

Maxillary Ameloblastoma: A Review With Clinical, Histological and Prognostic Data of a Rare Tumor

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Abstract. *Diagnosis of odontogenic tumors can be challenging due to their rarity and diverse morphology, but when arising near the tooth, the diagnosis could be suspected. When their location is not typical, like inside the paranasal sinuses, the diagnosis is less easy. Maxillary ameloblastomas are exceedingly rare with only sparse information on their epidemiological, histological and genetic characteristics. The aim of this report is to thoroughly review the available literature in order to present the characteristics of this tumor. According to available data, maxillary ameloblastomas can occur in all ages but later than mandible ones, and everywhere within the maxillary region without necessarily having direct contact with the teeth. No sex preference has been shown. The most common histological patterns seen in this location are the follicular and plexiform ones. Maxillary ameloblastomas are locally aggressive neoplasms, thus therapy aims for excision including normal bone beyond the lesion. In contrast to mandible ameloblastomas, maxillary ones most commonly show mutations of the SMO gene. Furthermore, differential tumor diagnosis is thoroughly discussed in the present review.*

Odontogenic tumors are rare and can pose diagnostic difficulties for non-specialized pathologists. Nevertheless, when the location is typical, *i.e.* molar region and when the histology shows the characteristic features of odontogenic

neoplasms, diagnosis could be straightforward. In locations outside the oral cavity or when rare histological variants are found, suspecting the correct diagnosis can be challenging. This is especially true for maxillary ameloblastomas, which are rare, possibly leading to low awareness of this neoplasm at this location and often show non-classical morphology, thus, rendering its diagnosis more complicated.

Thus, the aim of this review is to define and thoroughly describe maxillary ameloblastomas based on the available literature after a short introduction in the entity of ameloblastoma.

Introduction to Ameloblastomas. Ameloblastoma, initially called adamantinoma (from the greek word adamantinos ἀδαμάντινος-ἀ-δάμας, meaning very hard) from Broca (1) in 1867, belongs to odontogenic tumors. Odontogenic tumors are rare entities that constitute a heterogenous group of neoplasms with a variety of histological types and clinical behaviors (2). Their classification has seen many changes, from attempts to classify these lesions based on their histogenesis (3) or mechanisms of differentiation (4) to reach the final classification scheme set by the World Health Organization in 2017 (5) (Table I). Among all odontogenic tumors, ameloblastomas are the most common to encounter. Based on WHO 2017 (5), ameloblastomas are divided into i. ameloblastoma, which includes the previously named conventional, solid/multicystic and intraosseous ameloblastoma, ii. ameloblastoma, unicystic type, iii. ameloblastoma, extraosseous/peripheral type which includes the previously named soft tissue ameloblastoma, ameloblastoma of mucosal origin or of the gingiva and iv. metastasizing ameloblastoma.

Ameloblastomas are unusual entities that consist of approximately 1% of all benign tumors and cysts of the jaw (6). Their incidence is estimated to be 0.5 cases per million person-years worldwide (7), although in South Africa a slightly higher incidence has been reported (8). There is no

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Table I. WHO 2017 classification of odontogenic tumors (5).

Malignant odontogenic tumors	
Ameloblastic carcinoma	Histological features similar to ameloblastoma but with significant atypia and mitotic activity
Primary intraosseous carcinoma, NOS	Diagnosis of exclusion. Almost all lesions are composed of malignant nests or islands of squamous epithelium with minimal keratinization
Sclerosing odontogenic carcinoma	Sclerotic stroma in which bland, most commonly, compressed cells are found or less commonly arranged in thin cords or nests. Mitoses are infrequent.
Clear cell odontogenic carcinoma	Neoplasm composed of sheets and islands of vacuolated and glycogen rich clear cells. At the periphery of the islands there is a basaloid cell population (biphasic pattern).
Ghost cell odontogenic carcinoma	Highly infiltrating cystic or solid lesion composed of malignant rounded epithelial cells with high mitotic activity, variable number of ghost cells and aberrant keratinization. Dentine and necrosis may be present.
Odontogenic carcinosarcoma	A neoplasm similar to ameloblastic fibrosarcoma but with both mesenchymal and epithelial components being malignant
Odontogenic sarcoma	Bland epithelial component in variable amounts admixed with malignant stromal component showing nuclear crowding, atypia and increased mitoses.
Benign epithelial odontogenic tumors	
Ameloblastoma	Odontogenic epithelial islands peripherally palisaded by columnar cells with reversed polarity filled with loosely arranged angulated cells (simulating the stellate reticulum).
Ameloblastoma, unicystic type	Intraosseous cyst focally lined by characteristically ameloblastous epithelium (luminal type) or with additional intraluminal epithelial proliferations (intraluminal type).
Ameloblastoma, extraosseous/peripheral type	Ameloblastoma confined to the soft tissues, with no osseous involvement.
Metastasizing ameloblastoma	Simultaneous existence of ameloblastoma in a distal organ (<i>e.g.</i> lungs, lymph nodes, bones <i>etc.</i>) and primary ameloblastoma of either the mandible or the maxilla both with benign histological features
Squamous odontogenic tumor	Islands composed of bland epithelial cells showing squamous differentiation towards the center. The peripheral cells are flattened.
Calcifying epithelial odontogenic tumor	Polyhedral neoplastic cells with abundant cytoplasm, pleomorphic nuclei and low mitotic rate organized in island, cords, trabecula or sheets. Characteristic extracellular eosinophilic secretion (odontogenic amyloid protein) that ultimately calcifies into concentric rings (Liesegang rings)
Adenomatoid odontogenic tumour	Often encapsulated tumor with variable sized duct-like spaces lined by columnar or cuboidal epithelium with the nuclei displaced away from the lumen. Minimal stroma with spindle cells. Frequent eosinophilic material.
Benign mixed epithelial and mesenchymal odontogenic tumors	
Ameloblastic fibroma	Mesenchymal component: myxoid stroma with abundant spindle cells. Epithelial component: elongated strands with two tight epithelial layers of cuboidal or columnar epithelium. Occasionally there is a thickening towards the edges of the strands forming a stellate-reticulum like area.
Primordial odontogenic tumour	Loose fibrous tissue and stellate fibroblasts with minimal collagen deposition. The tumor is covered by columnar or cuboidal epithelium with underlying increased stroma cellularity
Odontoma	Compound: multiple teeth exhibiting dentin, cementum, enamel matrix, and pulp. Complex: disorganized or haphazard arrangement of pulpal tissues, enamel or dentin.
Dentinogenic ghost cell tumour	Ameloblastomatous cells with or without microcystic formation, basaloid type cells arranged in sheets, aberrant keratinization with variable number of ghost cells. Dentinoid or osteodentin-like material is formed directly adjacent to the epithelial cells.
Benign mesenchymal odontogenic tumors	
Odontogenic fibroma	It can be intraosseous or extraosseous. It consists of mature fibrous connective tissue with variable amount of inactive-looking odontogenic epithelium arranged in strands or islands. Calcification may be present.
Odontogenic myxoma/myxofibroma	Stellate and spindle cells dispersed with in abundant extracellular myxoid or myxofibrotic matrix.
Cementoblastoma	Calcified cementum-like tissue, which is deposited directly on a tooth root.
Cemento-ossifying fibroma	It is an ossifying fibroma that occurs in the tooth-bearing areas of the jaws.

sex preference and it is most commonly found in the fourth to fifth decade of life (5).

These tumors arise from remnants of the odontogenic epithelium, such as cell rests of the dental lamina, a

developing enamel organ, the lining of an odontogenic cyst or the basal cells of the oral mucosa (9). They mostly occur in the mandible (10). Conventional mandible ameloblastomas clinically present as a painless swelling of the posterior

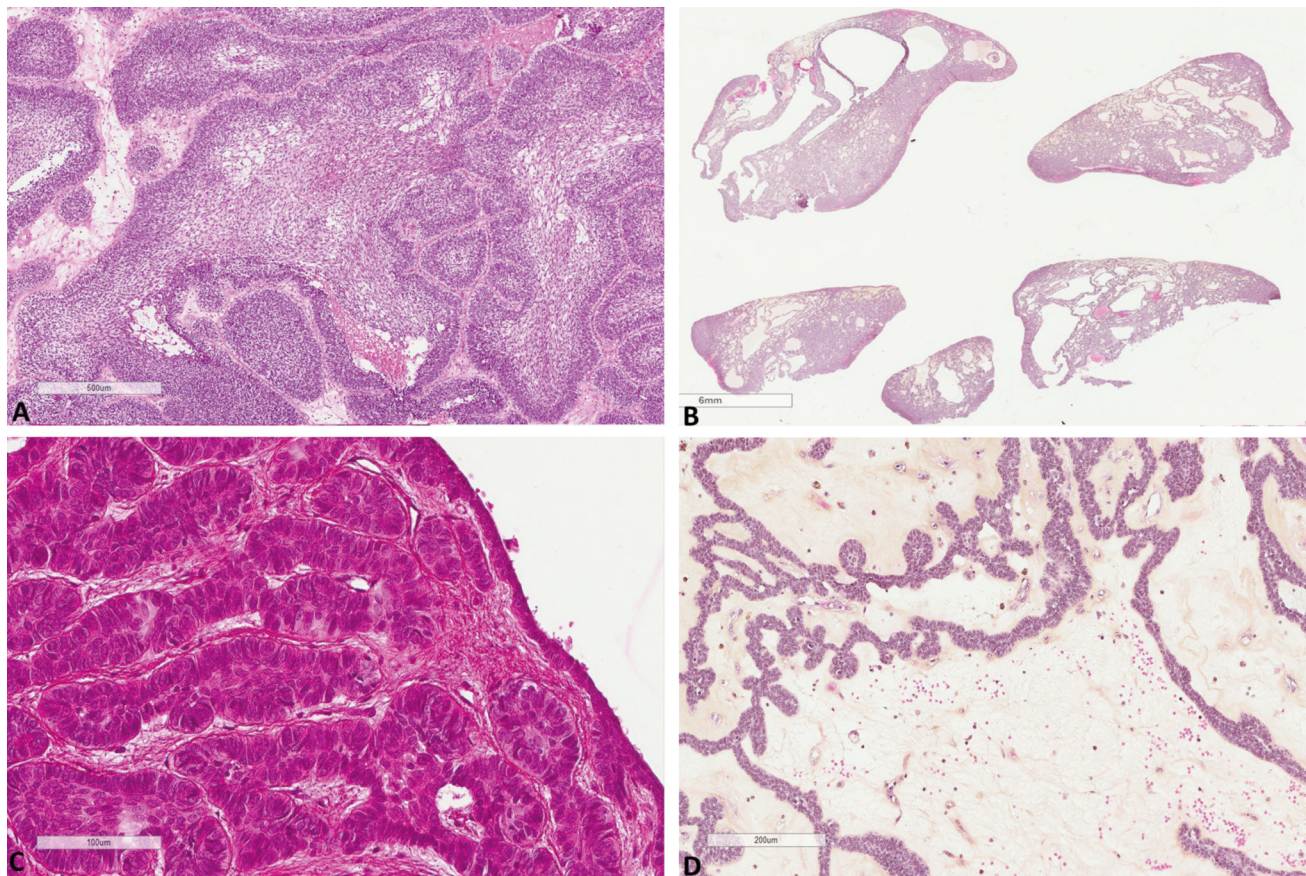


Figure 1. Different aspects of maxillary ameloblastomas. (A) Follicular pattern, showing large cell nests with palisading cell layers and a central part of stellate reticulum. (B) Microcystic areas can be seen. (C) Plexiform pattern, showing short strands of cells. (D) Plexiform pattern, showing very thin inter-anastomosing strands in an edematous background.

mandible, frequently being associated with an unerupted tooth and thus they can be easily detected (11).

The typical morphology of ameloblastomas is that of odontogenic epithelial islands simulating the stellate reticulum, peripherally palisaded by columnar cells with reversed nuclear polarity, filled with loosely arranged angulated cells (Figures 1 and 2, best appreciated in Figure 3D). No dentin or enamel (hard elements) formation is found. Ameloblastomas can present with a follicular, plexiform, acanthomatous, basaloid, granular cell or desmoplastic pattern, with no evidence of deviant biological behavior among them (Figure 1) (5). It is not uncommon to have a combination of two or more patterns in a tumor. The *follicular* pattern is the most common answered (5). It consists of neoplastic cellular nests with central loosening of short spindled epithelial cells resembling the stellate reticulum of the developing tooth germ, surrounded by palisading columnar cells with reverse nuclear polarity. The *plexiform* pattern shows a lace like architecture consisting of lamina like strands which show two distinct forms: one where the strands are formed by two layers of

basaloid cells and a second form where the strands are thicker and looser and the cells have a more squamous appearance. In both cases, this pattern can be deceiving as there is no evident peripheral palisading and reverse nuclear polarity. The *acanthomatous* pattern shows squamous metaplasia within the stellate reticulum with formation of keratin filled cavities. Granular cell type is characterized by granular change where all or some of the neoplastic cells of the stellate reticulum gain abundant deeply granular cytoplasm (accumulation of lysosomes). The basaloid ameloblastoma shows nuclear crowding and cells with basaloid appearance with or without peripheral palisading or reverse nuclear polarity. The desmoplastic variant is characterized by intense stromal desmoplasia which compresses the neoplastic islands of the epithelium, making it difficult if not impossible to identify the peripheral palisading and reverse nuclear polarity. Extra osseous/peripheral type ameloblastomas can show the same histological patterns as described above, but the follicular, plexiform and acanthomatous patterns, are the ones most commonly seen (5).

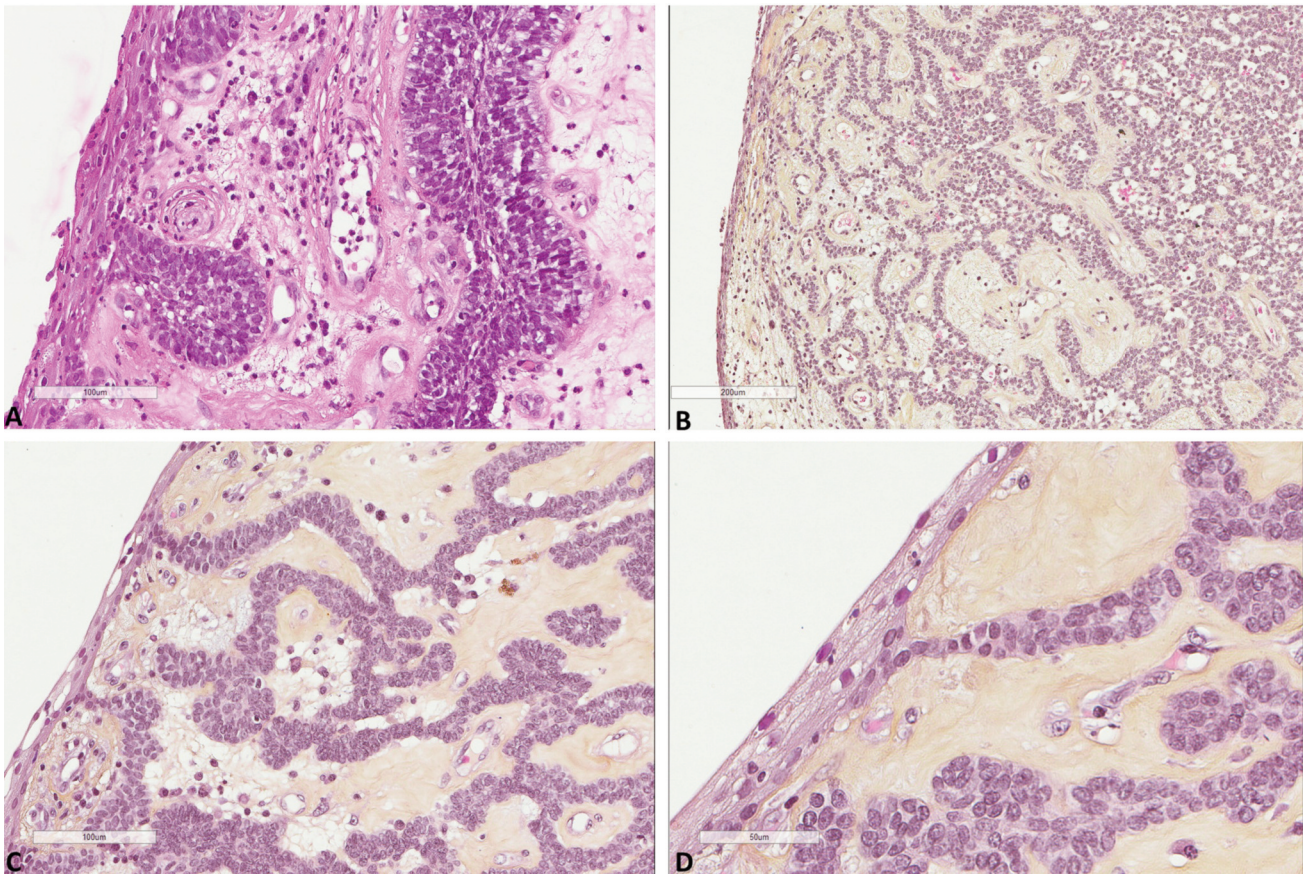


Figure 2. Continuity of tumor cells with surface epithelium. Three different cases of maxillary ameloblastomas (C and D, same case in different magnifications) showing the surface epithelium (left) communicating with the underlying tumor nests.

Recent studies have detected gene mutations in the mitogen-activated protein kinase (MAPK) pathway in most ameloblastomas, with mutations most commonly being *BRAF* V600E as well as *KRAS*, *NRAS*, *HRAS*, and *FGFR2* mutations (12).

Simple curettage of the neoplasm is linked to high incidence of recurrence (13). The current treatment of choice is wide surgical excision, including normal bone extending beyond the radiographical margins (5).

Maxillary ameloblastoma

Epidemiology. Ameloblastomas located in the maxillary region are rare compared to those arising in the mandible, the latter being five times more frequent (10). Indeed, maxillary ameloblastomas account for 15% of all ameloblastomas. Most of them arise posterior to the premolars and only 2% of them arise anterior to them (6, 10, 13). The natural history, epidemiology, localization, histopathology and prognostic factors remain unclear since there are only a few case series referring exclusively to maxillary ameloblastomas (Table II). A wide range of

ages has been reported for maxillary ameloblastoma, starting from early childhood, with a case of a six-year-old child being the younger patient reported (14) until elderly people with a case of an 81-year-old male were reported (15). It is worth noting that maxillary ameloblastomas occur about 10 years later than those arising in the mandible (11), probably representing the lack of evident early symptoms, while no sex predilection is found (16).

Signs and symptoms. Interestingly, maxillary ameloblastomas in contrast to mandibular ones, have a more aggressive clinical course (10). This is partially explained by the lack of early symptoms, leading to diagnosis at an advanced disease when the tumor has already extended beyond the maxilla (16, 17). When symptoms do develop, they include face deformity, usually unilateral, intraoral ulceration, toothache, headache, nasal obstruction, nasal epistaxis and visual disturbances (18, 19). Another reason for their aggressive behavior is the nature of the maxillary bone (20). In contrast to the compact mandible bone, the maxilla is a cancellous

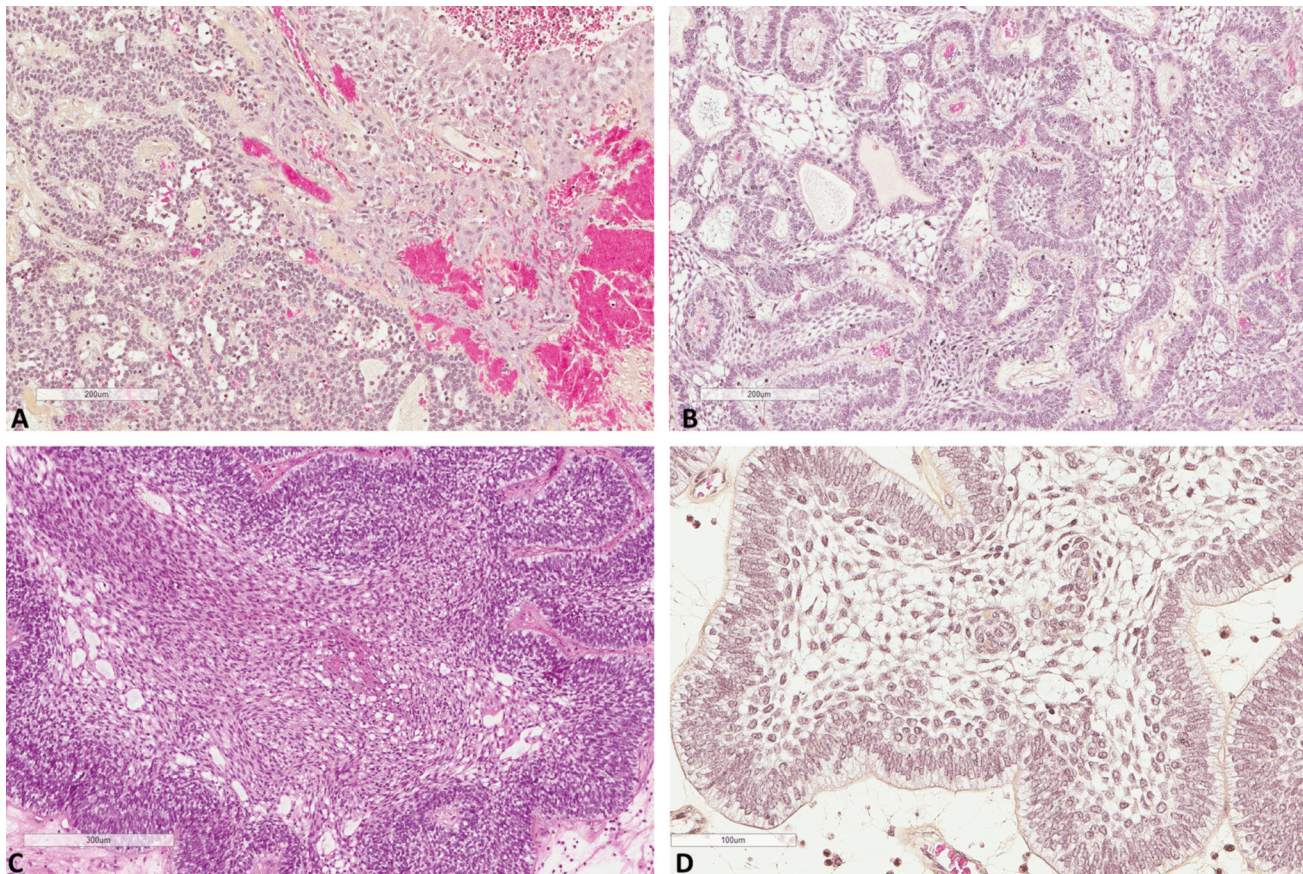


Figure 3. (A) Different components can be seen in the same tumor (left plexiform, right acanthomatous). (B) Follicular type maxillary ameloblastoma with evident stellate reticulum and palisading. (C) Follicular maxillary ameloblastoma with central spindle squamous cells. (D) The characteristic palisading cells with reversed polarity surrounding central stellate reticulum.

bone, making it easier for the tumor to invade and spread to adjacent structures such as the nasal cavity, paranasal sinuses, orbits, parapharyngeal tissues and skull base (2).

Histogenesis. The histogenesis of maxillary ameloblastomas remains controversial. In our experience, almost all maxillary ameloblastomas will show continuity of the tumoral cells with the overlying epithelium, if thoroughly examined (Figure 3). It has been suggested that maxillary ameloblastoma can derive from the odontogenic epithelium as mentioned above, but given this direct continuity with the overlying mucosal epithelium, an origin from the basal cells has been also hypothesized (15). Ide *et al.* studied 14 small ameloblastomas of the alveolar region and suggested that residues of odontogenic epithelium can be detected in all facial tissues, whether that is bone, the alveolar process or the gingiva (21). Thus, based on the latter theory, maxillary ameloblastomas can potentially arise everywhere within the maxillary region, without necessarily having direct contact with the teeth.

Location. The maxilla is a bone forming various facial cavities and walls. It is the roof of the mouth, the floor and lateral wall of the nasal cavity and the orbital floor. Thus, it forms part of the oral and nasal cavity, the maxillary sinus and part of the orbital cavity. Ameloblastomas can develop in all maxillary walls and cavities, in which case they are considered maxillary ameloblastomas. Physicians should carefully examine if these tumors are in contact with the maxillary bone. If the ameloblastoma is limited to the soft tissues, then it is considered to be of peripheral/extraosseous type. If bone infiltration is found, then additional characteristics should be used in order to classify it into the categories of conventional or unicystic, as described above for mandible ameloblastomas (Figure 4).

For descriptive reasons, maxillary ameloblastomas are also divided in posterior or anterior tumors (11). The first one is located posterior to the canine, thus it includes the molars and tuberosity and the second one is located anterior to the canine. Some authors also include the middle maxilla as a region of ameloblastomas origin, when they are situated between the

Table II. Maxillary ameloblastoma. Characteristics of published cases.

	No of cases Maxillary/ all cases	Age	Gender	Location	Histologic type	Recurrence	Metastasis	
Rockoff <i>et al.</i> 1963 (32)	SMALL IA 1951	173/925	32.7 average All cases	473F:514M	47% molar area 33% antrum and floor of nose 9% premolar area 9% canine area 2% palate	NA	NA	
	ROBINSON H.B.G. 1937	48/295	30.1 average All cases	142F:149M All cases	NA	NA	NA	
Sehdev <i>et al.</i> 1974 (13)	20/92		NA	9F:11M	NA	Follicular and plexiform most commonly	2/2 after RT 11/11 after initial curettage 1/3 treated with RM 1/2 after PM	1 with pleuro- pulmonary metastases
Shaw and Katsikas 1973 (18)	4/15		10-81	1F:3M	NA	Adamantinoma	2/4	NA
Tsaknis <i>et al.</i> 1980 (3)	NA		45.6 average	1F:2.4M	88% canine (posterior)	Follicular mixed	NA	NA
Bredenkam P <i>et al.</i> 1989 (33)	6		15-69	2F:6M	NA	Conventional: 1 Mixed, 2 follicular, 2 plexiform, 1 NA	4 cases	NA
Nastri <i>et al.</i> 1995 (22)	13		24-70	9F:4M	9 posterior maxilla 3 middle maxilla 1 anterior maxilla	Conventional: 4 follicular 7 mixed (4 follicular & acanthomatous, 3 follicular and plexiform) Unicystic: 1 plexiform	3 patients	NA
Reichart <i>et al.</i> 1995 (11)	*		Average 35.9%	1F:1.14M	49% molar region 14% maxillary sinus 5% nasal cavity	Follicular, plexiform, acanthomatous and mixed are the most common variants	Recurrence is twice as often in conservative therapy than in radical	NA
Schafer <i>et al.</i> 1998 (15)	24		43-81	5F:19M	Maxillary sinus or nasal cavity	Conventional: 22 plexiform 2 follicular	6 cases	NA
Zwahlen <i>et al.</i> 2002 (16)	5/26		26-73	3F:2M	Maxillary sinus, maxillary alveolar ridge, maxillary tuberosity, palate, sphenoidal sinus, ethmoidal complex	Conventional: 3 follicular 1 desmoplastic 1 acanthomatous 2 mixed: follicular & plexiform	2:5 1 after curettage 1 after n-block resection	1:5 brain, lungs, myocardium
Darshani Gunawardhana <i>et al.</i> 2010 (34)	31/286		NA	15F:16M	7 anterior 7 premolar 7 posterior 5 premolar+anterior 2 premolar+anterior +posterior 3 not specified	Conventional: 2 follicular, 2 plexiform, 2 acanthomatous, 1 mixed, 9 desmoplastic Unicystic: 15	Both mandible and maxillary 20/56 after curettage 2/27 after radical resection	NA

Table II. *Continued*

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	No of cases Maxillary/ all cases	Age	Gender	Location	Histologic type	Recurrence	Metastasis
Cosola <i>et al.</i> 2007 (35)	10	39.6 average	1F:1.3M	7 posterior 3 anterior 2 plexiform 1 acanthomatous 1 mixed	Conventional: 4 follicular	NA	NA
Ogunsalu <i>et al.</i> 2009 (36)	6	13-58	1F:1M	5 posterior 1 anterior	Conventional: 1 follicular Unicystic: 1 follicular NA for the rest cases	1 after multiple biopsies and hemi-maxilectomy	NA
Yang <i>et al.</i> 2016 (14)	51/890	6-79	13F:38M	15 anterior 36 posterior	Conventional: 23 follicular 24 plexiform 4 desmoplastic	29% after resection 10% after curettage (46,7% of the anterior located and 11,1% of the posterior located)	NA

RT: Radiotherapy, RM: radical maxilectomy, PM: partial maxilectomy. *This review includes case reports and reviews. Due to overlapping or missing data, the total number for each category varies, thus not included in this table. NA: Not available.

canine and maxillary molars (22). Ameloblastomas have a preference to the posterior maxilla, since only 2% have been reported to arise in the anterior region (22).

Histopathology. The most frequent histological patterns seen in maxillary ameloblastomas are the follicular and plexiform patterns followed by the acanthomatous one, which is observed as a part of mixed type frequently being focal and inconspicuous (Figures 1-3) (15, 22). Interestingly, the desmoplastic variant although being a rare variant, shows a predilection for the maxilla (23).

Immunohistochemistry. Although not pathognomonic, immunohistochemistry may be helpful in diagnosing ameloblastoma or excluding entities with histological characteristics similar to ameloblastoma (24). All ameloblastoma cells express CK19, which is considered an odontogenic epithelium marker, including areas of acanthomatous and granular differentiation (25, 26). The stellate reticulum cells usually stain for CK13 and Calretinin (24, 27), while the peripheral cells usually stain for CK14 and CD56 (28, 29). Ameloblastomas have a very low proliferation index (MIB1/Ki67), but malignant ameloblastomas can have a higher proliferation rate of almost 20% (30).

Differential diagnosis. A pathologist should be careful when rendering a diagnosis of ameloblastoma. Not only should he

include the possibility of such diagnosis in lesions of the maxillary lesion, but he should also exclude several entities that share similar histological features before reaching his final diagnosis.

Sinonasal papilloma enters this differential diagnosis especially due to the sinonasal location; inverted papilloma may show some overlapping histological features with ameloblastoma, especially the follicular and acanthomatous ones. However, epithelial cells of inverted papillomas show absence of reversed nuclear polarity, actual absence of stellate reticulum, and there is a basement membrane surrounding nests as well as numerous intraepithelial microcysts mostly containing neutrophils, both findings characteristic of the inverted sinonasal papilloma.

Ameloblastic and odontogenic fibromas characteristically have smaller nests, that generally do not fuse or anastomose and are set in an a more myxoid matrix with numerous stellate fibroblasts. Ameloblastic odontomas have similar epithelial elements as ameloblastoma but they also include hard elements (enamel and dentin). In contrast to ameloblastoma, adenomatoid odontogenic tumor has reverse polarity away from a central lumen and not in the basal layer surrounding nests of cells resembling the stellate reticulum (Table III).

Non-keratinizing squamous cell carcinoma has an anastomosing ribbon like architectural pattern that could resemble ameloblastoma, especially the plexiform pattern,

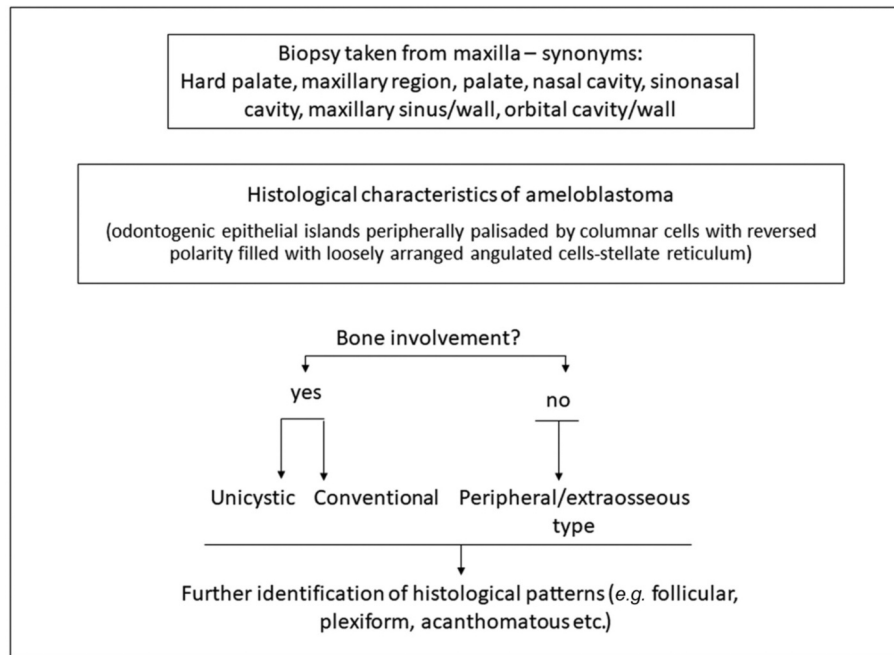


Figure 4. Maxillary ameloblastomas diagnostic approach.

Table III. Suggested references for further reading.

Yang <i>et al.</i> (14)	One of the largest and most recent series of ameloblastoma with prognostic data
Darshani Gunawardhana <i>et al.</i> (34)	Another large series comparing maxillary with mandibular ameloblastomas
Reichart <i>et al.</i> (11)	Molecular profile of ameloblastomas
Sweeney <i>et al.</i> (12)	Molecular profile of ameloblastomas
Slootweg (37)	Description of tooth formation to better understand odontogenic lesions
Bilodeau <i>et al.</i> (38)	A useful introduction in odontogenic tumors
Wright <i>et al.</i> (39)	A useful introduction in odontogenic and maxillofacial bone tumors

but there is marked nuclear atypia, loss of polarity and numerous mitoses, characteristics not compatible to the latter. Adenoid cystic carcinoma (ACC) in its typical form with cribriform structures may not be a diagnostic problem, however, its solid variant should enter the differential diagnosis of ameloblastoma. Immunohistochemical expression of CD117 in ACC cells could be helpful in this case. Mucoepidermoid carcinoma, may resemble ameloblastoma but attentive examination reveals three cell types, mucous, squamous and intermediate. Basal cell adenocarcinoma is a rare, yet worth to be included in the differential diagnosis entity. The main histological findings are the lack of reverse nuclear polarity, as well as the architectural pattern of basal cell adenocarcinoma, which shows a more confluent pattern rather than the anastomosing pattern seen in ameloblastomas. Basal cell carcinoma can be

easily excluded immunohistochemically using keratin 19 which is negative in basal cell carcinoma and positive in ameloblastoma (31).

Molecular biology. Maxillary ameloblastomas, as the mandibular ones, have been associated with certain gene mutations. Interestingly, maxillary ameloblastomas do not have the same gene mutations as the mandibular ones. They most frequently harbor a *SMO* mutation followed by a *RAS* mutation and less frequently a *BRAF* or *FGFR2* mutation (12).

Treatment. Despite the fact that treatment for mandibular ameloblastomas is relatively well defined, treatment for maxillary ameloblastomas has not yet been established. In brief, simple curettage of maxillary ameloblastomas has up to 100% possibility of local recurrence (13). In contrast,

more radical approaches, such as *en bloc* resection with the possibility of 10-15 mm thickness of normal bone as margin, have shown lower percentages of recurrence (13).

Conclusion

Ameloblastomas are odontogenic epithelial tumors mostly involving the mandible. Maxillary ameloblastomas, on the other hand, are rare and therefore not easy to be suspected. After collecting available literature data, we showed that there is no sex predilection and that maxillary ameloblastoma can arise in all ages, but a decade later than the mandible ones. They can be found anywhere within the maxillary region and they are not necessarily associated to a tooth. The follicular and plexiform types are the most frequently observed histological patterns. In contrast to mandible ameloblastomas, the maxillary ones show *SMO* mutations followed by *RAS* mutations and only a few have *BRAF* and *FGFR2* mutations. Excision should be wider for patients with maxillary ameloblastomas since it shows a more aggressive behavior threatening neighboring structures.

Conflicts of Interest

The Authors have no conflicts of interest to disclose.

Authors' Contributions

All Authors contributed to data collection and analysis. ZE drafted the manuscript. All Authors revised and approved the final form.

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