# Locally Aggressive Benign Odontogenic Neoplasms – A Review

**Pratyusha P Gaonkar[1], Sangeeta R Patankar[2], Nidhi Tripathi[3], Prachi Bhandare[4], Akansha Chaphekar[5], Gokul Sridharan[6,*]**

[1,3,4]Post Graduate, [2]Professor & HOD, [5]Lecturer, [6]Reader, Dept. of Oral Pathology and Microbiology
YMT Dental College and Hospital, Kharghar, Navi Mumbai-410210, Maharashtra

***Corresponding Author**
E-mail: drgokuls@gmail.com

## Abstract

Odontogenic neoplasms encompass a group of lesions with a varied clinical picture and biological behavior ranging from indolent hamartomatous proliferation to locally aggressive benign tumors and their very aggressive malignant counterparts. The benign neoplasms are normally slow growing, indolent with no invasive potential. However, there exists a few locally aggressive benign odontogenic tumors that have a tendency to invade and deform the surrounding structures. The exact reason for the aggressiveness of these benign neoplasms remained an enigma until recently but with the ongoing research and the tremendous progress in the molecular biology of tumors, great strides have now been made in our understanding of their molecular pathogenesis. Their biology and clinical expression can often be destructive and ominous. An appropriate treatment protocol needs to be followed to combat the high recurrence rate and aggressiveness of these entities. This review aims to give an understanding of the locally aggressive benign odontogenic neoplasms, their biologic behaviour and the therapy strategies employed to treat them.

**Keywords:** Locally aggressive lesions, Odontogenic neoplasms, Treatment

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## Introduction

The jaws are host to a wide range of cysts and neoplasms which are mainly of odontogenic origin traced back to various defects in odontogenesis. The ectomesenchymal and epithelial tissue interaction during odontogenesis is a complex process that may also lead to the development of lesions commonly derived from odontogenic epithelium that reside in the jaw bones or adjacent soft tissues and are collectively referred to as odontogenic tumors.[1,2] They are the derivatives of epithelial, ectomesenchymal and/or mesenchymal elements of the tooth-forming apparatus.[3] Also, the developmental stages of teeth formation are emulated in these tumors. Odontogenic neoplasms include a spectrum of heterogenous group of lesions ranging from tumor like malformations to benign neoplasms and their malignant counterparts, some with metastatic potential. Though they are broadly classified into benign and malignant types, there are odontogenic tumors that are described as benign lesion but display locally aggressive behavior. The word aggressive is often associated with the malignant neoplasms which have the ability to invade the adjacent tissue thus subsequently resulting in metastasis and finally death if left untreated.[4] On the other hand, the benign neoplasms exhibit a very characteristic slow, progressive and self-limiting growth. They are noninvasive, histologically benign with few mitotic cells and high differentiation of cells.[5] The locally aggressive benign tumors are characterized by their inherent potential of local tissue destruction and deformation with severe morbid results. The review thus attempts to highlight the various features of some of the locally aggressive benign odontogenic tumors for a better understanding of their pathogenesis behavior and implementation of appropriate treatment modalities.

## Biology of benign Odontogenic Tumors

A profound literature has been dedicated to elucidate the biology of malignant tumors worldwide. On the other hand, the biology of the benign tumors is not often studied. Benign neoplasms are dysmorphic proliferations of tissues that have the capacity for persistent, autonomous growth without the potential for metastasis. In benign tumors, the genetic alterations are generally not prone to mutations resulting in a stable clinical course thus evading the possibility of indolent infiltration into the surrounding tissues as observed in the malignant counterparts. Growth of a pathologic entity is attributed to the cell growth and proliferation and apoptosis in the cell cycle. The cell cycle often becomes the target of genetic alterations that may lead to the dysregulation of oncogenes and tumor suppressor genes which is a characteristic feature of tumor development. Normally, cell cycle consists of G1 (presynthetic), S (DNA synthesis), G2 (premitotic), and M (mitosis) phases. In a normal cell cycle, a main event

is the progression from the G1 to the S phase. In the case of DNA damage the G1-S checkpoint prevents the replication of cells with DNA defects. The G1-S checkpoint is generally controlled by a system of protein interactions whose balance and function are crucial to normal cell division. Over-production of inducing proteins or under-production of tumor suppressor proteins can lead to tumorigenesis. The neoplastic cell differentiation process in odontogenic tumors is complex, and it is believed that the cell differentiation and growth pattern are derivatives of the physiological system of the odontogenesis.[6]

The benign odontogenic tumors that exhibit local aggressiveness are ameloblastoma, keratocystic odontogenic tumor, odontogenic myxoma and the Pindborg tumor.

## Ameloblastoma

Ameloblastoma was defined by Robinson as unicentric, non-functional, intermittent in growth, anatomically benign and clinically persistent. It was as early in the late eighteenth century that ameloblastoma was first recognized and described under the name 'adamantinoma' by Broca and Malassez. It was later named ameloblastoma by Churchill. It accounts for almost 1 percent of all the oral tumors. It is the second most common benign epithelial odontogenic tumor.

The ameloblastoma is a locally aggressive, unencapsulated, but benign odontogenic tumor composed of proliferating odontogenic epithelial nests within a fibrous stroma. Based on the clinical, radiographic, behavioral and prognostic factors, they are classified into: solid multicystic, unicystic, desmoplastic and peripheral ameloblastoma. The unicystic variety shows an indolent behavior in comparison to the more aggressive solid multicystic (SMA) type and hence lower recurrence rate. The SMA shows local infiltration into the bone marrow.[7]The maxillary SMA usually presents with facial swelling and expansion of both the buccal and lingual plates, sometimes along with nasal obstruction, otalgia, proptosis and diplopia. If the ameloblastoma remains undetected lesions in the ascending ramus can penetrate into the paracranial structures.[8] Marx and Stern categorized ameloblastomas into three broad groups: ameloblastoma in situ, micro invasive ameloblastoma and invasive ameloblastoma. As the name suggests, the invasive ameloblastoma is the most aggressive variety which invades bone and sometimes invades and grows within the soft tissues. It exhibits cell replication and growth but seldom metastasizes.

The exact nature of pathogenesis of ameloblastoma is still unclear but the recent advances in research have revealed some key molecules that play a role in the genesis of odontogenic tumors. In the past numerous studies have been conducted to explore the tumor biology of ameloblastoma. In a study in intraosseous ameloblastomas it was observed that syndecan-1 (SDC1) was expressed by tumor epithelial cells and subsequently shifting to stromal cells and extracellular martix, which might be the reason for the local invasiveness of some intraosseous subtypes.[9] In a similar study conducted solid ameloblastoma showed lesser expression of syndecan-1 as compared to that in unicystic ameloblastoma, suggesting a more aggressive clinical course of the solid multicystic variants.[10] There have been results regarding the expression of proliferative markers like PCNA in solid and unicystic varieties of ameloblastoma. One study revealed gradual increase in the PCNA expression from unicystic to the follicular type to the plexiform type which can be positively correlated with the biologic behavior of the different types of ameloblastmas.[9] The anti-apoptotic markers like bcl-2 expressed in the neoplastic cells of ameloblastoma surrounding the basement membrane suggested reduced apoptosis in these cells.[11] Increased expression of MDM2 and p53 in both benign and malignant ameloblastomas inferred that the alterations in the $p14^{ARF}$-MDM2-p53 pathway can be one of the factors responsible for malignant transformation of odontogenic epithelium. MDM2 is the inhibitor of the most important tumor suppressor molecule p53, rightly called the housekeeper gene thus inhibiting the tumor suppressor function.[12] An elevated expression of MMP-1, 2 and 9 in ameloblastoma was found in a study which attributed the invasiveness of ameloblastoma to the intense MMP expression.[13]

## Keratocystic Odontogenic Tumor

The odontogenic keratocyst first described by Philipsen in 1956 has now been termed keratocystic odontogenic tumor (KCOT) by the most recent WHO classification (2005). This change in terminology has been brought about to stress on the neoplastic nature of this entity and it is attributed to its aggressive clinical behavior, histologically high mitotic rate and association with genetic and chromosomal abnormalities which is not typical of other cysts.[14] Also, the recurrence rate of this tumor is variable ranging from 2.5 to 62%.[14] KCOTs tend to grow quickly within medullary bone, while bony expansion becomes clinically evident only when the lesion reaches large size. Increased aggressiveness in the form of proptosis of the eye due to involvement of the maxillary sinus and the floor of the orbit has been reported. However, KCOT cannot infiltrate into the soft tissue unless seeded into it.[15] It is now defined as "a benign unicystic or multicystic, intraosseous tumor of the odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential for aggressive, infiltrative behavior."[3] However this lesion shows some features of a cyst one of them being response to decompression and so the controversial topic of its neoplastic nature prevails.

Over the years, the various molecular studies on KCOT have suggested the role of genetic mutations in

their pathogenesis. It is now a well-established fact that there is mutation of tumor suppressor gene PTCH1, which is an integral part of the sonic hedgehog signaling cascade. The PTCH protein along with SMO forms a receptor for SHH ligands and suppresses SMO mediated transcription of cellular proliferation genes. Its mutation results in increased transcription of genes responsible for increased cell proliferation which is a feature of neoplasia. Once PTCH mutations have set in, additional genetic alterations take place in KCOTs thus enabling the progression of tumors.[16] A study suggested that loss of function of PTCH is a striking characteristic of the KCOTs thus advocating the use of the term benign cystic tumors.[17] Studies in the past have shown that the frequency of allelic loss was 66% for p53 and 60% for PTCH gene. A clonal loss of heterozygosity of common tumor suppressor genes such as p16, p53, PTCH in sporadic KCOTs was observed by using genotypic analysis.[16] Evaluation of EGFR expression in odontogenic cysts demonstrated overexpression of EGFR in KCOTs thus supporting the concept of intrinsic growth potential of KCOT that is not evident in the cysts.[18]

In a study comprising of OKCs and periapical and dentigerous cysts, the highest number of PCNA positive cells was identified in the suprabasal epithelial layer of KCOTs, which points out their higher proliferative capacity in comparison to periapical and dentigerous cysts.[19] Correlation of PCNA and Ki-67 expression was also noted, confirming that suprabasal epithelial layer contains most of the actively proliferating cells. Even though mutations of TP53 gene were identified in most of the human malignancies and considered the hallmark of cancer, the over expression of p53 protein is sometimes very typical for malignant tumors. Thus, p53 over expression in KCOTs, compared to other cysts of the jaw, was demonstrated in several studies, but was lower than observed in malignancies like squamous cell carcinomas of the oral cavity. Owing to their inability to recognize mutations of TP53 gene in their sample, Li and co-workers concluded that increased expression of p53 in KCOTs is not a result of mutation, but a consequence of overproduction and stabilization of "normal" p53.

## Odontogenic Myxoma

Odontogenic myxoma in the jaw was first reported and described by Goldman and Thoma in 1947. It is classified by WHO (2005) as a benign neoplasm arising from odontogenic ectomesenchyme with or without odontogenic epithelium. It is a benign yet locally aggressive tumor with a recurrence rate of about 10 to 33%. Clinically it may present with tooth displacement and sometimes root resorption, displacement of the inferior alveolar canal which is suggestive of its benign process.

Microscopically, odontogenic myxoma presents with spindle shaped or angular cells scantily distributed in loose mucoid intercellular material. It is believed that these cells are myofibroblasts and they give rise to the stroma rich in acid mucopolysaccharides like hyaluronic acid and chondroitin sulfate. It is postulated that this mucopolysaccharide rich stroma is responsible for its infiltrative behavior.[15] In a study it was observed that most of the mesenchymal cells in odontogenic myxoma exhibited a tendency to show a higher content of RANKL than OPG. Ligation of RANKL to RANK produces fusion, differentiation and activation of osteoclasts, whereas inhibition of interaction by OPG.[20]

## Calcifying Epithelial Odontogenic Tumor (CEOT)

CEOT first described by Pindborg in 1955 as a rare benign epithelial odontogenic tumor with a variable biologic nature ranging from mild to moderate invasiveness. It normally presents as a slow growing swelling and grows by infiltration resulting in cortical expansion, tooth displacement and root resorption.[21] CEOT is said to arise from enamel organ's stratum intermedium. Its reduced invasive property as opposed to ameloblastoma can be credited to the reduced activity of the stratum intermedium compared to the tissue of origin of ameloblastoma.[15] The histopathology of CEOT comprises of sheets and islands of polyhedral epithelial cells with little stroma. Eosinophilic masses may be found within these tumor sheets and can undergo calcification giving rise to Liesegang rings. A characteristic finding of clear cell variant of CEOT is the presence of sheets or cords of clear cells with foamy cytoplasm containing glycogen in the matrix and is accountable for aggressiveness and higher recurrence rates as compared to the conventional CEOT.[22]

## Treatment of Locally Aggressive Odontogenic Tumors

Appropriate treatment plan of these tumors is of paramount importance due to their locally aggressive behavior and high recurrence rate post treatment. The biologic behavior of the locally aggressive tumor determines the surgical technique that should be employed. The treatment of odontogenic tumors is dictated by the tumor size, anatomical location, radiographic presentation, the histologic variant and the patient's age. Owing to their aggressive nature, extensive surgical treatment is recommended in solid multicystic ameloblastomas. A conservative local treatment is recommended for young patients to reduce the future growth problems, as also in the indolent unicystic ameloblastoma.[23] To avoid recurrence, radical resection including a healthy bone margin of atleast 1cm is the most preferred therapeutic approach.

A range of therapeutic modalities have been instituted to treat KCOT like decompression, marsupialization, enucleation and resection. Blanas et al (2000) reported that resection yielded lowest recurrence rate but the highest morbidity rate whereas enucleation

with Carnoy's solution application led to a recurrence rate as observed in resection.[24]

The odontogenic myxoma is best treated using resection with 1 to 1.5 cm bony margins thus reducing the recurrence risk associated with enucleation and curettage. The CEOT though less aggressive than ameloblastoma shows recurrence when treated with enucleation and curettage and hence a resection using 1 to 1.5 cm margins in bone is recommended.

## Conclusion

Locally aggressive benign odontogenic tumors though benign possess an inherent tendency to invade and deform. With a higher rate of their recurrence and aggressiveness as compared to other benign tumors it is crucial to decide upon an effective treatment modality. Also as these lesions exhibit a higher proliferation rate and invasiveness, early diagnosis and intervention is vital to avoid morbidity and mortality. The management of these locally aggressive benign odontogenic tumors should incorporate a surgical approach that is curative with no recurrence potential while preserving function.

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