue wall is composed predominantly of fibrous tissue and may contain odontogenic epithelial remnants, small daughter cysts, or epithelial islands. In an uncomplicated lesion, the cyst wall may demonstrate little or no inflammatory infiltrate. The epithelial lining is often delicate and friable and may become detached from the connective tissue wall during surgical manipulation or tissue processing. [7]

Satellite or daughter cysts may occur within the fibrous wall and are particularly important in syndromic lesions. These microscopic cystic structures may remain following enucleation and subsequently contribute to recurrence. Epithelial budding and small epithelial islands may also be identified and have been investigated as possible indicators of increased proliferative activity and recurrence risk. [7,12,16]

Inflammation can substantially alter the classic histological appearance. An inflamed OKC may demonstrate epithelial hyperplasia, increased epithelial thickness, loss of the characteristic corrugated surface, irregular epithelial-connective tissue interfaces, and formation of rete ridges. [7] Consequently, diagnosis may become difficult in extensively inflamed or fragmented specimens, and adequate sampling with clinicoradiographic correlation is essential.

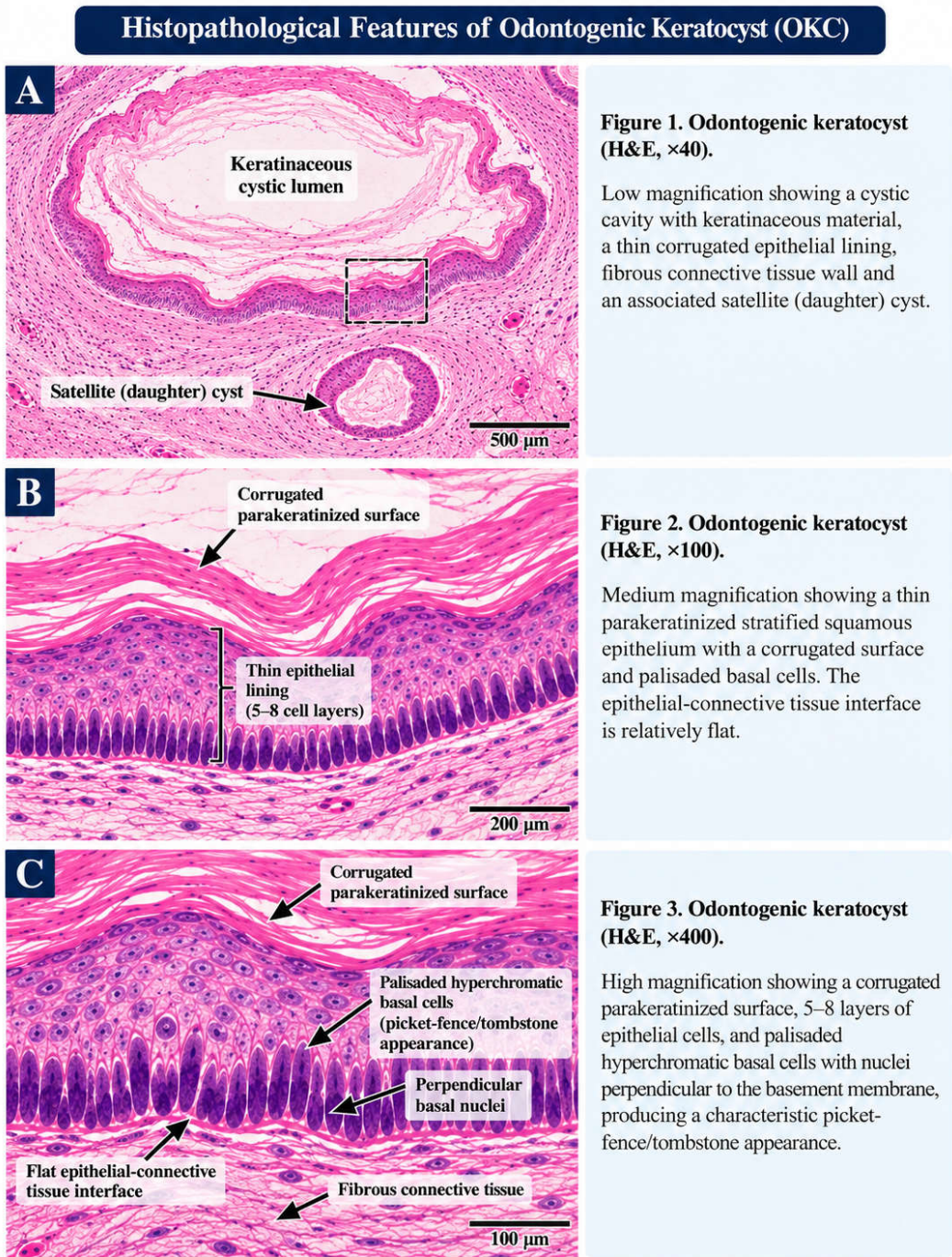
Figure 1. Low-magnification histopathology

Figure 1. Odontogenic keratocyst at low magnification (H&E). The section demonstrates a cystic cavity containing abundant keratinaceous material, surrounded by a thin parakeratinized epithelial lining and fibrous connective tissue wall. A satellite/daughter cyst is also demonstrated within the cyst wall.

Figure 2. Intermediate-magnification histopathology

Figure 2. Odontogenic keratocyst at intermediate magnification (H&E). The epithelial lining demonstrates a characteristic corrugated parakeratinized surface, a thin stratified squamous epithelial layer measuring approximately 5–8 cells in thickness, and palisaded hyperchromatic basal cells. The epithelial-connective tissue interface remains relatively flat.**Figure 3. High-magnification histopathology**

Figure 3. Odontogenic keratocyst at high magnification (H&E). High-power examination demonstrates the corrugated parakeratinized surface and prominent palisading of hyperchromatic basal cells with nuclei oriented perpendicular to the basement membrane, producing the characteristic picket-fence/tombstone appearance.



Immunohistochemistry

Although routine hematoxylin and eosin staining is generally sufficient for diagnosis, immunohistochemical investigations have contributed substantially to understanding the biological behavior of OKC. Ki-67 expression demonstrates proliferative activity within the epithelial lining and has been investigated as a marker of epithelial turnover. Bcl-2 expression has also been reported in the basal epithelial layer, while cytokeratin profiles have been studied in relation to epithelial differentiation. [15,17]

PTCH-related immunohistochemical and molecular investigations have provided further evidence for the involvement of Hedgehog signaling in OKC. Barreto et al. demonstrated PTCH mutations in OKCs, while subsequent investigations demonstrated PTCH protein expression in odontogenic lesions. [3,18] Nevertheless, immunohistochemistry should be interpreted as supportive evidence rather than as a replacement for conventional morphological examination.

Differential Diagnosis

The differential diagnosis depends on the patient's age, anatomical site, relationship to teeth, radiographic appearance, and histopathological pattern. A dentigerous cyst is an important differential diagnosis when an OKC is associated with an impacted tooth. Histologically, dentigerous cysts generally demonstrate a thin non-keratinized epithelial lining, although inflammation can modify their morphology. [7]

Ameloblastoma may demonstrate a similar multilocular radiographic appearance and generally produces more pronounced cortical expansion. Histologically, ameloblastoma demonstrates odontogenic epithelial islands or cords with peripheral palisading and characteristic central epithelial differentiation rather than the thin cystic lining characteristic of OKC. [7]

Unicystic ameloblastoma may be particularly difficult to distinguish from OKC when the lesion is predominantly cystic. Careful examination of the entire epithelial lining is therefore necessary to identify areas of ameloblastic differentiation. [7]

Orthokeratinized odontogenic cyst is another important histopathological differential diagnosis. Unlike conventional parakeratinized OKC, orthokeratinized odontogenic cyst demonstrates a prominent orthokeratin layer and granular cell layer and generally lacks the characteristic

palisaded basal cell arrangement. Molecular and clinical studies also indicate that orthokeratinized odontogenic cyst is biologically distinct from OKC and has a much weaker association with PTCH1 abnormalities and NBCCS. [19]

Inflammatory odontogenic cysts, including radicular and residual cysts, may also enter the differential diagnosis when extensive inflammation has altered the epithelial lining. Clinical history, radiographic findings, relationship to teeth, and microscopic evaluation remain essential for establishing the final diagnosis.

Pathogenesis and Mechanisms of Growth

Several mechanisms have been proposed to explain the characteristic growth behavior of OKC. The proliferative activity of the epithelial lining is considered an important factor, and the expression of proliferation-associated markers supports the presence of intrinsic epithelial proliferative activity. [15,17]

Earlier theories proposed that increased osmotic pressure within the cystic lumen may contribute to expansion through the accumulation of cellular breakdown products and other solutes. [20] Although this mechanism may contribute to cyst enlargement, it does not fully explain the distinctive biological behavior of OKC.

Bone resorption is another important component of lesion progression. Cytokines, prostaglandins, matrix metalloproteinases, and other mediators produced by epithelial and stromal cells may contribute to extracellular matrix degradation and osteoclastic bone resorption. [21] More recently, abnormal Hedgehog pathway activation has provided an additional molecular explanation for the proliferative characteristics of OKC. [3,4,14]

Recurrence

Recurrence is one of the most clinically important characteristics of OKC. Published recurrence rates vary substantially because of differences in treatment modality, follow-up duration, lesion characteristics, patient populations, diagnostic criteria, and definitions of recurrence. [8–10]

Large lesions, multilocular architecture, cortical perforation, satellite or daughter cysts, epithelial budding, previous recurrence, syndromic disease, and anatomically difficult locations have been associated with increased recurrence risk. [8,9,16] The thin and fragile epithelial lining can

fragment during enucleation, increasing the likelihood that epithelial remnants remain within the surgical cavity.

A large analysis of 6427 cases demonstrated that recurrence probability varies according to treatment method and lesion characteristics, emphasizing the importance of individualized risk assessment. [9] Long-term follow-up is therefore essential because recurrence can occur several years after the initial treatment. [10]

Mechanisms of Recurrence

Recurrence may result from incomplete removal of the original cyst lining, persistence of satellite or daughter cysts, or development of an independent new OKC in the same region. The first mechanism is particularly important because the epithelial lining is thin and fragile and may fragment during surgical manipulation. [8,9]

Satellite cysts and epithelial remnants within the fibrous wall may subsequently proliferate and form new cystic lesions. This phenomenon is especially relevant in syndromic disease, where patients may develop multiple independent OKCs because of the underlying genetic predisposition. [3,13]

Treatment

Treatment should be individualized according to lesion size, anatomical location, cortical perforation, relationship to teeth and neurovascular structures, patient age, syndromic status, previous treatment, and whether the lesion is primary or recurrent. [8–10] The principal objective is complete disease control while minimizing functional and anatomical morbidity.

Enucleation is commonly used for small and accessible lesions. However, the thin and friable epithelial lining may make complete removal difficult, and recurrence may occur if epithelial remnants remain. Peripheral ostectomy may be performed following enucleation to remove a thin layer of surrounding bone that could contain residual epithelial tissue. [8,9]

Carnoy's solution has historically been used as an adjunct following enucleation because of its tissue-fixative effect and ability to destroy residual epithelial remnants. Earlier systematic reviews suggested lower recurrence rates when Carnoy's solution was used as an adjunct, although the evidence is largely based on retrospective studies. [8,22] Modified formulations and concerns

regarding tissue toxicity must be considered, particularly when the lesion is closely related to important neurovascular structures.

Liquid nitrogen cryotherapy is another adjunctive method that produces controlled tissue necrosis and may destroy residual epithelial cells within cancellous bone. However, excessive freezing can damage adjacent structures and increase postoperative complications. [8,23]

Decompression and marsupialization are conservative approaches particularly useful for large lesions. Decompression reduces intracystic pressure and may allow progressive reduction in lesion size before definitive enucleation. Marsupialization similarly converts the cyst into an open cavity and requires patient compliance, regular irrigation, and prolonged follow-up. [8,10]

Resection provides excellent local control but is associated with greater morbidity and is generally reserved for selected aggressive or repeatedly recurrent lesions, extensive cortical destruction, or cases where conservative treatment is considered inappropriate. [8,9]

Contemporary Evidence on Treatment and Recurrence

Contemporary systematic reviews indicate that no single treatment modality is universally appropriate for all OKCs. A 2024 overview of systematic reviews reported that simple enucleation was associated with the highest recurrence among commonly used approaches, whereas the addition of adjuvant techniques reduced recurrence. However, the authors emphasized that the methodological quality of the available systematic reviews was critically low. [10]

A network meta-analysis involving 2989 patients from 40 studies evaluated several treatment approaches, including enucleation with peripheral ostectomy, cryotherapy, Carnoy's solution, modified Carnoy's solution, 5-fluorouracil, marsupialization, secondary enucleation, and resection. The analysis suggested favorable recurrence outcomes with some adjuvant approaches, but the evidence quality ranged from moderate to very low and was predominantly based on retrospective studies. [8]

More recent evidence has generated interest in topical 5-fluorouracil as an alternative to Carnoy's solution. A 2024 systematic review and meta-analysis comparing 5-fluorouracil with modified Carnoy's solution reported lower recurrence and fewer permanent peripheral nerve injuries in the

5-fluorouracil group. Nevertheless, these findings require confirmation in larger prospective studies before universal adoption. [24]

NBCCS should undergo appropriate clinical evaluation and, when indicated, genetic assessment.

Advances in Molecular and Targeted Therapy

The identification of aberrant Hedgehog pathway activation has generated interest in targeted molecular therapy. Smoothed inhibitors such as vismodegib have demonstrated biological activity in Hedgehog-pathway-driven conditions, particularly basal cell carcinoma associated with NBCCS. Experimental studies have also investigated Hedgehog pathway inhibitors in relation to OKC biology. [14,25]

At present, however, targeted molecular therapy cannot be considered a routine replacement for surgery in conventional OKC. Limitations include drug-related adverse effects, resistance, recurrence after treatment cessation, cost, and limited clinical evidence specifically addressing OKC. Further research is required to determine whether molecular profiling can identify patients who may benefit from targeted therapy.

Follow-up

Long-term postoperative surveillance is an essential component of OKC management. Follow-up should include periodic clinical examination and appropriate radiographic evaluation. Panoramic radiography may be adequate for routine surveillance in selected patients, whereas CBCT or CT may be required when assessment of cortical integrity, recurrence, or complex anatomical relationships is necessary. [10]

A retrospective study evaluating appropriate follow-up duration emphasized the importance of prolonged surveillance because OKC recurrence may occur several years following treatment. [10] Patients with NBCCS require particularly careful lifelong surveillance because new OKCs may develop independently of previously treated lesions. [13]

Conclusion

Odontogenic keratocyst is a distinctive developmental odontogenic cyst characterized by unique histopathological features, intrinsic proliferative potential, locally aggressive growth, and clinically important recurrence. Although the lesion was temporarily classified as a benign

odontogenic tumor in the 2005 WHO classification, subsequent evidence resulted in its reclassification as an odontogenic cyst in the 2017 WHO classification. [2,11]

The characteristic histopathological features, including a thin and relatively uniform parakeratinized stratified squamous epithelial lining, corrugated luminal surface, palisaded hyperchromatic basal cells, and relatively flat epithelial-connective tissue interface, remain the cornerstone of diagnosis. Molecular studies have demonstrated an important role for PTCH1 and the Sonic Hedgehog signaling pathway, particularly in syndromic disease, providing valuable insights into the biological behavior of the lesion. [3,4,7]

Management should be individualized according to lesion size, anatomical location, biological behavior, syndromic status, previous recurrence, and anticipated morbidity. Conservative approaches such as decompression and marsupialization can be valuable for selected large lesions, whereas enucleation with appropriate adjunctive treatment may provide effective disease control in many cases. Resection remains appropriate for selected aggressive or repeatedly recurrent lesions but should be balanced against its functional and anatomical consequences. [8–10]

Ultimately, successful management depends on accurate diagnosis, careful surgical planning, appropriate use of adjunctive treatment, recognition of syndromic associations, and prolonged postoperative surveillance. Continued research into molecular pathways, biomarkers, targeted therapies, and individualized risk stratification may further improve the management of OKC and reduce both recurrence and treatment-related morbidity.

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