Abstract. This article includes a comprehensive and up-to-date review on the cysts of the oral cavity. Several classifications of odontogenic (OC) and non-odontogenic (non-OC) oral cysts and the surrounding regions have been proposed. We suggest a new critical classification based on an established relationship between anatomical area, histological origin and clinical behavior (frequency, rate of recurrence, malignant potential). Moreover, the differential cytokeratin (CKs) expression of the various cysts is reported as epithelium-specific markers of differential diagnosis. Finally, issues related to differential diagnosis and therapeutic approaches of the cysts included in the two groups are described.

Oral cysts (1-8) are divided into two major groups based on odontogenesis: odontogenic cysts (OCs) and non-odontogenic cysts (non-OCs). The first group is characterized by specific odontogenic markers, histological similarities with odontogenic structures and anatomical considerations (9).

The second group (1, 3) includes cysts that originate from specific areas or organs of the oral cavity such as salivary cysts, naso-palatine duct/mid-palatine cysts and nasolabial cysts. In this group are included also some cysts, that are ubiquitous in the body, such as dermoid cysts, lymphoepithelial cysts, and aneurysmal bone cysts.

OCs arise from the tooth-producing tissues; alternatively, they originate from the remnants of dental lamina epithelium entrapped within the gingival named epithelial rests of “Serres” (8-10), or the epithelial remains of the “Malassez” (2, 10-12). These cellular remnants fall within the concept of the post-functional state of the dental lamina, which has limited growth potential. These two types of embryological residues can generate two different types of dental cysts (5, 13). From the remnants of Serres takes origin the periodontal cyst, and the orthokeratocyst, that is a more aggressive type of cyst with a neoplastic variant5. From the residues of Malassez originates the inflammatory radicular cyst (9). For this last type of cyst, an infectious and/or inflammatory stimulus acting on a genetic predisposition has been proposed as the first pathogenic event causing the proliferation of cellular odontogenic remnants (11-14).

Cytokeratins (CKs) are epithelium-specific markers of differentiation and have been proposed as ideal markers for differential diagnosis of these cysts, being involved in physiological odontogenesis (14-23). In detail, CKs 5 and 14 are expressed in the basal cell layer of both the keratinized and non-keratinized epithelia, with a reduction in the upper layers; CKs 1 and 10 are specific to the spinous layer; CK 19 is present in the basal stratum of the non-keratinized epithelia; CKs 4 and 13 are specific for supra-basal cells of the tongue epithelium; K2p is present in the supra-basal epithelial cells of the hard palate and gingiva. During odontogenesis CKs have a peculiar pattern of expression: CK7 is expressed in the “stellatum reticulum” at the early bell stages along with CK14; these two CKs, together with CK 19, are also expressed in the cells of the enamel epithelium.
CK14 is present at early “bell stage” and replaced by CK19 in differentiated ameloblasts; CKs 7 and 13 are found in the “rests of Serres” (16-18). It has been reported that the structure of CKs, as well as, their expression within the cells may be altered depending on environmental conditions (e.g. inflammation) (15, 19-21) and on changes in cellular function. Therefore, the detection of an altered expression is useful for the differential diagnosis of various diseases such as cysts and tumors. Indeed, CKs 5 and 6 are present in all layers of the odontogenic cysts, CK13 is expressed in the supra-basal cell layer of all odontogenic cysts, while CK20 is negative in all odontogenic cysts (18).

In this article, we propose a new classification for the cysts of the oral cavity. Briefly, we divide the different types of cysts in two major groups: 1) Cysts of oral bone tissue and periodontal, and 2) Soft tissue non-odontogenic cysts. Each group is, then, composed of different sub-groups, based on the established relationship with anatomical area, histological origin and clinical behavior (frequency, rate of recurrence, malignant potential). Table I depicts this classification with all the sub-groups. Following is a comprehensive description and discussion on this classification.

**Cysts and Pseudocysts of Oral Bone Tissue and Periodontal**

a) **Odontogenic cysts of “inflammatory origin”.** Radicular-necrotic cyst. The most common cyst of the oral cavity is due to the loss of the biological barrier (the pulp of the tooth) that follows from carious lesions or dental trauma (6, 13, 14) with pulp necrosis and derives from the cellular remnants of the “Malassez”. They can lead to the formation of an inflammatory radicular-necrotic cyst (RC), that can be periapical or peri-radicular. First event is the formation of a granuloma, that subsequently gives rise to a cyst, whose epithelium expresses a specific odontogenic CK such as 19 in the superficial cell layers (24-26) and co-expresses CK5 in the cyst lining (18). A peculiar variant of RC is considered the Residual Radicular Cysts that develop from apical granulomas or residual fragments of RC (5, 6).

**Collateral inflammatory cyst** (Paradental cyst, Juvenile paradental cyst). These cysts have overlapping histological features with RCs and their etiology is also considered inflammatory or meta-traumatic (3-5, 27). The inflammatory collateral cyst is located on the lateral side of a vital tooth and is the result of an inflammatory chronic process in the periodontal pocket (24-26). The juvenile paradental cyst of the lower molars (first-second) is located in the root area of the affected teeth of a young patient or distally to a lower wisdom tooth in adults (with appearance of pericoronitis) (27-29). These lesions are considered the same entity, regardless of localization (30). The histological features of these cysts are indistinguishable from those of the inflammatory RCs and this appearance emphasizes the origin from the remains of the Mallassez (14, 30-33).
It is important to differentiate these cysts from other radiolucent jaw lesions, such as unicystic ameloblastoma, keratocystic odontogenic tumor (KCOT), dentigerous cysts (DC), LPC. CKs expression can aid to make a differential diagnosis through a combination of immunohistochemical markers such as CK10, CK13, CK17, perlecan, PCNA and UEA, to discriminate between RC and the other pathological conditions (31-33).

b) Odontogenic cysts of “development origin”. Dentigerous cysts (DC). These cysts surround the crown of a tooth that has not migrated into the oral cavity and are named follicular, germinal, or eruptive cysts (Figure 1A) (7). The “primary event” is an accumulation of pathological fluid in the layer of the reduced enamel epithelium or between it and the crown of an un-erupted tooth. In this type of cysts, CK 5, 6, 19 are expressed, while CK7 is absent (18).

Periodontal tissue (parodontal cysts; Botryoid cyst). Because they are of dental origin and the periodontal tissue is contiguous to the teeth and bone, they form a single nosological-group, such as “cysts of the periodontal tissues”. The “cyst of the newborn” is its particular form discussed separately later. The cysts which affect the periodontal tissue are gingival cysts (frequently of the adults) (34) and periodontal cysts (lateral parodental cyst: LPC; its variant: botryoid cyst) (4, 31, 34-37) are unicystic (with differential diagnosis versus ameloblastoma cystic and “essential bone defects”) (36). There are two or three layers of flattened cells mimicking a squamous epithelium; with a careful search, it is possible to find areas of nodular type thickening and clear cells rich in glycogen (13). The LPC may have a variant, multilocular, defined as “botryoid cyst”. It can arise either from the remnants of Serres incorporated into the periodontal tissue, or, on the basis of an alternative hypothesis, from the reduced enamel epithelium of the follicle which expands to occupy a space in the periodontal ligament during the eruptive phase producing a paradontal cyst (38), while a portion of this may remain in the gum after the eruption forming a gingival cyst (39-42). LPCs are positive for CK13 and CK17 in the surface layers and perlecan and Ulex European Agglutinin (UEA) on the cell border of the whole layer, negative for CK10 (26). These cysts are made in relation to “remains of Malassez”, causing confusion: ERM expresses CK19 and periapical granuloma is positive for CK 4/13, while RC are positive for CK13 and 19 (8, 18, 24, 25, 29).

Botryoid odontogenic cyst (BOC). BOC is a rare pathological multilocular cyst (43, 44) with or without proximity to a root of tooth, considered a variant of the LPC (44-46), derived from more groups of converging cellular debris of Serres. However, because of the presence of mucous cells and of the columnar cells (metaplastic type) (16, 20, 45-47), it has been also considered to represent a variant of glandular odontogenic cyst (GOC) (3). CK 18, 13, specific for “rests of Serres”, show the origin from the odontogenic tissues (16,
oral cysts present neoplastic variants (3). In our opinion, it is important to underline the fact that in this site it is possible to find also neoplastic cysts (67, 68).

e) Cysts with malignant variants and misdiagnosis. Some oral cysts present neoplastic variants (3). In our opinion, it seems more useful to consider in the classification a specific group of cysts designed as "cysts with tumor variants and possible misdiagnosis", such as the calcifying odontogenic cysts (69-71), the orthokeratinized odontogenic cyst (72-75), and the glandular odontogenic cyst (71, 72).

f) Cysts and pseudocysts of the maxillary sinus. We think that it is important to report in this classification also cysts and pseudocysts of the maxillary sinus. For instance, secondary neoplastic cysts or pseudocysts of the maxillary sinus (Figure 1D) have a peculiar histological pattern with an epithelial lining with a basal layer of columnar cells and an overlying epithelium, thick and vacuolated. Moreover, groups of eosinophilic cells with not stainable cellular structures are visible in the epithelial lining or in the connective tissue capsule. We can distinguish three entities: simple intra-osseous COC, extra-osseous peripheral COC and the malignant form Calcifying Cystic Odontogenic Tumor (CCOT) (21, 23, 70-72, 79-81). COCs radiologically show a cystic imaging with small scattered areas of calcification, often resembling an odontoma (82). COCs (Figure 1D) have a peculiar histological pattern with an epithelial lining with a basal layer of columnar cells and an overlying epithelium, thick and vacuolated. Moreover, groups of eosinophilic cells with not stainable cellular structures are visible in the epithelial lining or in the connective tissue capsule in all layers of COC examined (85).
pseudo-cysts primitive of this anatomical region (94-103). The primary cysts of the maxillary sinus are of three types: a) true cysts, due to an occlusion of the excretory ducts of the sinus mucous glands; b) mucoceles, formed from the non-external drainage of normal mucous; c) secondary mucoceles, that result from post radical sinus surgery, probably due to residues of sinus mucosa forming a new mucocele in a closed compartment. The pseudocysts are formed between the inner surface of the bone wall and the connective tissue layer, the sinus mucosa remaining on the outside. Their etiology remains unknown, although allergies, inflammation of the maxillary sinus, and mucosal odontogenic inflammation have been considered (94, 99). Sometimes, the secondary odontogenic cysts (mostly follicular and radicular-necrotic), can develop in the bone base of the upper jaw and invade the maxillary sinus. These cysts are named “intrusive sinus oral cysts”.

g) Pseudocysts of the bone basis of the oral cavity (Solitary bone pseudo-cysts: SBP; aneurysmal bone cysts: ABP). SBPs are devoid of any epithelial lining and are considered of traumatic origin (36, 104). They are also known as bone pseudo-cysts or bone traumatic pseudo-cysts. ABPs are blood-filled sinusoidal or cavernous spaces without cystic epithelium (105, 106). The pathogenesis of these cysts is very similar to that of SBPs: a trauma can cause a bone hemorrhage and the clot may not be re-canalized leaving a cavity devoid of content (bone pseudo-cyst) or may present continuous micro-hemorrhages that may lead to the local reaction of macrophages (giant cell granuloma), or a vascular dilatation. Recently ABPs have been related to a ubiquitous protease USP-6 mapped on cromosoma16q22, that may be used as a diagnostic tool (107).

Soft Tissue Non-Odontogenic Cysts

In this group we consider: cysts related to the lymphatic tissue (cystic hygroma and lymphoepithelial cysts), and thyroglossal duct cyst (108-110).

Salivary cysts and pseudo-cysts. They should be referred to as salivary duct cysts and pseudo-cysts (111, 112). These cysts may be surrounded by salivary tissue and, thus, considered as retention cysts with an epithelial lining composed of one or two layers of flat or cuboidal epithelial cells. Alternatively, they may represent an extra-vasation of mucous in the peri-glandular connective tissue and, thus, considered pseudo-cysts by a rupture of the salivary duct with a partial epithelial lining, or mucous extra-vasation cysts.

The salivary retention cyst should be considered as a pseudo-cyst but this condition is the evolution of a process that begins with the formation of a retention cyst, and therefore it is considered as a "primary cause" of the salivary accumulation. Histologically, it may present oncocyte-like cells, a pseudo-stratified columnar epithelium or a stratified squamous epithelium. Ranula represents a mucocele of the floor of the mouth due to salivary accumulation in sublingual or submaxillary followed by its rupture and extravasation of saliva in the surrounding connective tissue. Since this happens frequently and prematurely, most of the ranulas do not have epithelial coatings. Ranulas can be located above the mylohyoid muscle (the simple type) or can grow downwards assuming an” hourglass shape” (the complex type or plumingranula) (110-112).

Nasolabial cyst (synonyms: naso-alueolar cyst, Klesia’s cyst). The concept that it is a fissural cyst, because it is related to the globule-maxillary cyst as its peripheral form is no longer valid, because there is no evidence of epithelial interruption of the interactions of his three embryological processes (56, 113-116). Histologically it consists of a cyst lined by a bi-layered epithelium with a cuboidal basal layer, sometimes pseudo-stratified, with goblet cells and areas of squamous metaplasia. CKs 5 and 6 are expressed in the basal layer cells, while CKs 7 and 19 are positive in all layers. The mucin in the goblet cells is MUC-2 and MUC-5AC positive similarly to the human lacrimal organs (113, 116). It is possible to speculate that it is a developmental non-odontogenic cyst of the soft tissue originating from the lower portion of the naso-lacrimal duct (116).

Dermoid and epidermoid congenital cysts (DEC). They (CK10 positive) derive from embryonic pluripotential cells trapped during the early weeks of intrauterine life; they, subsequently, develop into one or into all three ectoderm, mesoderm and endoderm tissues. The term “dermoid cyst” often refers to all types of these lesions (117-119). DEC are ubiquitous in the human body in sites where the embryonic parts fuse together. In the oral cavity they are classified as non-odontogenic cystic lesions of the soft tissue of the midline sites: the floor of the mouth (sublingual or submental), the tongue, cheek, parotid gland, mandibula (30, 112, 118).

Conclusion

A precise classification of cysts will always be subject to continuous revisions based on continuous scientific updates, however, it should be essentially based on the histological and clinical features of these diseases. The proposed classification takes into account the site of the primary growth, the histological origin, the frequency, the recurrences, and the potential malignancy, so drawing attention to those cysts that may present uncertainty concerning their immediate diagnosis. The use of new technologies such as the confocal laser microscope and new acquisitions on biology and genetic alterations in odontogenic lesions (120, 121) will be able to
add new data to the classification of the individual types of cysts. It is plausible to assume that in the future it will be possible to compile specific modules for each type of dental cysts with its peculiar structural and molecular features. This will allow a quick and very efficient comparison between the different types of cysts with a fast and safe diagnosis also versus tumors of the oral cavity.

References

1. Kramer IRH: Changing views on oral disease. Proc R Soc Med 67: 271-276, 1974.
2. Menditti D, Laino L, Milano M, Caputo C, Boccellino M, D’Avino A and Baldi A: Intraoral lymphoepithelial carcinoma of the minor salivary glands. In Vivo 26: 1087-1089, 2012.
3. Philipsen HP and Reichart PA: Revision of the 1992-edition of the WHO histological typing of odontogenic tumours. A suggestion. J Oral Pathol Med 31: 253-258, 2002.
4. Robson CD: Cysts and tumors of the oral cavity, oropharynx, and nasopharynx in children. Neuroimaging Clin N Am 13: 427-442, 2003.
5. Kumar M, Nanavati R, Modi TG and Dobariya C: Oral cancer: Etiology and risk factors: A review. J Cancer Res Ther 12: 458-463, 2016.
6. Philipsen HP and Reichart PA: Classification of odontogenic tumours. A historical review. J Oral Pathol Med 35: 525-529, 2006.
7. Menditti D, Laino L, Cicciù M, Mezzogiorno A, Perillo L, Menditti M, Cervino G, Lo Muzio L and Baldi A: Kissing molars: report of three cases and new prospective on aetio-pathogenetic theories. Int J Clin Exp Pathol 8: 15708-15718, 2015.
8. Speight, PM and Takata T: New tumour entities in the 4th edition of the World Health 8. Organization Classification of tumours of the mouth and pharynx. Head and Neck Pathol 5: 159-164, 2011.
9. Takada Y, Oikawa Y, Furuya I, Satoh M and Yamamoto H: Mucous and ciliated cell metaplasia in epithelial linings of odontogenic inflammatory and developmental cysts. J Oral Sci 47: 77-81, 2005.
10. Chatterjee S: Cytokeratin in health and disease. J Oral Maxillofac Surg 3: 198-202, 2012.
11. Kato T, Sato Y, Otsubo T, Koyama S, Kaneko S, Ikeda T: Keratocystic odontogenic tumor: a clinicopathological study of 50 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 107: 43-46, 2009.
12. Cibinovic BR, Reis BM and Freire-Maia B: Paradental (mandibular inflammatory buccal) cyst Head Neck Pathol 5: 159-164, 2011.
13. Tsuji K, Wato M, Hayashi T, Yasuda N, Matsushita T, Ito T, Gamoh S, Yoshida H, Tanaka A and Morita S: The expression of cytokeratin in keratocystic odontogenic tumor, orthokeratinized odontogenic cyst, dentigero-cyst and dermoid cyst. Med Mol Morphol 47: 156-161, 2014.
14. Ravi Prakash A, Sreenivas RP and Rajanikanth M: Paradental cyst associated with supernumerary tooth fused with third molar: A rare case report. J Oral Maxillofac Pathol 16: 131-133, 2012.
15. Schlagle WK, Ulles H, Riedricmhsa D, Uhna RI and Eredesai A: Cytokeratin expression patterns in the rat respiratory tract as markers of epithelial differentiation in inhalation toxicology. Determination of normal nykeratin expression patterns in nose, larynx, trachea, and lung. Toxypathology 26: 324-343, 1998.
110 Sameer KS, Mohanty S and Correa MM: Lingual thyroglossal duct cysts- a review. Das K. Int J Pediatr Otorhinolaryngol 76: 165-168, 2012.
111 Klestadt WD: Nasal cysts and the facial cleft cyst theory. Ann Otol Rhinol Laryngol 62: 84-92, 1953.
112 Suresh BV and Vorak S: Huge Plunging Ranula. Maxillofac. Oral Surg 11: 487-490, 2012.
113 Allard RH: Dissertations 25 years after date. Non-odontogenic cysts of the oral regions. Ned Tijdschr Tandheelkd 113: 278-283, 2006.
114 Falcis GM, Verli FD, Consolaro A and dos Santos CR: Morphological characterization of the nasopalatine region in human fetuses and its association to pathologies. J Appl Oral Sci 21: 250-255, 2013.
115 Toribio Y and Roehrl MH: The nasolabial cyst: a nonodontogenic oral cyst related to nasolacrimal duct epithelium. Arch Pathol Lab Med 135: 1499-1503, 2011.
116 Parwani R, Parwani S and Wanjari S: Diagnosis and management of bilateral nasolabial cysts. J Oral Maxillofac Pathol 17: 443-446, 2013.
117 Kurokawa I, Nishimura K, Hakamada A, Isoda K, Yamanaka K, Mizutani H and Tsubura A: Cutaneous dermoid cyst: cytokeratin and filaggrin expression suggesting differentiation towards follicular infundibulum and mature sebaceous gland. Oncol Rep 16: 295-299, 2006.
118 Aquino R, Laino L, De Marco G, Itro L and Menditti D: Dermoid cysts of the jaw. Intern J Clin Dentistry 3: 24-34, 2010.
119 Baisakhiya N and Deshmukh P: Unusual sites of epidermoid cyst Indian J Otolaryngol Head Neck Surg 63: 149-151, 2011.
120 Bonet C, Peñarrocha-Oltra D, Mínguez JM, Vera-Sirera B, Peñarrocha-Diago M and Peñarrocha-Diago M: Oral teratomas: a report of 5 cases. J Oral Maxillofac Surg 70: 2809-2813, 2012.
121 Wright JM and Vered M: Update from the 4th Edition of the WHO. Classification of Head and Neck Tumors: Odontogenic and Maxillofacial Bone Tumors. Head and Neck Pathol 11: 68-77, 2017.

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