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AMELOBLASTOMA

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Abstract
Ameloblastoma is a benign yet locally invasive epithelial neoplasm, predominantly originating from the enamel organ, remnants of dental lamina, or odontogenic cyst linings. Constituting approximately 10% of all mandibular and maxillary tumors, ameloblastomas are characterized by slow growth, high recurrence rates, and metastatic potential akin to malignant tumors. Histologically classified by the World Health Organization into types such as unicystic, extraosseous/peripheral, conventional, and metastasizing ameloblastomas, recent refinements have introduced adenoid ameloblastoma. Epidemiologically, ameloblastoma incidence varies regionally, with higher prevalence in developing countries. Clinically, it often presents as a painless jaw swelling, predominantly affecting the mandible. Diagnosis involves a combination of imaging techniques, including CT and MRI, and histopathological examination, revealing characteristic basal and epithelial cell patterns. Surgical resection remains the primary treatment, with radical surgery preferred over conservative approaches due to lower recurrence rates. Advanced techniques such as selective laser sintering 3D biomodels aid in surgical planning and reconstruction. Despite the limited role of chemotherapy and radiotherapy, targeted molecular therapies, especially BRAF inhibitors, show promise in specific cases. Comprehensive management includes addressing potential complications and recurrence monitoring.

Keywords *- Ameloblastoma, benign epithelial neoplasm, odontogenic tumor, jaw tumor, histopathological classification, surgical treatment, BRAF inhibitors, molecular therapy, recurrence, mandibular tumor, maxillary tumor.*

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I. Introduction

Ameloblastomas, while benign, have a tendency to invade locally. They are a type of epithelial neoplasm that originates from various sources. These sources could be the enamel organ, remnants of the dental lamina, the lining of an odontogenic cyst, or potentially the basal epithelial cells of the oral mucosa.(1)

Ameloblastoma makes up approximately 10% of all tumors originating in the mandible and maxilla. It‘s one of the most frequently occurring benign odontogenic tumors. Despite its slow growth rate, akin to benign tumors, it exhibits a puzzling nature. It is locally invasive, has a high likelihood of recurrence, and possesses a metastatic potential comparable to malignant tumors(2)

Definition

Ameloblastoma is a tumor that grows slowly and invades locally. It primarily originates from undifferentiated enamel tissue, which is part of the odontogenic epithelium. The tumor was first identified by Cusack in 1827 and was named ’adamantinoma ‘by the French physician Louis-Charles Malassez in 1885. The term ’ameloblastoma ‘was introduced by Ivey and Churchill in 1930. The World Health Organization classified it as a benign epithelial odontogenic tumor in 2017. Many ameloblastomas have mutations in genes of the MAPK pathway, with the BRAFV600E mutation being the most common. (2)

Classification of Ameloblastoma

In 1971, the World Health Organization (WHO) included odontogenic tumors in its inaugural histological classification and established the necessary clinicopathological criteria for diagnosis. The fourth edition of the WHO Classification of Head and Neck Tumors, released in 2017, simplified the classification from previous versions. It categorized ameloblastomas into four types: ameloblastoma, unicysticameloblastoma, extraosseous/peripheral ameloblastoma, and metastasizing ameloblastoma. The term ’solid/multicystic ‘ previously used for conventional ameloblastoma was removed due to its lack of prognostic significance and

potential confusion with unicysticameloblastoma. Desmoplasticameloblastoma, previously sub-categorized under ameloblastoma in the 2005 WHO classification, was also omitted. It was deemed a histological variant of conventional ameloblastoma, despite its unique clinical and occasional radiographic features. Similarly, odontoameloblastoma from the 2005 classification was redefined as ameloblastoma arising in an odontoma, not odontoameloblastoma. Metastasizing ameloblastoma was reclassified as a benign tumor, despite its metastatic potential, due to its benign histopathology, making it hard to differentiate from conventional ameloblastomahistopathologically. Recently, there has been a push to include adenoid ameloblastoma as a subtype of ameloblastoma in the next revision of the WHO odontogenic tumor classification. Adenoid ameloblastoma is a hybrid odontogenic tumor with histopathological features of both ameloblastoma and adenomatoidodontogenic tumor. It is demographically similar to conventional ameloblastoma but has histopathological differences and a higher rate of multiple recurrences, indicating its biological aggressiveness. (2)

In the latest 2022 5th edition of the World Health Organization (WHO) Classification of Head and Neck Tumors, the classification of ameloblastomas has been refined. The ameloblastomas are now categorized into Ameloblastoma, Unicystic, Ameloblastoma, Extraosseous/Peripheral, Ameloblastoma, Conventional, and Metastasizing Ameloblastoma. The Unicystic type is further divided into subtypes based on the distribution of ameloblastomatous epithelium: luminal, intraluminal, and mural. The Conventional type is described with islands and strands of odontogenic epithelium bounded by cuboidal/columnar cells with palisaded, hyperchromatic nuclei and reverse polarity. The Adenoid Ameloblastoma is a new entity added to benign epithelial tumors, characterized by ameloblastoma-like components with duct-like structures, whorls/morules, and cribriform architecture. The Metastasizing Ameloblastoma remains a benign tumor despite its metastatic potential, with both primary and metastatic tumors showing benign conventional ameloblastoma histopathology without cytological atypia or features of malignancy (4)

Subtypes	**Subtypes**	**Features**
Benign Epithelial		
	Ameloblastoma, unicystic	- Subtypes: luminal, intraluminal, mural
	Ameloblastoma, extraosseous/peripheral	- Occurs in soft tissue, histopathologic features as conventional ameloblastoma
	Ameloblastoma, conventional	- Islands/strands of odontogenic epithelium, reverse polarity
	Adenoid ameloblastoma	- Duct-like structures, whorls/morules, cribriform architecture
	Metastasizing ameloblastoma	- Benign conventional ameloblastoma with metastatic site: lung
MalignantOdontogenic		
	Ameloblastic carcinoma	- Histological resemblance to ameloblastoma with cytological atypia

TABLE 1: The classification of ameloblastoma according to the WHO Classification of Head and Neck Tumors, published in 2022

Epidemiology & Prevalence of ameloblastoma

The occurrence of ameloblastoma varies by region, with a worldwide rate of approximately 0.92 instances per million people annually. Epidemiological research commonly ranks ameloblastoma as the first or second most prevalent benign tumor originating from odontogenictissue[2].

Ameloblastoma, a significant odontogenic tumor, presents a higher incidence in developing countries, with India being no exception. A systematic review and meta-analysis conducted by ThuckanaickenpalayamRagunathanYoithapprabhunath et al., published in the Asian Pacific Journal of Cancer Prevention (Vol 23, 2022), aimed to establish a comprehensive epidemiological profile of ameloblastoma in the Indian subcontinent. The study meticulously analyzed data from January 2010 to December 2021, revealing a prevalence rate of 4.83 (95% confidence interval of 4.44-5.26). It highlighted a slight male predisposition, with the majority of cases occurring in the third decade of life. The posterior mandible emerged as the most common anatomical site for tumor manifestation. Histopathologically, the solid/multicystic type of ameloblastoma was predominant. This extensive research underscores the need for more epidemiological studies to accurately determine the national profile of ameloblastoma, which could significantly influence future healthcare strategies and resource allocation. Table 2 (5)

Topic	**Details**
1. Prevalence Rate	- Overall point estimate of **4.83** with 95% CI (4.44 -5.26)
2. Gender and Age Distribution	- Higher male predominance, average age in the **third decade of life**
3. Anatomic Site of the Tumor	- Predominantly affects the **posterior mandible**
4. Tumor Type	- Most common type: **solid/multicystic** with follicular and plexiform patterns

Table 2 summary of ThuckanaickenpalayamRagunathanYoithapprabhunath et al. (2022). Prevalence and Epidemiological Profile of Ameloblastoma in India: A Systematic Review and Meta-Analyses[1]. Asian Pacific Journal of Cancer Prevention, 23(11

Clinical Presentation

Typically, ameloblastomas present as a painless swelling in the affected jaw region.The symptoms are usually non-specific, and the condition might be discovered incidentally on radiographs for other reasons. Pain is not common but may occur due to hemorrhage in the adjacent soft tissue About 80% of ameloblastomas are located in the mandible, mainly in the third molar region, while 20% arise in the maxilla, particularly in the posterior region. Desmoplasticameloblastomas, a rare subtype, often occur in the premolar and anterior regions of the mandible and maxilla.(6)

Ameloblastoma be linked to a third molar tooth that has not emerged. Typically, the desmoplastic variant of this tumor is found in the front region of the upper or lower jaw. This tumor tends to expand sideways within the mouth, often leading to a noticeable enlargement. On average, ameloblastomas are about 4 cm in size when they are first identified. (2). While ameloblastoma is generally painless, it can cause discomfort if there is significant growth leading to pressure on surrounding structures. (7)

The majority of unicysticameloblastomas resemble dentigerous cysts due to their association with an unerupted tooth.(3)

Peripheral ameloblastoma is slow growing , usually does not cause pain unless there is hemorrhage in the adjacent soft tissue (6)

Ameloblastoma rarely metastasises with only about 2% - 5% of cases spreading to distant sites.(2) It can metastasise to lungs and lymph nodes in which lung is the most common site for metastases accounting for over 80% of cases. Exact mechanism for metastasis is not fully known but there are high chances that spread happens through hematogenous spread as endobronchial lesions developed without local recurrence. (16)

Ameloblastic can transform into squamous cell carcinoma it is characterized by atypical cytologic features within the histologic context of conventional ameloblastoma. Although the transformation of ameloblastomato squamous cell carcinoma remains controversial, Rehan Rais in 2018 published a case report which provides evidence of such a transformation. Notably, benign odontogenic epithelium progressed to squamous cell carcinoma, suggesting a potential pathway for metastasis. While the exact molecular mechanism remains unclear, p53 overexpression in the squamous cell carcinoma component hints at a role for p53 mutations.(15)

Diagnosis

The diagnosis of ameloblastoma requires imaging as well as a biopsy.Theradiological diagnosis of ameloblastoma involves several imaging modalities. Intraoral radiography provides initial assessment but lacks sensitivity and specificity. Extraoral radiography (such as orthopantomogram and cephalogram) is useful for overall evaluation. Cone Beam Computed Tomography (CBCT) offers detailed 3D images, especially helpful for assessing extent and localization. Computed Tomography (CT) demonstrates well-defined radiolucent uni/multilocularexpansile lesions. Magnetic Resonance Imaging (MRI) reveals a mixed solid and cystic pattern with thick irregular walls and solid papillary structures. Panoramic Radiography is used as an initial evaluation tool due to its accessibility and ability to provide a broad view of the jaw. It helps in detecting bone lesions and pathological processes not visible through physical examination(11)

Computed Tomography (CT) is considered advantageous for diagnosing ameloblastoma due to its ability to provide detailed cross-sectional images of the jaw and surrounding structuresThe CT scan shows a well-defined, uni- or multilocular radiolucent expansile lesion. It is also good for the evaluation of any cortical destruction or soft tissue extension.(2)

Type of Ameloblastoma	**CT Scan Appearance**
Classic Ameloblastoma	Well-defined, uni- or multilocular radiolucent expansile lesion, often with cortical destruction or soft tissue extension.
UnicysticAmeloblastoma	Appears as a lytic lesion with scalloped margins, often associated with impacted molars and resorption of tooth roots.
Peripheral Ameloblastoma	Usually not involving bone, may produce a superficial impression on the underlying bone.
Metastasizing Ameloblastoma	Similar well-differentiated benign histology at the primary site, with metastases showing similar foci in remote locations.

Table 3

Radiographically, ameloblastomas exhibit considerable variation due to their polymorphic features. The typical radiographic appearance involves multilocular bone destruction, although unilocularameloblastomas also occur . However, these features lack diagnostic specificity. In conventional radiography, differential diagnosis should consider odontogenickeratocysts, odontogenicmyxomas, dentigerous cysts, ameloblastic fibromas, giant cell granulomas, aneurysmal bone cysts, and other lesions. (8)

MRI offers superior soft-tissue contrast compared to CT, allowing detailed analysis of ameloblastoma internal structures. Multiplanar imaging capabilities enhance lesion examination. Gd-enhanced T1-weighted MRI detects mural nodules and thick walls, which CT may miss. Additionally, DCE-MRI distinguishes ameloblastomas from other lesions, a capability CT lacks (8).

Apajalahti, S.,in2015 published an article " Imaging characteristics of ameloblastomas and diagnostic value of CT and MRI in a series of 26 patients" From the study of 26 patients, the authors found that the majority (58%) were solid/multicystic types, often presenting with a mixed cystic and solid pattern on contrast-enhanced CT or MRI. Six cases were unicystic, showing thick rim-enhancement or mural solid components in otherwise cystic lesions. Two cases were diagnosed as peripheral ameloblastomas. Two cases suggested

neoplastic transformation from dentigerous cyst epithelium with ameloblastomatous growth. And In one case, the histological subtype was unclear. (12)

Type of Ameloblastoma	MRI Characteristics
Solid/Multicystic	- Homogeneous intermediate signal on T1-weighted images. - Homogeneous high signal on T2-weighted images. - Homogeneous enhancement after contrast administration.
Peripheral	- Homogeneous intermediate signal on T1-weighted images. - Bright high signal on T2-weighted images for the intraosseal cystic part. - Heterogeneous enhancement for the peripheric solid component.
Unicystic	- Homogeneous intermediate signal on T1-weighted images. - Bright high signal on T2-weighted images. - Contrast enhancement (thick rim or solid component enhancement) after gadolinium administration.

table 4 showing MRI charachtersitcs from Apajalahti, S., Kelppe, J., Kontio, R., &Hagström, J. (2015). Imaging characteristics of ameloblastomas and diagnostic value of CT and MRI in a series of 26 patients. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. doi: 10.1016/j.oooo.2015.05.002.

Histopathological Finding

Histologically, ameloblastoma contains two types of cells:

1. Basal Cells: These cells are peripherally situated and resemble ameloblasts. They exhibit hyperchromatic nuclei, a columnar shape, a palisaded arrangement, vacuolated cytoplasm, and nuclei displaced away from the basement membrane (reversal of polarity).

2. Epithelial Cells: Centrally situated, these cells resemble stellate reticulum. They have a bland cytological appearance with sparse mitotic figures, consistent with their slow rate of growth.

The histological analysis of ameloblastoma reveals that it resembles normal odontogenic/enamel epithelium and ectomesenchyme. The cells involved can originate from various sources, including the rests of the enamel organ, Hertwig‘s epithelial root sheath, the epithelial boundary of an odontogenic cyst, basal cells of the oral mucosa, or heterotopic epithelial cells from other parts of the body. Microscopically, ameloblastoma can present in different patterns, such as follicular, plexiform, acanthomatous, spindle, basal cell-like, desmoplastic, and granular cell patterns. These patterns may be uniform or mixed within the tumor (36).

In classical ameloblastoma (previously labeled as solid/multicysticameloblastoma), the basal and epithelial cells exhibit two distinct patterns: follicular and plexiform (as shown in Figure 1). In the follicular pattern, epithelial cells form islands or follicles surrounded by connective tissue. Conversely, the plexiform pattern features an interlacing network of epithelial cells. Occasionally, ameloblastomas can exhibit both of these patterns in

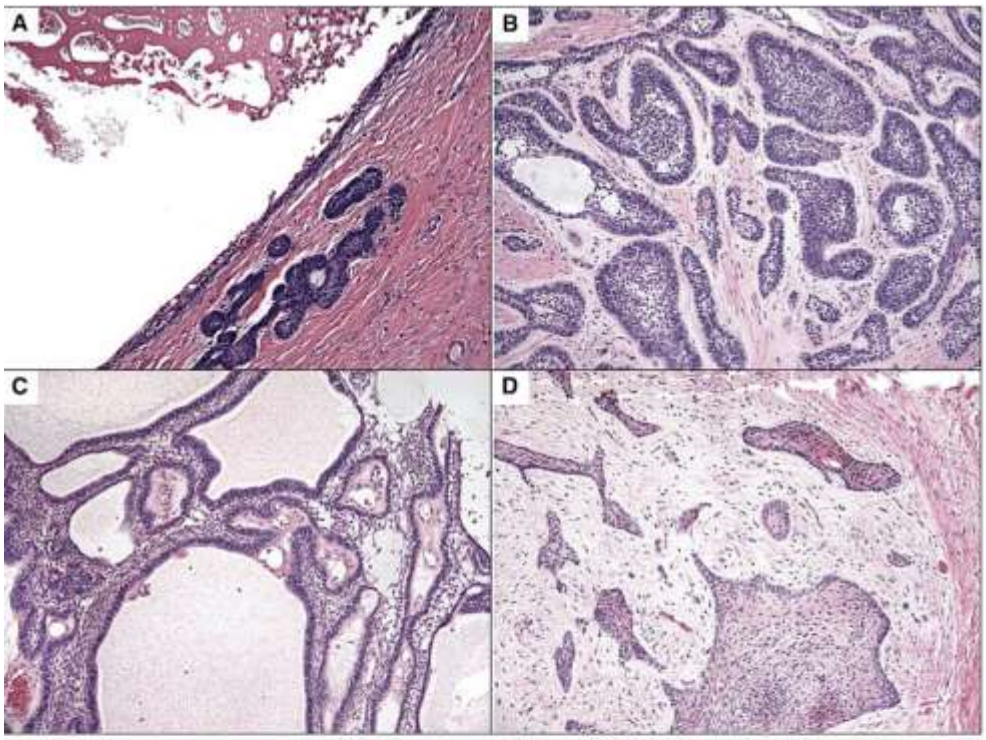

FIGURE 1: Figure depicting four histologic subtypes of ameloblastoma. A: unicystic, B: follicular, C: plexiform, and D: desmoplastic

Reproduced with permission from McClary AC, West RB, McClary AC, et al. Ameloblastoma: a clinical review and trends in management. Eur Arch Oto-Rhino-Laryngol. 2016;273(7):1649-1661

varying proportions within the same tumor. Additionally, several other histological variants of multicysticameloblastomas have been described, including desmoplastic, acanthomatous, basal cell, granular cell, and keratopapillaryameloblastomas. However, none of these variants significantly impacts tumor behavior, except for desmoplasticameloblastoma, which may exhibit increased aggressiveness (34)

Diagnosing unicysticameloblastoma poses challenges for pathologists due to the absence of classical diagnostic features. Typically, only membranous fragments of the cyst wall are recovered, and solid tissue is scarce. The basal cells exhibit limited elongation, and nuclear palisading is confined to a small cell group. While suprabasal cells may stratify into a stellate reticulum, they can also show signs of inflammation. Unicysticameloblastoma has two histological variants: luminal and mural. In the luminal variant, the cyst wall appears as a uniform sac lined by ameloblastoma epithelium. Occasionally, wall thickenings composed of ameloblastoma cells invaginate into the lumen. In the mural variant, tumor islands infiltrate the fibrous wall, resembling conventional ameloblastoma. (35).

In peripheral ameloblastoma, the stellate reticulum is rarely prominent, and most epithelial islands display palisading of columnar basal cells. Although bone or periosteum is not affected, the tumor can create a superficial impression on the underlying bone.

Histologically it is difficult to diagnosis plexiformameloblatoma as cystic formation and anastomosing cords of cells can be confused with other conditions like aneurysmal bone cyst (9)

Staging

Yang and colleagues classified ameloblastomas based on clinicopathological features into three stages. Stage I included tumors with a maximum diameter of 6 cm or less. Stage II encompassed larger tumors (>6 cm) or those invading the maxillary sinus or orbital floor. Stage III indicated tumor invasion of the skull base or metastasis to regional lymph nodes. Notably, their findings revealed a significant correlation between tumor stage and recurrence period, with stage III tumors exhibiting the earliest recurrence. (13)

Treatment

The treatment modality of choice for ameloblastoma is surgery. Other modalities like chemotherapy or radiotherapy have a limited role and only in select situations.

Surgery

Surgical treatment for ameloblastomas aims to minimize recurrences by ensuring complete tumor removal. Additionally, it focuses on restoring function and aesthetics, allowing patients to regain normal oral activities. To reduce morbidity, surgical methods are chosen carefully to minimize negative effects on the donor area.(26)

Selective laser sintering 3D biomodels play a crucial role in surgical planning. They enhance accuracy by allowing precise simulation and reconstruction, which is especially important for complex cases like ameloblastomas. These biomodels provide detailed representations of affected areas, improving the precision of osteotomies and graft placements. Additionally, utilizing 3D biomodels leads to more predictable surgical outcomes, reduced operation time, and improved postoperative conditions for patients(29) how ever in 2020 Benjamin Paula performed a 10 year retrospective cohort study comparing surgical techniques and margins distance and founded no significant difference in margin status between Computer Assisted surgery and non-Computer Assisted surgery groups; CAS may reduce close or positive margins.(21)

There are two types of surgical management of ameloblastoma 1. Conservative Surgery: This approach involves enucleation, curettage, or marsupialization, possibly combined with cryotherapy or tissue fixers likeCarnoy‘s solution. While it is less invasive and yields good aesthetic and functional results, it has a high recurrence rate.
2. Radical Surgery: In contrast, radical surgery entails marginal or segmental mandibulectomy with 1-1.5 centimeters margins. Although more invasive, it offers a lower recurrence rate, making it a favorable option to avoid further interventions.(26)

ChingChing Yew in 2020 published an article in which he talked about Modified conservative management of mandibular ameloblastoma which he used for 13 cases done in a span of 13 years between 2006-2019 in tertiary care centre in Northern Malaysia. Out of 13 cases 3 recurrences in the solid/multicysticameloblastoma group and no recurrence in unicysticameloblastoma cases over an average review duration of 57 months. Purpose of this method is to find an alternative to surgical resection, which can cause aesthetic and functional complications. It consists of surgical enucleation, peripheral ostectomy, and chemical cauterization. And in conclusion: MCM showed a relatively low recurrence rate, suggesting it could be a viable alternative treatment for mandibular ameloblastoma. Further prospective studies are recommended to understand its effectiveness fully.(17)

Radical Treatment (RT): Involves segmental resection and is associated with a lower recurrence rate of 9.1%. It can lead to cosmetic and functional sequelae and may require free flap reconstruction(19)

Reconstruction can be done from vascularised bone flaps and non vascularised bone graft. Vascularised bone flaps are generally accepted treatment strategy for mandibular reconstruction such as free fibula flap is **u**sed for immediate reconstruction after segmental mandibulectomy, providing good long-term esthetic and functional results and Deep Circumflex Iliac Artery Flap is another option for immediate reconstruction with similar benefits to the free fibula flap. If we are using non vascularised bone graft such as iliac crest an adjutant of hyperbaric oxygen therapy can be given for wound healing by controlling vascular permeability , reducing tissue edema and minimising inflammatory damage which supports bone new formation (19,27)

The iliac crest-internal oblique free flap is a suitable option for mandibular reconstruction due to the internal oblique muscle‘s utility in forming soft tissue closure over the bone. Specifically for mandibular angle defects, the iliac crest is preferred, avoiding the need for multiple osteotomies as required with the fibula . Patients who undergo reconstruction with an osteomyocutaneous free flap may be candidates for osteointegrated dental

implants . Research by Pappalardo et al. indicates that osseointegrated implants lead to improved masticatory function, fewer psychological consequences, and better quality of life . Additionally, distraction osteogenesis is gaining popularity in mandibular reconstruction after surgical tumor resection . The recent adoption of virtual 3D surgical planning has enhanced outcomes by providing more precise and predictable reconstructive surgery. (2)

When reconstructing a maxillary defect, a skin graft is used to line the cavity. An obturator is then fitted, allowing convenient access to the resection bed during surveillance. Unlike the mandible, the cortical bone of the maxilla is more susceptible to tumor invasion, resulting in a higher local recurrence rate after surgery for maxillary ameloblastoma. Consequently, free flaps are avoided in maxillary defects to prevent covering a potential recurrence site (2)

Non Surgical

Systemic chemotherapy is not recommended for localized ameloblastoma, it becomes a treatment option in metastatic cases. Various agents and combinations have been used, including cyclophosphamide, methotrexate, 5-fluorouracil, vinblastine, cisplatin, bleomycin, adriamycin, paclitaxel-carboplatin, doxorubicin, and gemcitabine. Notably, ameloblastoma may exhibit sensitivity to platinum-based anticancer agents. (33)

Surgery is the mainstay of treatment for ameloblastoma, with radical excision and bone reconstruction preferred over conservative enucleation due to high recurrence rates.
The role of systemic therapy has been ill-defined due to the disease‘s rarity and limited experience. However, molecular characterization has shown high frequency of BRAF-V600E mutations, suggesting potential for molecular-based therapies.
Targeted neoadjuvant therapy may be useful in certain clinical settings of primary ameloblastoma, potentially altering the extent of surgery or providing options where surgical choices are limited.

Lucas Alves da Mota Santana reported that the BRAF V600E mutation is commonly found in ameloblastomas, which are odontogenic tumors. This mutation is often associated with more aggressive tumor behavior.The presence of the BRAF V600E mutation has led to the exploration of BRAF inhibitors as a therapeutic option. The article mentions the use of drugs like vemurafenib and dabrafenib, which have shown promise in reducing tumor size and allowing for more conservative surgical approaches.Two cases were described where aggressive ameloblastomas were treated surgically, and both demonstrated strong positivity for the BRAF V600E mutation. These cases highlight the potential for BRAF inhibitor therapy in managing such tumors.
The immunohistochemical BRAF marker is suggested as a useful tool for predicting patient outcomes and aiding in the surgical management of ameloblastom (30-31)

Radiotherapy

Radiotherapy (RT) plays a limited role in managing ameloblastoma. It is considered in specific scenarios:

1. Post-Surgical Residual Disease: RT may be used for patients with microscopic or gross residual disease after surgery.
2. **Poor Surgical Candidates**: Patients who are not suitable candidates for further surgery can benefit from RT.
3. **Inoperable Cases**: RT is an option for cases where re-resection is not feasible.
   Dose-Fractionation Schedules for tumor control are similar to those used for carcinomas:

- For **microscopic residual disease**, a dose of **66 Gy** in **33 once-daily fractions** (five fractions per week) is recommended.
- For **gross disease**, a dose of **70 Gy** in **35 once-daily fractions** over a treatment duration of **seven weeks** is used.
  In a recent pooled analysis of three studies, local tumor control was achieved in 78% of patients irradiated for gross disease and 100% of patients treated for microscopic residual disease after surgery.
  Advanced Techniques: Newer radiotherapy technologies, such as image-guided radiotherapy, stereotactic radiotherapy, intensity-modulated radiotherapy, and proton beam therapy, may benefit patients with extensive maxillary ameloblastomas extending to the skull base. These techniques allow effective tumor treatment while minimizing dose to critical structures like the central nervous system (CNS) and visual apparatus. (2, 24)

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