Transformation of Odontogenic Cysts to Neoplasms - A Systematic Review

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Abstract

Background: Odontogenic cysts have the potential to transform into neoplasms. However, the characteristics of those which transformed to neoplastic tissues have not been well described and the exact causes of that phenomenon are not yet clear. **Objectives:** This study aims to describe characteristics of odontogenic cysts that transformed into neoplasms and to look for their potential etiologies. **Data Sources:** English-written studies indexed in PubMed, Science Direct, and Proquest were assessed using keywords verified by Medical Subject Headings: 'Odontogenic Cyst' and 'Neoplastic Cell Transformation'. **Study Eligibility Criteria:** Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines were used as guidance. **Participants:** Following steps in PRISMA guidelines, 19 articles were fully reviewed (three case series and 16 case reports) with 27 subjects of 16 males (59%) and 11 females (41%) from 15 to 86 years old. **Results:** Cystic origins were eight dentigerous cysts, four odontogenic keratocysts, two residual cysts, one radicular cyst, one calcifying odontogenic cyst, one follicular cyst, one glandular odontogenic cyst, and nine unspecified odontogenic cysts that transformed to ameloblastoma (3 cases) and carcinoma (24 cases). **Limitations:** Neoplastic transformations of odontogenic cysts arose from epithelial remnants of inadequate odontogenic cyst removal and chronic inflammation due to infection. However, the exact causes of their transformations remain unclear. **Conclusions:** Therefore, careful removal of odontogenic cysts and regular postoperative follow-ups are key to prevent recurrence and neoplastic transformation. Future studies are needed to investigate potential causes of neoplastic transformation of odontogenic cysts.

Keywords: Odontogenic cyst, neoplastic cell transformation, neoplasm

Introduction

The jaw acts as the 'host' for cysts and tumours because its tissues are involved in tooth formation.[1] Odontogenic cysts are pathological cavities lined with epithelium and filled with fluid, semisolid, or gaseous material, which develop from the remnants of odontogenic apparatus, while odontogenic tumours are solid tissue masses, which are not necessarily neoplastic.[2,3] A considerable amount of odontogenic lesions have been reported in the literature globally.[3] Among all cysts, odontogenic cysts had a prevalence of 15.31%, with radicular cysts being the most frequently found odontogenic cysts (48.67%), then dentigerous cysts, odontogenic keratocysts, and calcifying odontogenic cysts.[3]

In addition to their high prevalence, odontogenic cysts have the potential to transform into neoplastic lesions.[4] Several studies stated the epithelial remnants of odontogenic cysts as the main origin of odontogenic cysts transforming into neoplastic lesions, such as ameloblastomas, adenomatoid odontogenic tumours, and even nonodontogenic malignant tumours.[4] However, the frequency of these neoplastic transformations are known to be low.[4] In the literature, studies that purposefully investigated the characteristics of those cystic lesions that transformed into neoplastic tissues and the causes of those transformations have not been reported.

In this systematic review, we assessed 19 studies reporting the transformation of odontogenic cysts to neoplasms to systematically review the characteristics of odontogenic cysts that transformed into neoplastic lesions and to look for potential etiologies of those phenomena.

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Methods

An electronic search was performed using Science Direct, ProQuest, and PubMed databases for English-written scientific literatures published between April 2012 and April 2022 on odontogenic cyst transformation to neoplasms using keywords specified as shown in Table 1.

Inclusion criteria were analysed based on the PICOS components as follows:

- P = population = all odontogenic cyst lesions
- I = intervention = analysis of neoplastic transformation of odontogenic cysts
- C = comparison = comparison of various types of odontogenic cysts and transformed neoplastic lesions
- O = outcomes = clinical, radiological, histopathological, and genetic analysis
- S = study type = all English-written research articles, case reports and case series, except review articles.

Research questions being asked are as follows:

1. How are the characteristics of odontogenic cysts that underwent transformation to neoplasms?
2. What causes odontogenic cyst transformation to neoplastic tissues?

The title of each article was independently reviewed by four researchers. The papers assessed were clinical trials, randomised controlled trials, case reports, case series, and prospective and retrospective cohort studies reporting odontogenic cysts that transformed into neoplasms. Studies reporting irrelevant topics were not included. Papers that met the inclusion criteria were retrieved in full for eligibility assessment and further review.

After planning the search and review strategy, this study was registered in PROSPERO with registration number: CRD42022340739 on June 30, 2022. The data extracted from eligible papers were: Titles, authors, year, study design, total samples, age, sex, clinical appearance, radiographic appearance, histologic appearance, diagnosis, differential diagnosis, and recurrence.

Table 1: Keywords used in the literature search in PubMed, Science Direct and Proquest databases

Databases	Keywords
PubMed	((((((odontogenic cyst[MeSH Terms]) OR (Cyst, Odontogenic)) OR (Cysts, Odontogenic)) OR (Odontogenic Cyst)) OR (Keratocysts)) OR (Keratocyst)) AND ((((((((((((Cell Transformation, Neoplastic[MeSH Terms]) OR (Transformation, Neoplastic Cell)) OR (Neoplastic Transformation, Cell)) OR (Cell Neoplastic Transformation)) OR (Cell Neoplastic Transformations)) OR (Neoplastic Transformations, Cell)) OR (Transformation, Cell Neoplastic)) OR (Transformations, Cell Neoplastic)) OR (Tumorigenic Transformation)) OR (Transformation, Tumorigenic)) OR (Transformations, Tumorigenic)) OR (Tumorigenic Transformations)) OR (Cell Transformations, Neoplastic)) OR (Neoplastic Cell Transformations)) OR (Transformations, Neoplastic Cell))
Science Direct	Odontogenic cyst neoplastic transformation
Proquest	Odontogenic cyst neoplastic transformation

An independent risk of bias assessment was conducted by two reviewers using Quality Assessment Tool for Case Series Studies by the US National Institutes of Health. We categorised 0–1 not reported (NR) items as good quality, 2–3 NR as fair quality, and 4–5 NR as poor quality. The data obtained in this study were then analysed and reported with descriptive statistics.

Results

Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines were used in selecting the articles [Figure 1]. In the identification stage, 346 records, 26 from PubMed, 179 from ScienceDirect, and 141 from ProQuest were identified, then 320 records were removed due to duplicates and irrelevant titles. In the screening stage, 26 articles were obtained. The full paper of one article was not found, full paper of one article was not available in English, two were review articles, and three of them apparently were out of topic. Finally, only 19 articles were included in this review.

The complete description of selected studies is shown in Annexure. The types of the studies found were three case series and 16 case reports. Within the 19 articles, there were 27 subjects assessed in total, consisted of 16 males (59%) and 11 females (41%), ranging from 15 to 86 years old. Meanwhile, types of the cystic origins were classified as dentigerous cysts (8 cases), odontogenic keratocysts (4 cases), residual cysts (2 cases), radicular cyst (1 case), calcifying odontogenic cyst (1 case), follicular cyst (1 case), glandular odontogenic cyst (1 case), and many were unspecified odontogenic cysts (9 cases). Meanwhile, the cases show that odontogenic cysts could transform into ameloblastoma (3 cases) and carcinoma (24 cases), ranging from ameloblastic carcinoma (1 case), mucoepidermoid carcinoma (3 cases), primary intraosseous squamous cell carcinoma (13 cases), and other squamous cell carcinoma (7 cases). The quality assessments for the risk of bias of each reviewed paper were conducted based on the nine questions in the Quality Assessment Tool for Case Series Studies by the US National Institutes of Health. Assessment results rated all studies as good quality [Table 2].

Discussion

Odontogenic cysts arise as a result of inflammation or development of the epithelium of the tooth-forming apparatus.[5] The epithelial lining of the odontogenic cysts arises from reduced enamel epithelium, the epithelial cell rest of Serres, and the epithelial cell rest of Malassez.[5] Reduced enamel epithelium is the covering epithelium of the developing tooth crown, the epithelial cell rest of Serres is remaining degenerated dental

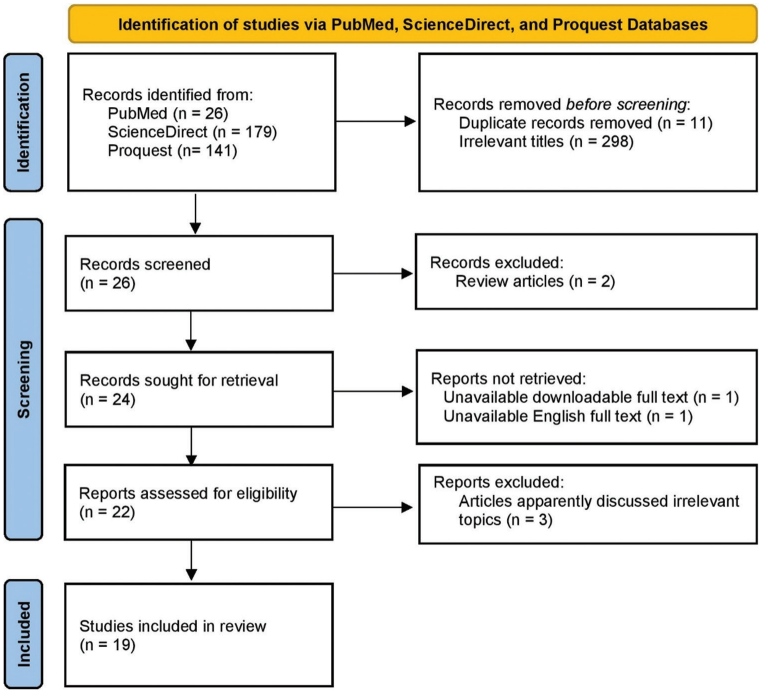

Figure 1: PRISMA flow of this study. PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis

Table 2: Quality assessment for risks of bias of the 19 reviewed articles

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Quality rating
Isshiki-Murakami *et al*. (2021)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Garzino-Demo *et al*. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Nagasaki *et al*. (2018)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Kondamari *et al*. (2018)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Jalali *et al*. (2017)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Razavi *et al*. (2017)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Martinez *et al*. (2016)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Hino *et al*. (2016)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Singh *et al*. (2016)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Gurugubelli *et al*. (2016)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Morita *et al*. (2016)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Prasad *et al*. (2015)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Adachi *et al*. (2014)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Mahajan *et al*. (2014)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Bereket *et al*. (2013)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Zapala-Pospiech *et al*. (2013)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good
Jain *et al*. (2013)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Colbert *et al*. (2012)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Good
Pirklbauer *et al*. (2012)	Yes	Yes	NA	NA	Yes	NA	Yes	NA	Yes	Good

Rating criteria: 0–1 NR=Good quality, 2–3 NR=Fair quality and 4–5 NR=Poor quality, NA: Not applicable, NR: Not reported

lamina which initiated tooth formation at the sixth week of embryonic development, while the epithelial cell rest of Malassez is remnants of Hertwig's epithelial root sheath disintegration which plays a role in dental root formation.[2,6] All of these remnants will be trapped in the gingiva and embedded in bone.[6] The epithelium trapped in gingiva and bone can develop into odontogenic cysts and may undergo neoplastic transformation.[6-8] The incidence of neoplasms which developed from odontogenic cysts accounts for <3%.[9-11]

The neoplastic lesions that developed from odontogenic cysts most likely arose from epithelial remnants of the cysts.[9,12,13] Prolonged inflammation, persistent intracystic pressure, and incomplete removal of the cystic epithelium have been associated with the transformation of odontogenic cysts to neoplasms.[9,11,13-17] Jain *et al*. stated that signs of odontogenic cyst long-standing chronic inflammation, such as the development of a sinus tract and pus discharge are considered as a feature of carcinoma.[18] Chronic inflammation may

trigger the instability of the cell genes due to reactive oxygen species (ROS) formation.[9,19] ROS, such as superoxide ions, hydrogen peroxide, and hydroxyl ions, are produced in cells and able to react with nitric oxide to form reactive nitrogen ions as intermediates.[18] These reactive nitrogen intermediates can trigger carcinogenesis by damaging DNA, proteins, and cell membranes.[18] Chronic inflammation also induces cell apoptosis, cytokine production, keratinisation of the cystic epithelium, and causes DNA, protein, and cell membrane aberration, thus stimulating the transformation of normal cells to neoplastic cells.[11,18,19] However, a study by Borrás-Ferreres *et al*. reported a neoplastic transformation from a follicular cyst without chronic inflammation, suggesting the presence of additional physiopathological mechanisms which may be associated with oncogenes.[9] The exact causes of those transformations are still unknown.

There are characteristics that indicate the transformation of odontogenic cysts to neoplasms, one of which is the delay in healing after cystectomy (with or without dental extraction), swelling, pain, and the presence of the sinus tract.[9] Malignant changes are usually not seen radiographically in the early stages.[9] However, they will be seen as unilocular radiolucency with irregular scalloped and poorly defined edges, accompanied by eroded osseous cortical bone, indicating an invasive behavior.[9]

Among 19 studies reviewed in this study, the odontogenic cysts transformed into central mucoepidermoid carcinoma, primary intraosseous squamous cell carcinoma, ameloblastoma, squamous cell carcinoma, and ameloblastic carcinoma. Those neoplastic tissues originated from dentigerous cysts, odontogenic keratocysts, calcifying odontogenic cyst, glandular odontogenic cyst, residual cyst, radicular cyst, follicular cyst, and some unspecified odontogenic cysts. Some odontogenic cysts were unspecified due to late detection of the transformation, so it was difficult to trace the origin of the cystic lesions. In addition, the total samples from all cases were 27, consisted of 16 males (59%) and 11 females (41%), ranging from 15 to 86 years old. It can be noted that the transformation was slightly higher in male and irrespective of patients' age. Young patients can also experience the transformation of odontogenic cysts into neoplasms, for example, in case report by Isshiki-Murakami *et al*., which reported an 18-year-old patient.[20]

These findings stress the importance of early diagnosis, early treatment, and long-term follow-ups.[13,20] Most reports suggest routine monitoring of odontogenic cysts, both clinically and radiographically, not only to avoid recurrence but also to monitor potential transformation to neoplasms. It is important to make an early diagnosis through an accurate radiological and histological examination, even if the lesion looks benign.[4,21-24] A histologic examination is considered as '*sine qua non*' in diagnosing cystic and neoplastic lesions.[22] A thorough histologic examination is necessary to ensure that the patients are receiving adequate therapy.[25]

Neoplasms that arise from cystic lesions were reported to have radiological 'red flags', such as bone erosion, large dimensions, and inferior alveolar nerve involvement,[26] that can help in early diagnosis. Other supporting examinations to confirm the diagnosis of neoplasms have been reported, such as MAML2 gene analysis[27] and immunohistochemistry examination.[28] Nagasaki *et al*. reported the first case of mucoepidermoid carcinoma from a glandular odontogenic cyst using MAML2 gene fusion analysis.[27] While Martinez *et al*. used immunohistochemistry in diagnosing odontogenic keratocysts that exhibit the potential for neoplastic transformation by detecting p53 gene.[28] This gene is usually negative in conventional odontogenic keratocysts, but p53 was positive in the primary intraosseous squamous cell carcinoma that developed from odontogenic keratocysts.[8,28] Moreover, Magic *et al*. also reported the association of genetic polymorphism of the PTCH1 IVS1-83 and GLI1 rs2228224 with the neoplastic transformation of odontogenic cysts.[29] These findings suggest that MAML2, p53, PTCH1 IVS1-83, and GLI1 rs2228224 can be useful to determine the potential for neoplastic transformation of odontogenic cysts, as well as pose as the target genes for potential treatment modalities.[27-30]

Treatments of odontogenic cysts to prevent neoplastic transformation were not yet standardised.[29,31] Many of the reports that we reviewed suggested that the treatment of odontogenic cysts should be carried out as conservatively as possible with sufficient margins. In the case of dentigerous cysts, the impacted tooth concerned should also be removed immediately to prevent the neoplastic transformation of the remnants of the cystic epithelium.[32-34] If the cyst is large, marsupialisation is recommended to prevent fracture or damage of important organs or tissues during enucleation. However, most literatures suggest that cyst enucleation is the preferred option as marsupialisation carries the risk of cystic cell retention and transformation to neoplasms.[35]

Conclusions

With the limit of this study, it can be concluded that most neoplastic transformation occurred from epithelial remnants of inadequate odontogenic cyst removal and from chronic inflammation due to infection, with or without predisposing genetic cofactors. Thus, the removal of odontogenic cysts must be carried out as optimally as possible to ensure the cystic lining is removed with sufficient margin to reduce the risk of neoplastic transformation from remnants of the cyst epithelium. In addition, monitoring odontogenic cysts both clinically and radiographically, before and after surgery, is essential to avoid recurrence and neoplastic transformation. Thorough radiological and histological examinations are keys for early diagnosis to determine accurate treatment plans for the patients. Although genetic mutation and the presence of some genes, such as MAML2 and p53 have been suspected to have crucial roles in the neoplastic transformation of

odontogenic cysts, the exact causes of this phenomenon remain unclear. Further studies, especially randomised controlled trials are still needed to investigate potential etiologies and the exact mechanisms of the neoplastic transformation of odontogenic cysts.

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Conflicts of interest

There are no conflicts of interest.

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Annexure

Annexure: Data extraction of the 19 reviewed articles

Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
Central MEC of the maxilla developing from a calcifying odontogenic cyst: A rare case report	Isshiki-Murakami *et al.*, 2021[20]	Case report	1	18	Male	Extraoral: Facial asymmetry, bilateral lymph nodes not palpable Intraoral: A 4.0 cm × 3.0 cm dome-shaped mass on the left side of the hard palate, extending anteriorly to the distal first pre-molar region and posteriorly to the soft palate. The mucosal surface of the mass was smooth, but partially ulcerated. On palpation, the consistency of the hard mass was elastic	The panoramic radiograph showed the opacity of the left maxillary sinus with impacted teeth and the floor of the left maxillary sinus was lower than on the right side. CT showed a well-defined multilocular radiolucent lesion in the left maxillary sinus with an impacted tooth on the posterior wall. MRI showed an inhomogeneous and slightly elevated lesion of the left hard palate and alveolar process, along with a highly elevated homogeneous lesion of the left maxillary sinus. CT of the neck showed no bilateral lymph node enlargement and CT of the abdomen and chest revealed no other specific findings	Microscopically, the epithelium was composed of mainly squamous epithelial cells and the presence of clear and ghost cells along with calcifications, which suggested a possible benign odontogenic tumour or odontogenic cyst Macroscopically, surgical specimens consist of white-grey a solid area within the alveolar process and hard palate on the excised surface. The tumour was well-defined and not completely encapsulated. The tumour was composed of multiple cystic lumina of various sizes lined by odontogenic epithelium and this cystic space was filled with a carcinomatous component, which was mainly composed of abundant intermediate cells and mucin-producing cells. Mucicarmine staining indicated mucin production. Nuclear atypia was slight and mitotic rate was rare in the carcinomatous component. The palatal salivary glands were intact	Intraosseous low-grade central MEC of the maxilla arising from a calcifying odontogenic cyst	Calcifying epithelial odontogenic tumour or calcifying odontogenic cyst	No recurrence after 19-month follow-up

Contd...

Annexure: Contd...

Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
PIC developing from odontogenic cysts: Clinical and radiological considerations on a series of 6 cases	Garzino-Demo *et al.*, 2020[26]	Case series	6	55.2	5 females, 1 male	Swelling, pain, pathological fracture and sensory disturbance in the inferior alveolar nerve region or infraorbiter nerve territory. In maxillary lesions, symptoms of nasal obstruction sometimes appear	OPG has not provided specific signs, which distinguish cystic lesions from cancerous cystic lesions. In only three cases (cases 2, cases 3 and 5), the lack of sclerotic margins characteristic of odontogenic cysts were detected. From this type of examination, it was difficult to tie in further important or specific data	The surface of the tumour was covered with non-cancerous oral mucosa with severe dysplasia; tumour cell growth in the bone marrow with intense inflammatory infiltrate	Primary intraosseous SCC arising from odontogenic cysts	-	-
Central MEC arising from glandular odontogenic cyst confirmed by analysis of MAML2 rearrangement: A case report	Nagasaki *et al.*, 2018[27]	Case report	1	57	Male	Swelling and discharge of pus in the left posterior mandible	Multiocular radiolucent cystic lesion with cortical bone resorption involving the mandibular left molar region. Wired treatment available for bone fracture 9 years later: Multiocular radiolucent lesion from left pre-molar to mandibular molar	Proliferative cystic and cystic spaces contain eosinophilic material supported by a fibrous stroma. Infiltrate into retromolar connective tissue and salivary glands. The cystic assemblage consisted of a mixture of squamous, mucosal and intermediate cells; columnar or cuboidal shape. Lymphoid proliferation with follicles within the tumour. To confirm clinical and histopathological findings, MEC specific CRTC1/3-MAML2 gene fusion analysis was performed for primary and recurrent lesions by RT-PCR	Low grade central MEC arising from a glandular odontogenic cyst	-	After 2 years, no recurrence or metastasis

Contd...

Annexure: Contd...

Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
Ameloblastoma arising in the wall of dentigerous cyst: Report of a rare entity	Kondamari *et al.*, 2018[4]	Case report	1	19	Male	Extraoral: Facial asymmetry with diffuse swelling on the left of the face, extending from the ala tragus line to the lower border of the mandible. Size 5 cm × 6 cm. Positive palpation, tender swelling area and firm to firm consistency. Positive palpation of the left submandibular gland was firm, there was tenderness with a size of 0.5 cm × 0.5 cm Intraoral: Swelling with a smooth surface, obliteration of the buccal vestibule extending anteroposteriorly 35 to the alveolar ridge 37, followed by ascending ramus to occlusal teeth 26 and 27. There was expansion in the buccal and lingual cortical. There was tender swelling in the 35 and retromolar regions with the remainder of the lesion being	OPG: Multiocular radiolucency on the left side extending from 35 to the proc condylus. Perforation of lingual cortex region 37 and resorption area 37 with impacted tooth 38 CT: Lingual and buccal cortical bone expansion with region 37 perforation	Cystic cavity surrounded by cystic epithelium resembling reduced enamel epithelium. The epithelial line consists of high basal columnal cells, reversal of polarity of the hyperchromatic nucleus, degenerated star reticulum-like cells and areas of foci of subnuclear vascularisation. The connective tissue beneath the stroma showed epithelial odontologenic rest with focal areas of ameloblastomatous follicular	Ameloblastoma arising from a dentigerous cyst	-	-

Contd...

Annexure: Contd...

Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
						of the firmest consistency. There were missing teeth 28, 36, 38, 48 with tooth mobility at 37					
SCC arising within a maxillary OKC: A rare occurrence	Jalali *et al*., 2017[17]	Case report	1	43	Female	Extraoral: A tender, fluctuating swelling that extended from the right nasolabial region to the right infraorbital region. The skin over the mass was unremarkable except for minimal erythema Intraoral: Diffuse buccal swelling in the missing right maxillary canine area. The mucosa overlying the area was intact, with no evidence of tract fistula or ulceration. Teeth in the maxillary right quadrant are of great importance in electrical pulp testing. There is no evidence or report of anesthesia, paresthesias,	Panoramic radiograph revealed impacted right maxillary canine with pericoronal radiolucency. Closely related to the apical region and involving most of the floor and cavity of the right maxillary sinus, there was a large, indistinct, destructive radiolucency. The radiolucency appears to 'blow out' most of the recognisable antral region, with an indistinct boundary extending superiorly to involve the orbital floor region. Examination also revealed multiple edentulous spaces, maxillary midline diastema and mild crestal alveolar bone loss	Histopathological examination revealed several intraosseous soft tissue fragments, most of which consisted of: Well-differentiated SCC. In some foci there were strips of cystic epithelium. Cyst layer showing the pathognomonic findings of OKC. The layer is uniform in thickness with basal cell hyperchromasia and regimentation. Surface wrinkling and parakeratinisation are considerable. The cyst lining appears atypical and is frankly dysplastic in focus. Next door to and arise from within these dysplastic cystic foci, there are there are numerous infiltrative nests of neoplastic epithelium consistent with SCC. Lymphovascular and perineural invasion was not observed. Inflamed antral mucosal fragments were also noted. This	SCC arising from an OKC	-	

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
						visual disturbances or nasal obstruction. No evidence of tooth mobility or tenderness		finding is diagnostic of SCC adjacent to and arising from the epithelial lining of the OKC			
A case of central MEC associated with dentigerous cyst	Razavi *et al.*, 2017[34]	Case report	1	43	Female	Extraoral: Pain and swelling were normal. The submental and submandibular lymph nodes were not palpable or tender Intraoral: Swelling was smooth, firm and tender on palpation involving the anterior region of maxilla from the left lateral incisor to the left firth pre-molar with the expansion of buccal cortical plate with intact overlying mucosa. The left canine tooth was absent in the anterior portion of maxilla since 2 months. There was no significant medical or familial history and tobacco use	Panoramic radiograph showed well-defined unilocular radiolucency in the anterior left maxillary bone with an unerupted maxillary left canine tooth	Histopathological examination showed a thin odontogenic epithelium 3–5 cell layers thick with non-keratinised squamous cells and a few mucous cells in the superficial layer. The connective tissue wall was made up of loosely arranged collagen fibers and fibroblasts that suggested a dentigerous cyst. Connective tissue wall had numerous cystic spaces with foci of mucous, epidermoid and clear cells which these cells stained by PAS	Central mucoepidermoid cyst arising from a dentigerous cyst	Dentigerous cyst, KCOT, and AOT	
Primary intraosseous SCC arising in an OKC previously treated with marsupialisation:	Martínez-Martínez *et al.*, 2016[28]	Case report	1	37	Female	Slowly growing, asymptomatic swelling located on the right side of the mandible,	Panoramic and occlusal radiographs showed an extensive, relatively well-delimited	An incisional biopsy was performed and histology showed a cystic lesion lined by epithelium formed by seven to eight	Primary intraosseous SCC arising from an OKC		Yes, 7 months

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
Case report and immunohistochemical study						clinically apparent for 9 months. Intraoral examination revealed a lesion involving the lower right pre-molar and first molar region, showing evident buccal and lingual cortical expansion. The mucosa overlying the affected area was intact	radiolucent lesion, extending from the lateral incisor up to the mandibular ramus, projecting into the interdental spaces, and without bone sclerosis at the periphery. There was no tooth resorption, and the mandibular canal was displaced to the inferior portion of the mandible. The lingual aspect of the cortical bone showed focal areas of destruction	layers of cuboidal squamous cells with parakeratotic surface; the cells of the basal layer were more columnar and basophilic and in some areas, the epithelium was detached from the adjacent underlying thin fibrous capsule			
Primary intraosseous SCC derived from a dentigerous cyst	Hino *et al.*, 2016[21]	Case report	1	57	Male	There were swelling and bone growth from the molar alveolus to the mandibular ramus, the teeth and mucosa appear normal, and there is no lymphadenopathy or mental nerve paresthesias	Panoramic: Well-defined radiolucent and extending with impaction of the left mandibular third molar, extending from the inferior portion of the mandibular left first molar to the angle and left ramus of the mandible CT: Visible cystic cavity and resorption in the lingual cortex	Biopsy before surgical treatment: Non-keratinising stratified squamous epithelium in the cyst lining Histopathological examination of post-operative specimens: Cystic lumen lined with squamous epithelium and connective tissue with inflammatory cell infiltration, dysplasia occurs	SCC arising from a dentigerous cyst	-	No recurrence after 5 years of follow-up
Ameloblastomatous transformation in dentigerous cyst: A case report	Singh *et al.*, 2015[22]	Case report	1	15	Male	There was a hard swelling with crepitus on the right side of the face, extending from the body of the mandible to the sigmoid notch (covering the ramus) On intraoral examination,	Panoramic: Cystic lesion extending from right sigmoid notch of mandible to body of mandible, buccal cortex involved. There is perforation of the ramus and root resorption of the dental disc of 46 CT: There is involvement	Biopsy before surgical treatment: Indicated a dentigerous cyst. Biopsy on post-operative specimens: Non-keratinised stratified squamous epithelium without rete processes,	Ameloblastoma arising from a dentigerous cyst	-	No recurrence after 24 months follow-up

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
						tooth 48 was found missing. On palpation, the buccal cortex was found to be wide with perforation. The lingual cortex was dilated in the 46–47 region. There was no intraoral fluid discharge	of the lingual cortex with perforation of the ramus and body of the mandible	connective tissue devoid of inflammatory cells, at the mesial border visible proliferation of the cystic layer into the lumen			
A silent transformation of keratocystic odontogenic tumour to SCC: A case report and review of literature	Gurugubelli *et al.*, 2016[24]	Case report and literature review	1	60	Female	Swelling in the anterior mandible (looked prognathic), oval, measuring 7 cm × 5 cm, smooth surface, shiny, and the colour is the same as around. Palpation: Hard and soft consistency with slightly increased temperature, no fluctuations. No paraesthesia. On aspiration, the fluid is mixed with blood	Periapical: Loss of crown structure in teeth 32 and 33 with periapical ill-defined radiolucency and loss of trabecular bone Panoramic: Unilocular radiolucency lesion with clear margins and extends to the right and unclear borders extending to the left. Unrelated to tooth resorption and dental dysplasia	Hyperplastic epithelial dysplasia and islets showing extensive areas of necrosis with rete peg and from other soft tissue sections showing stratified squamous cystic epithelium with dysplastic features, such as nuclear hyperchromatism and hyperplasia, along with nuclear pleomorphism and mitotic features	Moderately differentiated SCC arising from an odontogenic keratocystic	Central giant cell granuloma, ameloblastoma, dentigerous cyst, odontogenic myxoma, sialo odontogenic tumour	-
Primary intraosseous SCC derived from a maxillary cyst: A case report and literature review	Morita *et al.*, 2016[31]	Case report and literature review	1	37	Male	There was a fistula after the diagnosis of apical periodontitis. Extraoral: Swelling without paraesthesia in the left buccal region Intraoral: Painful ulcer on the	CT: There was an area of bone resorption on the lateral nasal wall OPG: No cyst like radiolucent. Contrast CT: Soft tissue mass 30 mm × 16 mm × 2 mm with irregular borders and heterogeneous density in the left maxillary anterior	Tumour located centrally in the maxillary bone, without attachment to the oral or maxillary sinus mucosa, consisting of a solid and cystic component, the solid component consisting of squamous islets of	Primary intraosseous SCC arising from a maxillary odontogenic cyst	Apical periodontitis	No recurrence after 53 months follow-up

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
						maxillary buccal gingiva on the left canine due to a previous biopsy. OPG: No radiolucent cyst-like appearance	MRI: High density lesion on T2	neoplastic epithelium with centralised keratinisation and necrosis			
SCC arising from a dentigerous cyst - report of a case and review of literature	Prasad *et al.*, 2015[25]	Case report and literature review	1	50	Male	There were no extra and intraoral deformities, on palpation of the lingual wall and on the right, soft and depressible molars indicating erosion of the lingual cortical	OPG: Horizontally impacted tooth 48 with large radiolucency, unilocular and well-defined borders extending anteroposteriorly from distal 46 to tooth 48 and inferior border area thinning	The stratified cystic epithelium was composed of two to three layers of squamous cells. In some areas the epithelium showed dysplastic changes. Sheets and islets of dysplastic epithelial cells were seen invading into the underlying connective tissue capsule, some of which also showed keratin pearl formation. Islets of malignant epithelial cells, some of which showed keratin pearl formation, were seen invading into the capsule. An intense chronic inflammatory infiltrate is also seen in the connective tissue. Lingual soft-tissue margins obtained from the area of cortical plate perforation were found to be positive for tumour expansion and subsequently, the patient underwent radiotherapy	SCCs arising from odontogenic cysts	Dentigerous cyst	No recurrence after 2 years follow-up

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
Primary intraosseous carcinoma arising from an odontogenic cyst: A case report	Adachi *et al.*, 2014[15]	Case report	1	59	Female	Extraoral: Right buccal swelling and mental nerve paresthesias Intraoral: Normal mucosa, percussion (+) between 44 and 47	Panoramic: There was residual root of the right M3 tooth and an irregular radiolucency area between the lower right molar and the mandibular angle with an indistinct edge CT: 44 mm × 31 mm × 35 mm oval mass at right angle of mandible between P2 and ramus with extension of bony damage to the lingual and buccal cortex	SCC with intact squamous epithelium	Primary intraosseous carcinoma arising from a maxillary odontogenic cyst	-	No recurrence
Unicystic ameloblastoma arising from a residual cyst	Mahajan *et al.*, 2014[33]	Case report	1	68	Male	Asymptomatic, swelling in the right lower jaw since 6 months ago Extraoral: Bilateral facial asymmetry Intraoral: Swelling measuring 2 cm × 2 cm in the lower region of the alveolar ridge and obliteration of the buccal and lingual vestibule. No pus and sinus tract. Smooth swollen surface and well-defined edges	CT: Radiolucent oval and well-defined radiopaque margin, buccal and lingual alveolar ridge resorption. The expansion was more buccal than lingual	A cystic cavity surrounded by stratified non-keratinised squamous epithelium, consisting of ameloblast-like cells that were usually long columnar with nuclei arranged with reverse polarity. There are stellate reticulum-like cells in the superficial area and ameloblastoma follicles in the connective tissue	Unicystic ameloblastoma arising from a residual cyst	Residual cyst, aneurysmal bone cyst, metastatic tumour to the jaws, traumatic bone, ameloblastoma, keratocystic odontogenic tumour	No recurrence after 3 months of follow-up and the patient was lost to follow-up
Intraosseous carcinoma arising from an odontogenic cyst: A case report	Bereket *et al.*, 2013[35]	Case report	1	26	Male	There was an area of vestibular and palatal extension of the anterior maxilla, especially on the right side. There was a yellowish liquid seeping	Panoramic radiograph and CBCT showed a radiolucent cyst-like lesion that was well demarcated between the right second pre-molar and left first pre-molar involving the roots of neighboring teeth	There was SCC along with keratinised odontogenic cystic epithelium	Intraosseous carcinoma arising from odontogenic cysts	-	No recurrence occurred

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
Malignant transformation in the course of a dentigerous cyst: A problem for a clinician and a pathologist. Considerations based on a case report	Zapała-Pośpiech *et al.*, 2013[23]	Case report	1	66	Male	Edema on the left side of the face and enlarged lymph nodes (1B level). Expansion of bone in the left mandible and purulent fistula in the region of tooth 36, when palpated there was crepitus in this region	Unilocular ratio lesion, regular, extending from the region of tooth 41 to tooth 36. Inferior left alveolar canal pushed inferiorly	There was non-keratinised stratified squamous epithelium surrounded by granulation tissue with purulent and chronic inflammatory infiltrate	SCC arising from a dentigerous cyst	-	There was no recurrence
Primary intraosseous SCC arising in odontogenic cysts: An insight in pathogenesis	Jain *et al.*, 2013[18]	Case report	3	70, 45, 38	2 males, 1 female	On the extraoral, there was hard swelling on the right side of the lower jaw and chronic discharging sinus. On the intraoral, there was swelling on the right side of the mandible in the canine to pre-molar region (buccal and lingual expansion) Extraoral examination found hard swelling in the left angle of the mandible and chronic discharging sinus. The intraoral part is difficult to examine because there is trismus, but there is swelling in the left M3 region of	Unilocular radiolucency with ill-defined margin surrounding the impacted right mandibular canine Panoramic: Unilocular radiolucency with ill-defined margin surrounding the impacted left M3 of the mandible, extending from the left m2 of the mandible to the midramus region. CT: Soft tissue density lesion 2 cm × 2.7 cm × 2.5 cm in the left mandibular region, with cortical bone perforation buccally and lingually Panoramic: Diffuse radiolucent lesion with ill-defined border in the periapical region of the maxillary left incisor. CT: Osteolytic lesion 3.2 cm × 3.2 cm × 3.2 cm in the maxillary left alveolus	Parakeratin-coated squamous epithelium was seen, in connective tissue, islands of anaplastic squamous cells were seen, in subepithelial connective tissue, chronic inflammatory infiltrate was seen consisting of lymphocytes, plasma cells, and giant cells Non-keratinised stratified squamous epithelium was seen, the connective tissue was seen with islands of anaplastic squamous cells and chronic inflammatory infiltrate Non-keratinised cystic epithelium with severe dysplasia is seen, the connective tissue shows anaplastic epithelial cells	Primary intraosseous SCC arising from an OKC, a dentigerous cyst, and a radicular cyst	-	No recurrence after 3 years follow-up No recurrence after 1 year follow-up Not mentioned

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
						the lower jaw Extraoral examination found a hard swelling in the left anterior maxilla with a smooth margin. Intraoral found 21 non-vital teeth and intraoral sinus tract	with bony erosion and extending to the nasal aperture, cortical bone perforation occurred on the buccal and lingual side				
SCC arising in dentigerous cysts	Colbert *et al.*, 2012[32]	Case report	2	66, 42	2 males	Unexplained Unexplained	Unilocular radiolucency, associated with impacted M3 tooth Unexplained	An invasive SCC was seen within a dentigerous cyst Malignant changes in the dentigerous cyst, infiltrating the mandible and extending laterally to bone, soft tissue and subcutaneous tissue	SCC arising from dentigerous cysts	-	No recurrence after 3 years follow-up There was a recurrence after a year, progressing to extensive functional carcinoma
Manifestation of an ameloblastic carcinoma 10 years after follicular cyst enucleation in the mandibular ramus	Pirklbauer *et al.*, 2012[16]	Case report	1	86	Male	Decreased mouth opening, widespread lesion at left mandibular angle with recurrent oral bleeding, and swelling. Loss of sensation on the left inferior alveolar nerve, weakened sensation/ response of the left mandibular marginal facial nerve, and deafness in the left ear	OPG: Pathological fracture of radiolucent uniocular CT lesion with non-homogeneous contrast medium: Lesion extending transversely from the left palatine tonsil to the parotid gland and vertically from the body of the mandible to the skull base MRI with contrast medium: Skull base infiltration with a small intracranial tumour mass in the foramen ovale and cervical vascular infiltration. Cervical	Biopsy after decalcification in 1997: Trabeculae and atypical cells formed a microcystic structure and several solid areas were found between the fragments of the bone lamellae. An infiltrated, poorly vascularised septum is seen between the tumours. The tumour cell cytoplasm was poor, the nucleus was round to oval, the chromatin looked like powder/dust, the nucleus was dominant and the intranuclear	Ameloblastic carcinoma arising from a follicular cyst	-	CT after 3 months: No significant reduction in tumour mass. Significant tumour infiltration caused blindness in the left eye and dementia. The patient died in December 2007

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Title	Authors	Study design	Samples	Age	Sex	Clinical appearance	Radiographic appearance	Histologic appearance	Diagnosis	Differential diagnosis	Recurrence
							lymph nodes without obvious malignancy criteria on both sides Positron emission tomography: Lymph nodes at the hilum of the lung	vesicles are pre-dominant. Lots of mitoses. Lymphocytes and plasma cells were scattered. Histological reevaluation of 2007 specimen: Thick cyst wall with rare epithelial lining of non-keratinised squamous cells with acanthosis and irregular rete ridges. The cyst wall was beneath the epithelial tissue which consists of collagen-rich connective tissue with abundant lymphocytes and plasma cells. No epithelial rest of Malassez or Serres and no signs of neoplasia			

OPG: Orthopantomography, CT: Computed tomography, MRI: Magnetic resonance imaging, CBCT: Cone-beam computed tomography, MEC: Mucoepidermoid carcinoma, RT-PCR: Reverse transcription polymerase chain reaction, SCC: Squamous cell carcinoma, OKC: Odontogenic keratocyst, PAS: Periodic-acid-Schiff, KCOT: Keratocystic odontogenic tumour, AOT: Adenomatoid odontogenic tumour