



INVITED MEDICAL REVIEW

Ameloblastoma: current etiopathological concepts and management

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Ameloblastoma is a benign odontogenic tumor of epithelial origin. It is locally aggressive with unlimited growth capacity and has a high potential for malignant transformation as well as metastasis. Ameloblastoma has no established preventive measures although majority of patients are between ages 30 and 60 years. Molecular and genetic factors that promote oncogenic transformation of odontogenic epithelium to ameloblastoma are strongly linked to dysregulation of multiple genes associated with mitogen-activated protein kinase, sonic hedgehog, and WNT/ β -catenin signaling pathways. Treatment of ameloblastoma is focused on surgical resection with a wide margin of normal tissue because of its high propensity for locoregional invasion; but this is often associated with significant patient morbidity. The relatively high recurrence rate of ameloblastoma is influenced by the type of molecular etiological factors, the management approach, and how early the patient presents for treatment. It is expected that further elucidation of molecular factors that orchestrate pathogenesis and recurrence of ameloblastoma will lead to new diagnostic markers and targeted drug therapies for ameloblastoma.

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Introduction

Ameloblastoma is an aggressive odontogenic tumor that forms from odontogenic epithelium within a mature fibrous stroma devoid of odontogenic ectomesenchyme (Sciubba *et al*, 2005). Although classified as a benign

tumor, ameloblastoma is also the most common odontogenic tumor of epithelial origin with severe clinical implications (Bassey *et al*, 2014). Ameloblastoma has a locally aggressive growth pattern; about 70% of cases undergo malignant transformation, and up to 2% metastasize to other sites (Odukoya and Effiom, 2008; DeVilliers *et al*, 2011).

Ameloblastoma constitutes about 14% of all jaw tumors and cysts, and it is the most prevalent odontogenic tumors in developing countries (Lasisi *et al*, 2013; Oginni *et al*, 2015). The global incidence of ameloblastoma is 0.5 cases per million persons per year (Brown and Betz, 2015), and it is a highly encountered odontogenic tumor in Africa and China (Bassey *et al*, 2014). In the Western Hemisphere, ameloblastoma is second to odontoma as the most common odontogenic tumor, but the African American population is five times more likely to develop ameloblastoma compared to the Caucasian population (McClary *et al*, 2016). Most patients with ameloblastoma are between ages 30 and 60 years, but average age at time of diagnosis varies from continent to continent estimated to be approximately 42.3 and 30.4 years in Europe and Africa, respectively (Olusanya *et al*, 2013; Oomens and van der Waal, 2014). Only 10–15% of ameloblastoma cases occur in the pediatric population, but this can be as high as 25% in Africa and Asia (Bansal *et al*, 2015).

Ameloblastoma histologically resembles the enamel organ of a developing tooth that has no intention of forming dental hard tissues because the stroma lacks the properties of dental mesenchyme. Despite the similarities, it is intriguing that ameloblastoma still displays a distinctive clinically invasive and aggressive growth pattern. Due to naivety and limited healthcare facilities, ameloblastoma patients in developing countries often present with massively grown lesions before seeking care (Anyanechi and Saheeb, 2014; Bassey *et al*, 2014; Figure 1).

Advances in etiopathogenesis of ameloblastoma

Etiological factors associated with ameloblastoma have evolved over the years and are yet to be conclusively established. Earlier etiological theories were related to

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Figure 1 Maxillary Ameloblastoma. Extensive maxillary ameloblastoma in an African male patient. Note the extensive ameloblastoma-induced facial disfigurement and teeth displacement due to delayed access to treatment (Picture courtesy of Professor G. T Arotiba, Faculty of Dental Sciences, University of Lagos, Lagos Nigeria)

trauma, inflammation, nutritional deficiencies, non-specific irritation from extractions, and dental caries (Brown and Betz, 2015). As development of odontogenic tumors was associated with remnants of the migrating epithelium at the cervical loop of the enamel organ, it was not surprising that development of ameloblastoma was also linked to the enamel organ, remnants of odontogenic epithelium, and lining of odontogenic cyst (Sciubba *et al*, 2005). This odontogenic etiological origin was further supported by the similarities in the expression profiles of cytokeratin and vimentin between the developing tooth germ and ameloblastoma (Brown and Betz, 2015). Another earlier theory was associated with morphodifferentiation of pre-ameloblasts to ameloblasts during the bell stage of tooth development. It was believed that affected pre-ameloblasts propagate in the bell stage during tooth development instead of functionally inducing enamel protein synthesis and matrix deposition (Fan *et al*, 2012). Other studies have proposed that the absence of stratum intermedium hinders the differentiation of pre-ameloblasts to ameloblasts because the stratum intermedium produces alkaline phosphatase needed to breakdown nutritional elements that will be passed on to ameloblasts during the bell stage. This theory has been strengthened by the impaired ameloblast function and enamel deposition observed in *Msx-2* null mice that lacked functional stratum intermedium cells (Jussila and Thesleff, 2012). It should also be taken into account that the stellate reticulum within the tumor nests of columnar epithelium can degenerate to form microscopic cysts. The coalescing of these microcysts to form larger cystic spaces gives the multicystic features of ameloblastoma (Gupta *et al*, 2011).

At the molecular level, the genetic factors involved in tooth development, morphogenesis, cytodifferentiation, and tooth patterning have been associated with development of ameloblastoma because some of these are altered

significantly in ameloblastic tissues. An analysis of 34 different genes demonstrated 11 overexpressed and 23 under-expressed genes relative to normal (Heikinheimo *et al*, 2002). Some of the overexpressed genes include *c-fos* proto-oncogene (FOS), tumor necrosis factor receptor 1A (TNFRSF1A), collagen type VIII alpha 1 (COL8A1), cyclin-dependent kinase inhibitor 1A (CDKN1A), matrix metalloproteinase 12 (macrophage elastase) (MMP-12), and matrix metalloproteinase 13 (collagenase 3) (MMP-13). The genes highly underexpressed included sonic hedgehog (SHH), TNF receptor-associated factor 3 (TRAF3), deleted in colorectal carcinoma, Rho GTPase-activating protein 4 (ARHGAP4), cadherin 12 (CDH12), cadherin 13 (CDH13), teratocarcinoma-derived growth factor 1 (TDGF1), transforming growth factor beta 1 (TGFB1), patch (PTCH), and bone morphogenetic protein 2 (BMP2; Heikinheimo *et al*, 2002). More recent studies have also identified overexpression of WNT5A (wingless-type MMTV integration site family, member 5A) and WNT-1 that suggests they might be associated with the development of ameloblastoma (Sukarawan *et al*, 2010; Siar *et al*, 2012b). These earlier genetic studies were performed using microarrays, but more recently, some of these candidate genes have been sequenced to identify the mutations and variants associated with ameloblastoma (Heikinheimo *et al*, 2002). The molecular pathogenesis of ameloblastoma is now attributed to dysregulation of the mitogen-activated protein kinase (MAPK) pathway based on studies using ameloblastoma tissues, cell lines, and transgenic mice (Brown and Betz, 2015). BRAF, a serine/threonine protein kinase activating the MAPK/ERK signaling pathway strongly associated with melanoma, has also been implicated in over 63% of ameloblastoma (Brown *et al*, 2014; Kurppa *et al*, 2014; Sweeney *et al*, 2014). Interestingly, over 90% of BRAF mutations involve a substitution of valine for glutamate at codon 600 (V600E; Kurppa *et al*, 2014; Brown *et al*, 2015; Fregnani *et al*, 2017). The mutation causes constitutive activation of BRAF protein downstream of MEK/ERK that ultimately results in neoplastic transformation (Niault and Baccarini, 2010). To further strengthen the association of MAPK signaling with ameloblastoma, the mutations in the RAS gene that acts upstream of BRAF and fibroblast growth factor receptor 2 (FGFR2), a membrane-bound activator of MAPK signaling, have also been identified in ameloblastomas (Brown *et al*, 2014; Sweeney *et al*, 2014). Additionally, mutations in non-MAPK signaling genes especially smoothened (SMO), a G protein-coupled receptor and signaling effector component of the SHH signaling pathway, have also been described in ameloblastoma (Mishra *et al*, 2015). Taken together, these more recent molecular data strongly indicate the existence of unique genetic abnormalities that eventually lead to development of ameloblastoma (Sweeney *et al*, 2014; Brown and Betz, 2015; Brown *et al*, 2015).

Advances in histopathogenesis of ameloblastoma

As our understanding of odontogenic tumors including ameloblastoma increases, the classification of

ameloblastoma will continue to evolve (Wright *et al*, 2014). According to an established World Health Organization (WHO) report on odontogenic tumors, ameloblastoma was classified into benign and malignant types based on its biologic behavior (Sciubba *et al*, 2005). Based on this report, each type was further subdivided into four subtypes based on anatomic location and histopathology. In order of frequency, the benign ameloblastomas include (i) solid/multicystic ameloblastoma, (ii) unicystic ameloblastoma, (iii) peripheral (or extraosseous) ameloblastoma, and (iv) desmoplastic ameloblastoma. Similarly, malignant ameloblastomas based on order of frequency include (i) metastasizing ameloblastoma, (ii) primary ameloblastic carcinoma, (iii) secondary intraosseous ameloblastic carcinoma, and (iv) secondary peripheral ameloblastic carcinoma (Table 1; Reichart *et al*, 1995; Sciubba *et al*, 2005). While the WHO classification provided a good guidance for management, it lacks precise terminology which limits its diagnostic application and international acceptance (Wright *et al*, 2014). A more contemporary classification of odontogenic tumors including ameloblastoma was proposed recently (Wright *et al*, 2014). The recommendations indicate that there is an authentic and existing concept of

unicystic ameloblastoma, and most conventional ameloblastomas microscopically and macroscopically present with cystic degeneration. Therefore, the term ‘multicystic’ adds no worth but misperception to the designation ‘solid multicystic ameloblastoma’. Hence, conventional lesions should simply be called ‘conventional ameloblastoma’ and the term ‘solid/multicystic’ be discarded. Additionally, the predominance of plexiform ameloblastoma in the posterior maxilla is not a reason for separating it as a different entity because it is still the distinctive site of occurrence for conventional ameloblastoma, so it should be considered as a histological type of conventional ameloblastoma. It was also proposed that the unique radiographic features of desmoplastic ameloblastoma, distinct from other histological types/subtypes, are a function of the desmoplasia. So, desmoplastic ameloblastoma should be simply noted for its distinctive radiographic and clinical presentation and considered a histological type like plexiform ameloblastoma rather than being considered as a separate entity (Wright *et al*, 2014). The proposed recommendations also stated that unicystic ameloblastoma is comprised of luminal and mural histopathological variants. Luminal unicystic ameloblastoma presents as a cystic

Table 1 Clinicohistological types of ameloblastoma. Clinical, histologic, and radiographic features of the histological subtypes of ameloblastoma

<i>Clinicohistologic types of ameloblastoma</i>				
<i>Types of ameloblastoma</i>	<i>Synonyms</i>	<i>Salient features</i>	<i>Conventional radiographic features</i>	<i>Histopathological variants</i>
Benign				
Solid/multicystic	Conventional/Classical ameloblastoma	Mean age: 36 years Male > female Slightly higher in mandible	Unilocular radiolucency Multilocular radiolucency Unerrupted tooth Root resorption	Cystic, acanthomatous, granular, basaloid, spindle, clear cell, hemangiomatous
Unicystic	Cystogenic ameloblastoma	Dentigerous type: Mean age: 16.5 years Male > female Non-dentigerous type: Mean age: 35.2 years Female > male Slightly higher in mandible (posteriorly)	Unilocular radiolucency Multilocular radiolucency Unerrupted tooth Unilocular radiolucency Multilocular radiolucency	Luminal (plexiform unicystic, intraluminal), mural
Peripheral	Extraosseous/soft tissue ameloblastoma	Mean age: 51 years Male > female Slightly higher in mandible Exophytic Mean size 1.3 cm	Saucerization	Not applicable
Desmoplastic	Ameloblastoma with pronounced desmoplasia	Mean age: 41.6 years Female = male Maxilla = mandible	Mixed radiolucent/radiopaque Root resorption	Hybrid Desmoplastic ± osteoplasia
Malignant				
Metastasizing	Malignant ameloblastoma	Mean age: 34.4 years Male > female Slightly higher in mandible Distant sites: lungs and other areas	Same as solid/multicystic	Same as solid/multicystic
Primary ameloblastic carcinoma	Not applicable	Mean age: 53 years Male > female Higher in mandible (posteriorly)	Ill-defined multilocular radiolucency Foci of calcification	Not applicable
Secondary ameloblastic carcinoma (intraosseous)	Carcinoma ex intraosseous ameloblastoma	Rapid growth, 7th decade Male > female Slightly higher in mandible	Ill-defined multilocular radiolucency Foci of calcification	Not applicable
Secondary ameloblastic carcinoma (peripheral)	Carcinoma ex peripheral ameloblastoma	Male = female Alveolar bone resorption	Interradicular radiolucency	Not applicable

lesion lined by ameloblastomatous epithelium which may protrude into the lumen in plexiform proliferations (referred to as intraluminal subtype), while mural unicystic ameloblastoma presents with ameloblastomatous epithelial cells within the cyst wall. The recommendations suggested that mural invasion should be viewed as conventional ameloblastoma due to its relatively higher recurrence rate when compared with the luminal type (Wright *et al*, 2014).

The most common ameloblastoma is the solid/multicystic/conventional type, making up about 91% of all cases of ameloblastoma. It is slow growing and runs a benign course. Histologically, the solid/multicystic/conventional ameloblastoma displays two distinct histological patterns: the follicular and plexiform types. The follicular type displays proliferating odontogenic epithelial cells arranged in islands, while plexiform type displays epithelial cells arranged in continuous anastomosing strands (Figure 2). It is not uncommon for an ameloblastoma to display both histological patterns. In addition to these two histological types, cystic, granular, acanthomatous, spindle cell, basal cell, clear cell, and other microscopic subtypes have been reported (Table 1).

Unicystic ameloblastoma is the second most common ameloblastoma and accounts for about 5–15% of all cases (Dhanuthai *et al*, 2012). It is most often seen in younger patients with average age of 26.1 years, and its main location is the posterior mandible where it often presents as an asymptomatic swelling (Bansal *et al*, 2015). The majority of unicystic ameloblastomas resemble dentigerous cyst because of their association with an unerupted tooth. The WHO classification (Sciubba *et al*, 2005) and the more recent recommendations (Wright *et al*, 2014) consider two main histopathological variants of unicystic ameloblastoma, the luminal and mural (Figure 3). The luminal variant displays a cystic pattern lined by ameloblastomatous epithelium that protrudes into the lumen as plexiform proliferations that look like an intraluminal subtype. The mural variant displays either follicular or plexiform arrangement of ameloblastomatous epithelial cells within the cystic wall. It is not uncommon for both variants to be observed in the same ameloblastoma lesion (Figure 3).

Peripheral ameloblastoma is the least common variant of ameloblastoma, accounting for just 1% of ameloblastoma cases (Odukoya and Effiom, 2008; Siar *et al*, 2012a). Mostly affected are middle-aged patients with an average age of 52 years. These lesions are more common in the mandible than the maxilla and are found on posterior gingiva or alveolar sulcus. Histologically, peripheral ameloblastoma consists of islands of ameloblastic epithelium with similar histological pattern as solid/multicystic/conventional ameloblastoma (Figure 4a).

Desmoplastic ameloblastoma presents as a slow-growing painless swelling, but radiologically, it displays a mixed radiolucent/radiopaque pattern and irregular borders. The histological feature of extensive stromal dysplasia is pathognomonic (Figure 4b). It consists of islands of odontogenic epithelium with variable shapes and sizes proliferating within a highly collagenous connective tissue. The thick collagen fibers tend to compress the odontogenic epithelial islands from the periphery, giving rise to the bizarre shapes and sizes. It is not uncommon for desmoplastic ameloblastoma to contain metaplastic bone formations.

Metastasizing or malignant ameloblastoma is a previously benign ameloblastoma that has metastasized to a distant site usually the lungs. It is diagnosed based on clinical features and the rationalization that both primary and metastatic lesions display similar histological features of solid/multicystic/conventional ameloblastoma. Ameloblastic carcinoma can develop *de novo*: This is the primary type. Alternatively, it can develop secondarily from an initially benign ameloblastoma that loses differentiation to become a carcinoma. Ameloblastic carcinomas grow more rapidly and aggressively and can present as painful swellings that perforate the cortical bone. Histologically, ameloblastic carcinoma combines the overall histological patterns of an ameloblastoma with cytological atypia consisting of abnormal mitotic activities, cellular and nuclear hyperchromatism, and focal necrosis (Sciubba *et al*, 2005) (Figure 5).

Ameloblastoma presents clinically as a slow-growing relatively painless tumor. Due to its locally aggressive growth characteristics, ameloblastoma can rapidly become

Solid/multicystic/conventional ameloblastoma

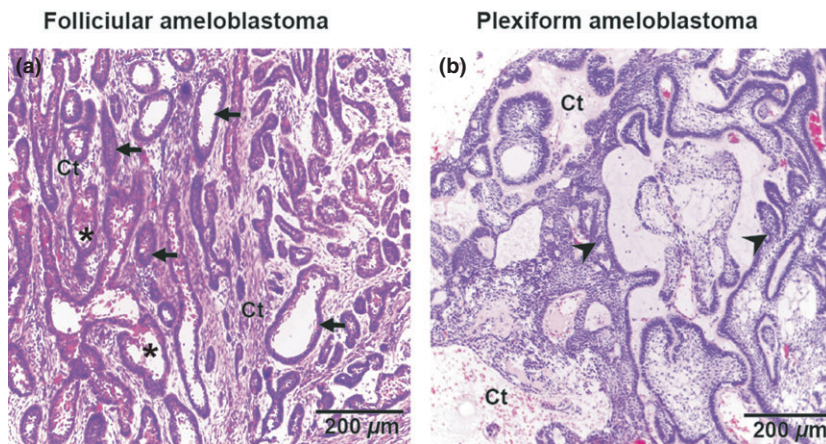


Figure 2 Solid/Multicystic/Conventional ameloblastoma. (a) Follicular ameloblastoma connective tissue (Ct) contains islands of odontogenic epithelium (black arrows) delineated by peripheral columnar cells that display reverse polarization. There are islands of cystic degeneration containing central loose stellate reticulum-like cells (*). (b) Plexiform ameloblastoma connective tissue contains long anastomosing cords of odontogenic epithelium (black arrowheads) delineated by peripheral columnar cells that display reverse polarization and central loose stellate reticulum-like cells

Unicystic ameloblastoma

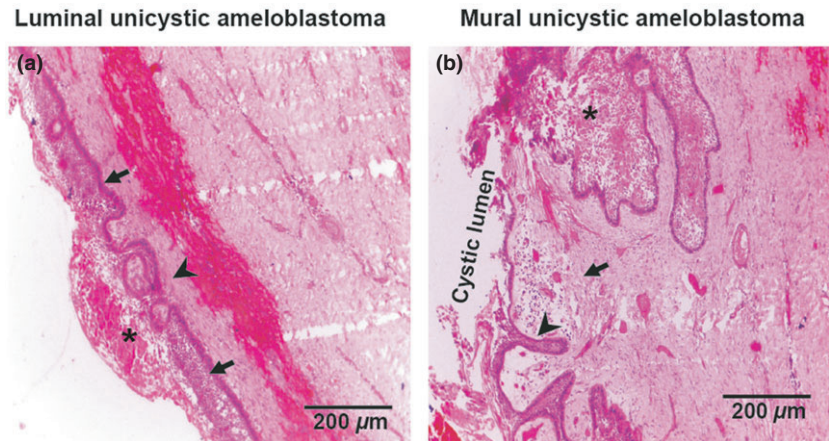


Figure 3 Unicystic ameloblastoma. (a) Luminal unicystic ameloblastoma demonstrates a fibrous cystic wall (black arrowhead) lined by ameloblastic epithelium (black arrow) and loose stellate reticulum-like cells (*). (b) Mural unicystic ameloblastoma demonstrates fibrous cystic wall (black arrow), infiltration of ameloblastic epithelium into the cystic wall (black arrowhead), and loose stellate reticulum-like cells (*)

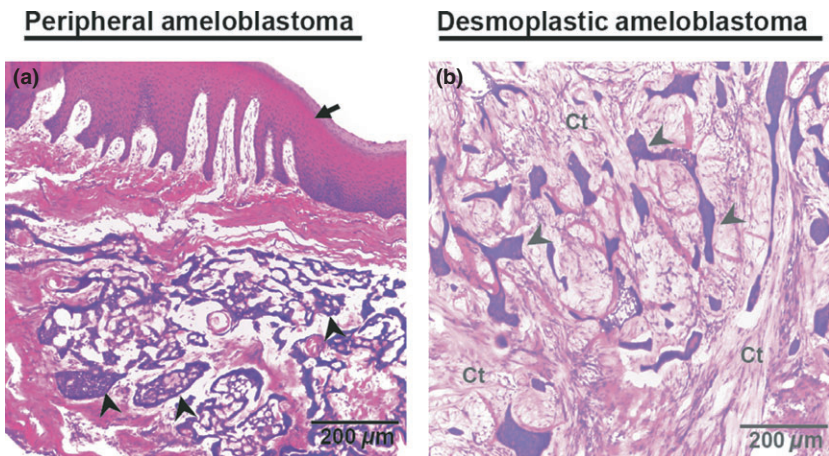


Figure 4 Peripheral and desmoplastic ameloblastomas. (a) Peripheral ameloblastoma demonstrates odontogenic epithelial islands within the connective tissue overlaid by stratified squamous epithelium of the oral mucosa (black arrow). (b) Desmoplastic ameloblastoma demonstrates hyalinized densely collagenized connective tissue stroma (Ct) embedded with islands of cords of odontogenic epithelium (black arrowheads)

Ameloblastic carcinoma

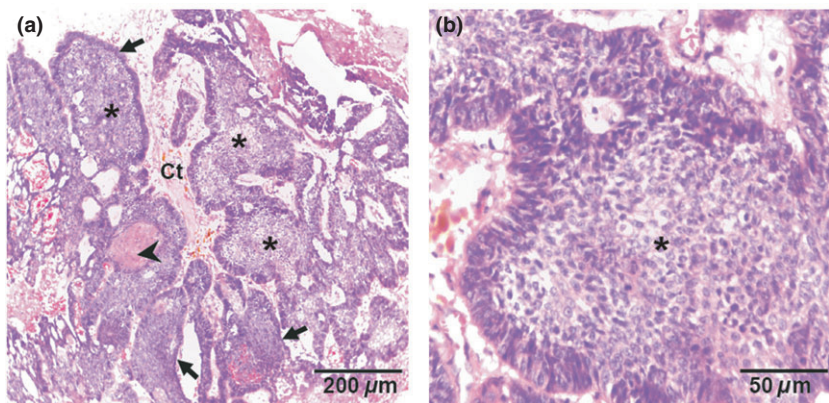


Figure 5 Ameloblastic carcinoma. (a) At low magnification, ameloblastic carcinoma contains odontogenic epithelial islands (black arrows) lined by peripheral ameloblast-like cells within the connective tissue stroma (Ct). The epithelial islands contain central stellate reticulum-like cells (*) that display acanthomatous changes (black arrowhead). (b) At higher magnification, the central stellate reticulum-like cells (*) surrounded by peripheral ameloblast-like cells display nuclear hyperchromatism, pleomorphism, and mitotic figures

a massive and expansile tumor causing tooth mobility, tooth displacement, and a grotesque facial appearance if the patient delays getting treatment (Figures 1 and 6). The constitutive activation of BRAFV600E associated with development of ameloblastoma has also been attributed to its progression (Kurppa *et al*, 2014). This mutation correlates with several clinicopathological features of

ameloblastoma such as location within the jaw, age of patient at diagnosis, histology, and possibly prognosis. For example, BRAF mutations have been shown to occur more in the mandible and in younger patients (Brown and Betz, 2015), while BRAF wild-type ameloblastomas occurred more in the maxilla and displayed shorter recurrence-free survival (Brown *et al*, 2014).



Figure 6 Postsurgical recurrence of mandibular ameloblastoma. Extensive mandibular ameloblastoma (a) in a young female African patient was treated by radical mandibulectomy (b) with acceptable postsurgical appearance (c). Another ameloblastoma developed in the maxilla 14 years later (d) (Picture courtesy of Professor G. T Arotiba, Faculty of Dental Sciences, University of Lagos, Lagos Nigeria)

Normal bone remodeling is regulated by the interactions of receptor activator of nuclear factor kappa B (RANK) on osteoclast precursors with its osteoblast membrane-bound ligand (RANKL). Osteoblasts also secrete osteoprotegerin (OPG), a soluble receptor that interacts with RANKL to control RANK–RANKL interactions (Stefanik *et al*, 2008). As RANK, RANKL, and OPG are expressed in different variants of ameloblastoma, dysregulated RANK-RANKL signaling and altered levels of OPG have been associated with lesional bone loss in ameloblastoma (de Matos *et al*, 2013). The caspase-mediated apoptotic system is also disparately regulated in different variants of ameloblastoma leading to aberrant survival of ameloblastic tissue. The strong immunoreactivity of pAKT and PI3K in some variants of ameloblastoma, especially the plexiform histological pattern, suggests that AKT/PI3K pathway may be promoting proliferation of ameloblastic cells (Jhamb and Kramer, 2014).

Matrix metalloproteinases (MMPs) are capable of degrading extracellular matrixes, and ameloblastomas express high levels of MMP-1, MMP-2, and MMP-9 (Ribeiro *et al*, 2009). The local aggressiveness of ameloblastomas correlates with activity of MMP-2 that can degrade type IV collagen abundant in the basement membrane. As MMP-2 level is regulated by the activating and inhibitory actions of MMP-14 and tissue inhibitor of

matrix mettaloproteinases-2 (TIMP-2), respectively, altered levels of the MMP-14/MMP-2/TIMP-2 complex especially in solid multicystic and recurrent ameloblastoma have been attributed to the invasive growth properties of ameloblastoma (Zhang *et al*, 2010; Florescu *et al*, 2012). Also, as MMP-2, MMP-9, and MMP-13 interact with WNT signaling pathway, the local invasiveness of ameloblastoma is further enhanced by WNT-mediated proliferative signals (Yamagata *et al*, 2012). In the same vein, podoplanin, a mucin-type transmembrane glycoprotein, has been shown to be much more strongly expressed in the peripherally located columnar cells than the central stellate reticulum-like cells of ameloblastomas. Hence, a differential expression pattern of podoplanin possibly contributes to the migration, aggregation, and recurrence of ameloblastoma cells (Siar *et al*, 2015).

Other molecular pathways that have been associated with the pathogenesis, invasiveness, and recurrence of ameloblastoma include but are not limited to p53-MDM2 (Kitkumthorn *et al*, 2010) and Notch signaling pathways (Siar *et al*, 2010) as well molecular markers such as syndecan-1 (CD138) (Al-Otaibi *et al*, 2013; Safadi *et al*, 2016) and CD10 (Abdel-Aziz and Amin, 2012). Some of these have also been considered as either diagnostic or prognostic markers of ameloblastoma (Jhamb and Kramer, 2014).

Current management approaches in ameloblastoma

Diagnostic imaging

The outcomes of a thorough clinical evaluation combined with different imaging modalities and histopathology are paramount to successful management of ameloblastoma irrespective of the histological subtype. Depending on how early the patient presents for evaluation, the clinical appearance of ameloblastoma may range from an innocuous intraoral swelling that the patient is unaware of to a grotesque orofacial swelling. Due to delayed access to health care in some developing countries in Africa and Asia, patients often present with a dramatically large ameloblastoma lesion (Figures 1 and 6). Different imaging modalities may have to be combined for evaluation, diagnosis, and treatment planning of ameloblastomas. These include plain film radiography, cone-beam computed tomography (CT), conventional CT, magnetic resonance imaging (MRI), and functional imaging that combines positron emission tomography (PET) with conventional CT (PET/CT; Fujita *et al*, 2013). The use of plain film radiography is a good starting point. While it displays to some extent the multilocular pattern of ameloblastoma, it cannot demonstrate the three-dimensional structural expanse of ameloblastoma. Conventional CT with or without contrast is the gold standard for evaluation of both primary and recurrent ameloblastomas. It accurately defines the radiodensity as well as multilocular and marginal details of ameloblastoma, which are vital for treatment planning (Figure 7). The use of MRI provides valuable details of the bone marrow and soft tissue components within and beyond the lesional margins of

ameloblastomas. This is especially useful in delineating the extensions of maxillary ameloblastomas within the maxillary sinuses, orbits, and skull (Fujita *et al*, 2013). Functional imaging combining PET/CT is particularly useful for diagnosing malignant ameloblastoma as well as its extensive soft tissue infiltration and distant metastasis. As imaging studies do not provide definitive diagnosis of an ameloblastoma, it is imperative to biopsy the lesion for histopathological analysis and subtyping.

Surgical approaches

Both primary and recurrent ameloblastomas are treated by either surgical or non-surgical approach. The surgical approach could be conservative (type I) or radical (type II) surgery (Figure 6). The conservative surgical treatment could be in the form of enucleation and cauterization, curettage, cryotherapy, or marsupialization. Conservative surgery preserves the patient's normal tissues, minimizes facial disfigurement, and supports adequate quality of life postsurgery; but it is prone to higher recurrence especially if the ameloblastoma is the aggressive subtype (Dandriyal *et al*, 2011). Radical surgical treatment is customarily the treatment of choice for biologically aggressive subtype of primary and recurrent ameloblastomas. It involves *en bloc* tumor resection with wide bone margin followed by immediate or delayed bone reconstruction of the surgical defect with tissue grafts and prosthetic rehabilitation (Shen *et al*, 2015). The interrelationship between clinical and histological properties of the ameloblastoma determines its aggressiveness which in turn dictates the treatment approach and recurrence. However, treatment is also affected by the patient's physical and medical conditions, the patient's wishes regarding potential facial deformity,

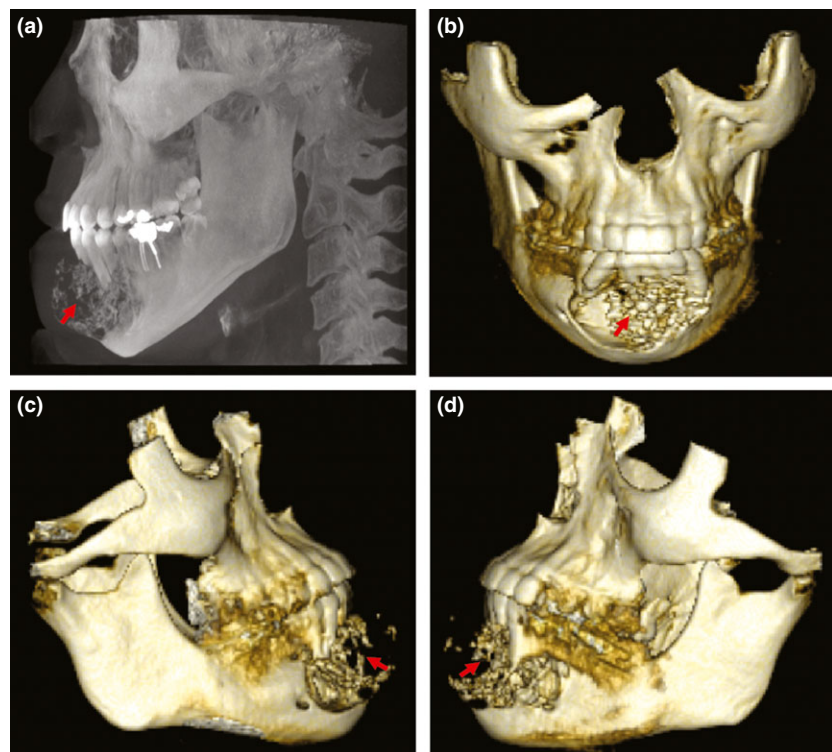


Figure 7 Tomographic imaging of ameloblastoma. Reconstructed conventional computer tomography (a) and volume rendering (b, anterior; c, right; d, left views) demonstrate outlines of anterior mandibular ameloblastoma (red arrows). (Image courtesy of Drs. Mel Muparappu and David M. Graham, School of Dental Medicine, University of Pennsylvania)

compliance, and the psychological effect on quality of life postsurgery. The impact of surgery on facial growth and development in pediatric patients should also be considered during treatment planning. Surgical treatment in pediatric ameloblastoma patients is still controversial. Advocates for conservative surgery favor maintaining a good quality of life post-treatment over recurrence for a pediatric ameloblastoma patient (Huang *et al*, 2007). Others, however, support radical surgery for cases with multiple recurrences, in poorly compliant pediatric patients and in environments where follow-up procedures are limited (Odukoya and Effiom, 2008; Bassey *et al*, 2014). However, if recurrence is the major consideration, surgeons are encouraged to select aggressive radical surgery irrespective of the patient's age except in patients with poor health due to other underlining medical conditions. Conservative surgical excision with peripheral ostectomy is the usual treatment approach for primary or recurrent peripheral ameloblastomas because it presents as a peripheral soft tissue lesion. Interestingly, rate of recurrence of peripheral ameloblastomas after conservative surgery is very low (Hertog *et al*, 2011).

Non-surgical approaches

Different forms of radiation therapy have been used successfully for non-surgical management of ameloblastomas especially in patients medically unstable for surgery (Kennedy *et al*, 2016). These include helical tomotherapy, image guided radiation therapy, intensity-modulated radiation therapy, and proton beam therapy. Some of these treatment modalities have been combined with surgery and/or chemotherapy. The therapeutic use of adjuvant radiotherapy with or without chemotherapy for positive margins of recurrent and unresectable ameloblastomas has resulted in mixed outcomes. However, their use is still strongly advocated to treat ameloblastic carcinoma and recurrent ameloblastoma after multiple postsurgical recurrences (Huang *et al*, 2014). During treatment planning, it is imperative to balance the efficacy of radiotherapy with risks of developing future life-threatening malignant transformations.

The efficacy of chemotherapy in the management of primary and recurrent ameloblastomas is still being explored as chemotherapy can improve clinical outcomes in non-surgical patients. Several drug regimens may be used in combination with surgical resection and/or radiotherapy. These include the combinations of vinblastine + cisplatin + bleomycin; adriamycin + cisplatin + cyclophosphamide; doxorubicin + cisplatin; and gemcitabine + carboplatin (Van Dam *et al*, 2010; Amzerin *et al*, 2011). However, there is still a need for more multicenter randomized controlled clinical studies to validate the use of radiation and chemotherapy as treatment options for ameloblastoma. Interestingly, bone loss in ameloblastoma associated with dysregulated RANK/RANKL/OPG interactions (de Matos *et al*, 2013) has led to the suggestion that antiresorptives such as denosumab may be effective in controlling the local aggressiveness of ameloblastoma (Jhamb and Kramer, 2014). Unfortunately, a major side effect of antiresorptives is osteonecrosis of the jaw (Akintoye and Hersh, 2016; Omolehinwa and

Akintoye, 2016), so the potential clinical benefits must be balanced with their established side effects to justify their use in ameloblastoma therapy.

Targeted directed therapies

Recent advances in the molecular signaling pathways associated with pathogenesis of ameloblastoma have led to development of targeted therapies for management of ameloblastoma (Sauk *et al*, 2010). Several MAPK-specific drugs selectively inhibit the functions of mutated BRAF and MEK to stop the dysregulated proliferation and differentiation of ameloblastic cells. These include vemurafenib and dabrafenib, which inhibit mutated BRAF gene; trametinib, an inhibitor of mutated MEK gene; and ponatinib and regorafenib that inhibit mutated FGFR2 genes. Regrettably, resistance mechanisms such as compensatory activation of the MAPK kinase pathway by epidermal growth factor receptor have been associated with vemurafenib treatment for ameloblastoma (Kurppa *et al*, 2014; Heikinheimo *et al*, 2015). This had led to the suggestion that mutated MEK inhibitors may be desirable than mutant BRAF inhibitors for treating ameloblastoma (Heikinheimo *et al*, 2015).

Similarly, targeted therapies have been developed to control the effect of SMO mutation associated with pathogenesis of ameloblastoma (Mishra *et al*, 2015). These include vismodegib and itraconazole, which unfortunately have been less successful in controlling ameloblastoma associated with SMO mutations W535L and L412F due to resistance mechanisms that block binding of SMO-targeted drugs (Sweeney *et al*, 2014). On the contrary, arsenic trioxide and KAAD-cyclopamine are known to be highly effective against these same mutations and may be useful in the treatment of ameloblastoma associated with SHH signaling pathway (Sweeney *et al*, 2014). As SHH expression is high in ameloblastomas, several drugs already developed to antagonize SHH signaling offer other non-surgical targeted therapeutic options for ameloblastoma patients (Mishra *et al*, 2015). Among these, cyclopamine is the most widely used, but its main drawback is the inhibition of osteoblastic proliferation and differentiation that are important for bone healing (Stanton and Peng, 2010; Schaefer *et al*, 2013).

Recurrence of ameloblastoma

The relatively high post-treatment recurrence of ameloblastoma is a major challenge (Figure 6). This can be attributed to its local invasiveness, different histological variants with peculiar tissue components, the treatment approach, and how early the patient presents for treatment (Ribeiro *et al*, 2009; Zhang *et al*, 2010). The potential for tumor seeding at the surgical site is also attributed to high recurrence of ameloblastoma. Solid/multicystic/conventional ameloblastoma is associated with the highest rate of recurrence (Antonoglou and Sandor, 2015) especially if treated by conservative surgery. Similarly, the tendency to treat luminal unicystic ameloblastoma by conservative approach also leads to recurrence, but recurrence is much lower for unicystic than solid multicystic ameloblastoma and malignant ameloblastoma (Antonoglou and Sandor,

2015). Interestingly, SMO gene mutation appears to be associated with higher recurrence of ameloblastoma than other genetic mutations identified in ameloblastoma (Sweeney *et al*, 2014). This has led to the assertion that BRAF and other non-SMO genetic mutations might confer better prognosis (Brown *et al*, 2014). A conservative surgical approach to treat ameloblastic carcinoma also leads to high recurrence, so radical surgery is mostly advocated for treatment of ameloblastic carcinoma irrespective of its histological features. The recommended treatment approach for recurrent ameloblastoma is radical surgery which confers disease-free survival and the absence of secondary recurrence for at least 10 years (Hertog *et al*, 2011). There are promising results that higher expression levels of cancer stem cells as indicated by CD44 in ameloblastoma may be associated with tumor recurrence, but the sensitivity and specificity of CD44 as a test for ameloblastoma recurrence are yet to be fully clarified. (Sathi *et al*, 2012).

Taken together, successful management of primary and recurrent ameloblastomas involves balancing radical surgery that has a margin wide enough to prevent recurrences with another less tissue destructive therapeutic option (Kennedy *et al*, 2016). The goals are to minimize morbidity and improve survivorship and the patient's quality of life. Adequate periodic clinical and radiographic follow-up for at least 10 years is highly essential. There is optimism that ongoing research will eventually lead to newer therapies targeting both MAPK and non-MAPK signaling pathways.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

O.A. Effiom, O.M. Ogundana and A.O. Akinshipo participated in literature review and writing of the manuscript. S.O. Akintoye conceptualized the review project and participated in the literature review, writing and editing of the manuscript.

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