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REVIEW ARTICLE

Ameloblastoma: a clinical review and trends in management

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Abstract Ameloblastoma is a rare odontogenic neoplasm of the mandible and maxilla, with multiple histologic variants, and high recurrence rates if improperly treated. The current mainstay of treatment is wide local excision with appropriate margins and immediate reconstruction. Here we review the ameloblastoma literature, using the available evidence to highlight the change in management over the past several decades. In addition, we explore the recent molecular characterization of these tumors which may point towards new potential avenues of personalized treatment.

Keywords Ameloblastoma · Head and neck surgery · Clinical review · Genomics · Personalized medicine · SHH · BRAF

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Introduction

Ameloblastoma is a rare, benign, slow-growing but locally invasive neoplasm of odontogenic origin involving the mandible (80 %) and maxilla; conservative treatment results in a high recurrence rate. The neoplasm was first described by Cusack in 1827 [1]. Etymologically, the name derives from the old French word "amel," which means enamel, and the Greek word "blastos," meaning germ or bud. Over time, this tumor has been referred to by many different names including "cystosarcoma," "adamantine epithelioma," "adamantinoma," and finally "ameloblastoma" [2, 3].

Ameloblastoma shows variable geographic prevalence, being the most common benign odontogenic tumor in China [4] and Africa [5, 6], while it is the second most common in the United States and Canada [7, 8] (odontoma being most common). African Americans have an overall fivefold increased risk of disease as compared to Caucasians [8]. Global incidence has been estimated at 0.5 cases per million person years, and most cases are diagnosed in patients 30–60 years of age [9].

In this review, we summarize the natural history and clinicopathological variants of ameloblastoma. Diagnostic evaluation and surgical management of the various histologic variants of ameloblastoma will be discussed. As controversy has existed for some time now with regard to enucleation/curettage versus resection with wide margins, we will highlight the evidence supporting adequate surgical bony margins. Additionally, the potential role of adjuvant radiation and chemotherapy will be addressed. This discussion is complicated by the lack of a staging system and the absence of prospective studies for this rare disease, both of which make it difficult to compare treatment outcomes, especially when recurrences can occur decades after initial

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treatment. Lastly, emerging molecular data are improving our understanding of the pathogenesis of ameloblastoma and may have treatment implications.

Patient presentation and diagnostic workup

The most common presentation for ameloblastoma is a painless swelling of the mandible or maxilla [10], though in a series of 60 patients, up to 35 % had their lesion identified as an incidental finding on imaging [11]. Pain is uncommon but can occur because of hemorrhage, especially following a fine needle aspiration (FNA) [12]. Pain with rapid growth may represent the rare malignant ameloblastoma. Tooth displacement and root resorption are infrequent but have been reported in up to 25 % of desmoplastic ameloblastomas [13]. Paresthesias are uncommon, with rare reported cases of perineural invasion.

Up to 80 % of ameloblastoma cases occur in the mandible, with a predilection for the posterior mandibular region [14]. Rare cases have been reported as primary to the sinonasal cavities [13]. Ameloblastoma can be associated with unerupted third molar teeth [11, 15], particularly in the unicystic type (histopathology is discussed below). Desmoplastic ameloblastomas often occur in the anterior or premolar regions of the mandible or maxilla. Ameloblastic carcinomas also favor the mandible ($\sim$2/3) over the maxilla [16]. Maxillary ameloblastomas also mostly occur in the posterior molar region.

Preoperative diagnostic evaluation includes imaging and possible biopsy. Ameloblastomas originate within bone, apart from the peripheral subtype which arise in the gingiva or buccal mucosa, and thus are often detected incidentally on dental X-rays (pantomography) or plain films; X-rays usually show a lytic lesion with scalloped margins, resorption of tooth roots, and impacted molars (unicystic) [17, 18]. The classic "soap bubble" appearance is seen with the most common ameloblastoma, the multilocular/solid type (Fig. 1) [18]. Although sometimes adequate for complete evaluation, plain X-rays lack sensitivity and specificity for the extent of bone and soft tissue invasion. Computed tomography (CT) is the most useful diagnostic imaging modality, typically demonstrating well-defined radiolucent uni/multilocular expansile lesions [11]. CT is also useful for the evaluation of cortical destruction (revealing a window for biopsy) and soft tissue extension, identifying the full extent of the tumor to support surgical planning (Fig. 1) [19, 20]. MRI provides potentially more complete information than CT about soft tissue extension and marrow extension beyond the lytic bone cavity [21]. MRI is particularly useful for ameloblastomas arising from the maxilla, as it helps to characterize extension to the orbit, paranasal sinuses, and skull base. MRI should be considered in desmoplastic ameloblastomas because they have poorly defined soft tissue borders and are often misdiagnosed as a fibro-osseous lesion [22]. PET-CT is generally reserved for metastatic ameloblastoma, where it may aid with staging of the distant metastasis.

Imaging findings are characteristic but not pathognomonic, and the diagnosis is classically established by histology. Biopsy may be helpful prior to treatment to avoid unnecessary operations on lesions of alternative etiology that should be alternatively treated or simply observed, such as osteomyelitis, cystic fibrous dysplasia, giant cell tumor, ossifying fibroma, multiple myeloma, and rare sarcomas. Biopsy also allows for proper preoperative staging in malignant ameloblastomas [23]. Furthermore, over-treatment of benign dentigerous cysts that cannot be differentiated from some unicystic ameloblastomas must be avoided; these cannot be diagnosed on FNA and need open biopsy in the form of curettage. A biopsy should be done at the start of the case to sort this out. Maxillary ameloblastomas often present with involvement of adjacent soft tissue, resembling adenocarcinomas and squamous cell carcinomas. Fine needle aspiration can be acquired via a window of cortical erosion as identified by imaging or from the dental socket. Incisional biopsy can provide a more accurate diagnosis but requires disruption of the mucosa,

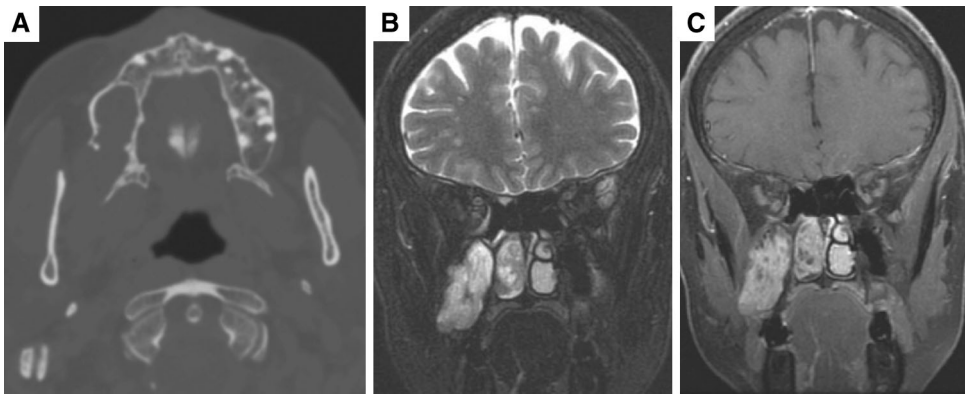

Fig. 1 **a–c** 69-year-old woman. CT and MRI scans showing erosive lesion of posteroinferior R maxillary alveolus, without intact bony shell, and extension of mass into the R maxillary sinus

which will ultimately need to be removed at surgery. Peripheral ameloblastomas are not covered by bone and can be biopsied without difficulty.

Histopathology

Histopathologically, ameloblastoma resembles normal odontogenic/enamel epithelium and ectomesenchyme. Odontogenesis consists of chronographic and reciprocal interactions between the ectomesenchymal cells, which are derived from the neural crest, and the oral cavity lining epithelium [24]. Ameloblastic epithelium has been hypothesized to arise from (1) cells from the rests of enamel organ, but also from (2) cells of the sheet of Hertwig's or epithelial cell rest of Malassez, (3) epithelial boundary of an odontogenic cyst, particularly a dentigerous cyst, (4) basal cells of the oral mucosa, (5) heterotopic epithelial from other parts of the body, perhaps pituitary [25, 26].

The 2005 WHO classification for ameloblastomas includes four subtypes. The solid/multicystic is the most common type, comprising 91 % of the ameloblastomas in the largest series [14]. This is followed by the unicystic type 6 %, the extra osseous ameloblastoma 2 %, and the desmoplastic type 1 %. The most aggressive clinical/pathologic association is seen in the solid/multicystic type, which is associated with the highest recurrence rate of up to 90 % with conservative operations such as enucleation and curettage [27, 28]. The unicystic type is the most benign and is further classified into intraluminal and intramural subtypes. The intraluminal unicystic subtype does not exhibit invasion of the supporting connective tissue, has the lower recurrence rate of the two subtypes, and may be the only histology amenable to conservative surgical treatment [27, 29–32]. Contrary to the WHO's data on desmoplastic ameloblastomas, some series show this subtype at a much higher prevalence of 4–13 % of resected ameloblastomas [33, 34]. Furthermore, the WHO reported lower recurrence rates with this subtype, though other reports have demonstrated aggressive biologic behavior with higher recurrence rates [6, 35, 36]. Unlike solid, unicystic and desmoplastic ameloblastomas which are centered within the marrow space, encapsulated by bone, and thus are designated "central ameloblastoma", the peripheral ameloblastomas are extra-osseous and do not involve the underlying bone [32, 37–39]. They share similar histology, but grossly this is the only ameloblastoma that can have its boundaries evaluated during an oral exam, as it typically demonstrates a pedunculated or exophytic lesion on the gingiva [9]. Cellular atypia and mitotic activity are rarely present in any histologic subtype of ameloblastoma, and any increase in either parameter should raise the suspicion for a malignant process such as ameloblastic carcinoma or odontogenic sarcoma.

Additionally, microscopic patterns of ameloblastoma include follicular, plexiform, acanthomatous, spindle, basal cell-like, desmoplastic, and granular cell (Fig. 2). Patterns can be uniform or mixed. It is not clear that there is any clinical significance to these patterns, though as discussed in the Molecular Biology section, mutation status may correlate with microscopic pattern.

Malignant subtypes of ameloblastomas are not included in the WHO classification. Despite this, it is thought that these tumors can either arise de novo or can progress from the benign form. Elzay, Slootweg and Muller coined two types: metastatic ameloblastoma and ameloblastic carcinoma, comprising 2 % of all ameloblastomas [16, 40, 41]. Metastatic ameloblastoma typically demonstrates well-differentiated benign histology similar to the solid/multicystic type at the primary site, but additional foci of the benign histology are identified in location(s) remote from the primary and considered to be a metastasis. Kruse et al. [42] described a classification system for malignant ameloblastomas in 2009, splitting ameloblastic carcinomas into three subtypes with the predominant distinction based on the presence of a known primary neoplasm. Ameloblastic carcinoma, defined by showing malignant histologic features such as increased or abnormal mitoses and cytological atypia, is the most aggressive of the subtypes [6, 38]. Ameloblastic carcinoma can be diagnosed based on the histology of the primary site, independent of metastasis [43]. Distant metastases have been reported to occur 4 months–12 years posto-peratively [44]. Metastatic ameloblastomas and ameloblastic carcinomas are most commonly metastatic to the lung (70–85 % of total cases), followed by bone, liver, and brain [44–46]. Regional neck metastasis is more common in cases of malignant transformation of primaries originating in the mandible and reported to comprise 35 % of metastatic sites in one series [51, 53, 62]. Common characteristics among patients with malignant transformation of their benign ameloblastoma include long duration of tumor, many recurrences often treated conservatively, and late-appearing metastatic disease [47]. Despite previous speculation on the route of spread to the lung as being topical via aspiration of tumor from multiple trans-oral conservative procedures, the pattern of lung metastasis does not favor the right middle and lower lobe as seen with aspiration [48]. The current belief is that metastasis occurs via lymphatic (rare) or hematogenous spread [49].

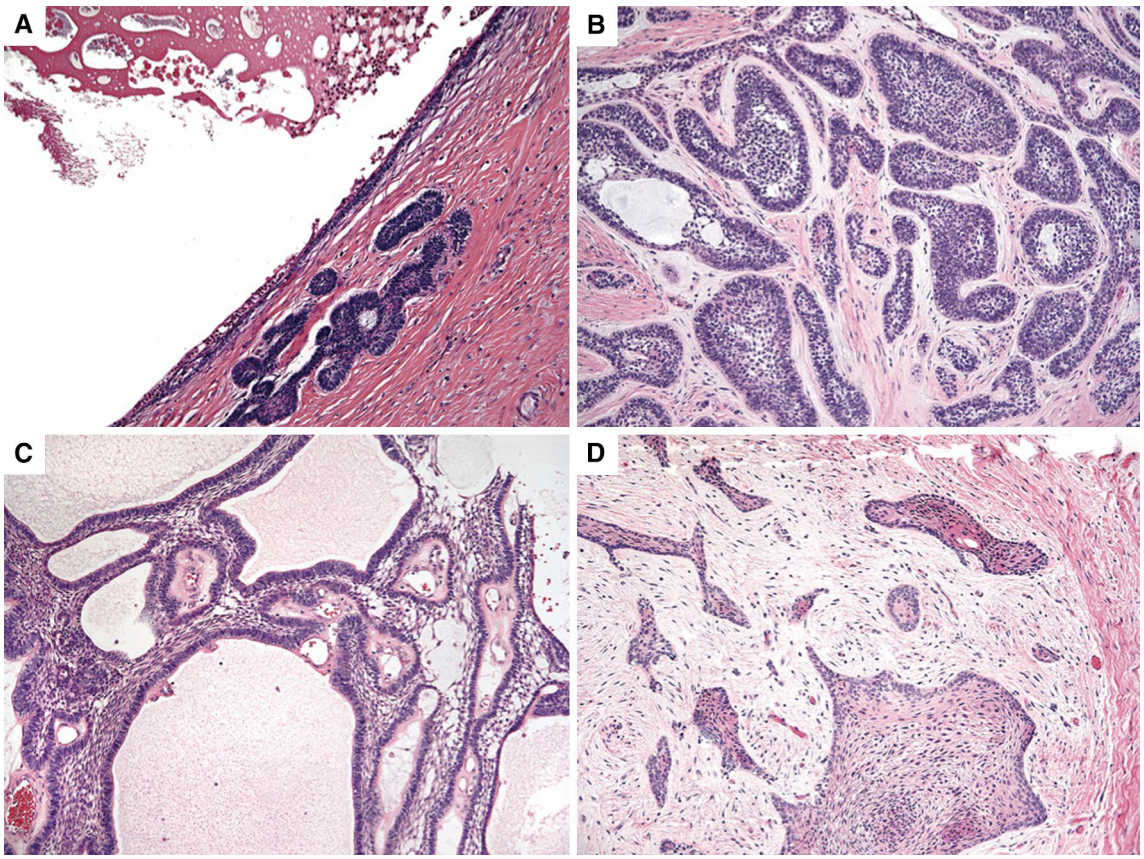

Fig. 2 Figure depicting four histologic subtypes of ameloblastoma. **a** Unicystic, **b** follicular, **c** plexiform, and **d** desmoplastic

Molecular biology

A specific etiology for ameloblastoma has yet to be elucidated. A study by Kahn showed three of ten cases of ameloblastoma in persons under the age of 19 to be positive for human papilloma virus (HPV) by immunohistochemical techniques, whereas none of the cases from older persons showed positivity [50]. Further studies have found various subtypes of HPV associated with a minority of ameloblastomas [51–54], the most common being HPV 6, though a large study ($n = 18$) using laser capture micro dissection showed no evidence of HPV, arguing against an etiologic association [55]. Non-specific irritation from extractions, dental caries, trauma, inflammation, and nutritional deficiencies has all anecdotally been proposed as etiologies [54].

Until recently, little was known about the molecular aberrations driving ameloblastoma, due both to the tumor's rarity and to the fact that technologies to query the tumor genome do not work as efficiently in formalin-fixed paraffin-embedded tissue. In 2014, however, three separate reports, including one from our group, profiling ameloblastoma via DNA sequencing were published, all showing the vast majority of tumors to contain somatic mutations impacting the mitogen-activated protein kinase (MAPK) signaling pathway (FGFR2 → RAS → BRAF) that controls cell proliferation (Fig. 3) [56–58].

In particular, all three studies reported a high frequency of BRAF-V600E (valine to glutamic acid substitution at amino acid 600) activating mutations at high allele frequencies in ameloblastomas. Interestingly, in each of these reports, the BRAF-mutated neoplasms were almost exclusively located in the mandible. Furthermore, two of the three reports went on to characterize the sensitivity of BRAF-mutated ameloblastoma cells to vemurafenib, a V600E-targeted small molecule inhibitor that is FDA-approved for metastatic melanoma. Both studies showed that AM-1, a mandibular-derived ameloblastoma cell line harboring the BRAF-V600E mutation, was exquisitely sensitive to vemurafenib at concentrations similar to BRAF-V600E mutated melanoma and colorectal cancer cell lines. In addition to the functional profile, Brown et al. [57, 58] also reported a statistically significant association of BRAF-mutated ameloblastomas recurring later than their wild type (non-mutated) counterparts, portending a better prognosis. Of diagnostic relevance, expression of BRAF-V600E was readily detectable by immunohistochemistry.

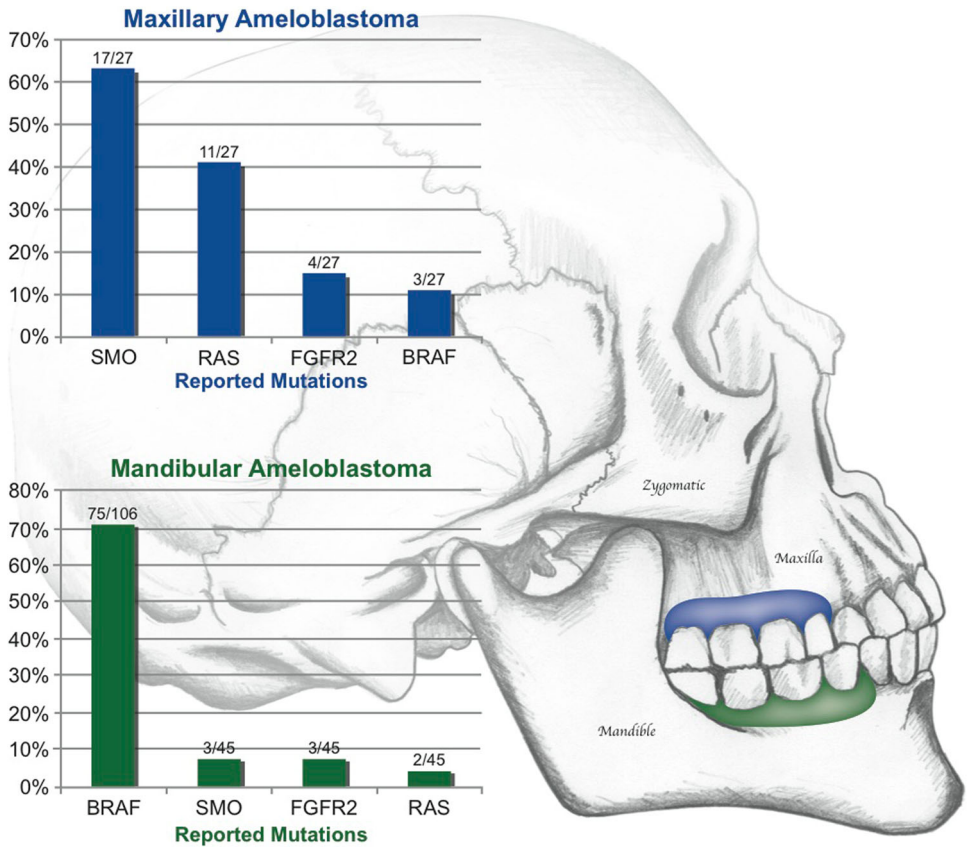

Fig. 3 Relationship of anatomic location to mutational status pooled from three recently reported studies [56–58]. Numbers above bar graphs represent number of patients/total cohort tested for specified anatomic site (Maxilla or Mandible). Mutations included: BRAF-L597R and V600E, SMO-L412F, G416E, and W535L,RAS-KRAS G12R, HRAS G12S, HRAS Q61R, HRAS Q61 K, NRAS Q61R, and NRASQ61 K, and FGFR2-C382R, V395D, and N549 K

The studies by Sweeney et al. and Brown et al. [57, 58] also reported that a high percentage of the BRAF-negative maxillary ameloblastomas harbored a mutation in the sonic hedgehog (SHH) pathway, specifically activating mutations in Smoothened (SMO). Furthermore, the effect of the activated SMO mutation could be blocked by select pharmacologic inhibitors of SHH signaling, including KAAD-cyclopamine and arsenic trioxide. Current evidence suggests that the SHH pathway is instrumental in the formation of the tooth bud [59]. A microarray study performed earlier by Heikinheimo et al. [60] showed both SHH and PTCH (Patched-also in the SHH pathway) to be underexpressed in ameloblastomas when compared to human tooth germs, though this finding might reflect negative feedback regulation by the activated SHH pathway or the anatomic site studied.

Of note, both recent genomic studies also found that most SMO-mutated ameloblastomas harbored an additional mutation in either fibroblast growth factor receptor 2 (FGFR2) or Ras (KRAS,HRAS or NRAS), perhaps arguing for a necessary "second-hit" to transform [57, 58]. Nonetheless, SMO and BRAF mutations were nearly always mutually exclusive, occurring predominantly in tumors of the maxilla and mandible, respectively. This finding may reflect differences yet to be understood in tooth developmental pathways and/or mutational processes in the upper versus the lower jaw. Lastly, Brown et al. [58] also reported less common mutations in ameloblastomas, including in PIK3CA (in the PI3-kinase pathway that controls cell survival), CTNNB1 (β-catenin, in the Wnt signaling pathway), and SMARCB1 (involved in chromatin remodeling).

Ameloblastoma shows many similarities to basal cell carcinoma at the developmental stage. Histologically, ameloblastoma and basal cell carcinoma are both typically composed of uniform basaloid cells in nests with peripheral palisading surrounded by variable stroma. Molecularly, the two neoplasms both share mutations in the SHH pathway, with a large minority of sporadic basal cell carcinomas harboring an activating SMO mutation [61]. Further emphasizing the relationship between oncogenesis and ontogenesis, SHH is integrally involved in the epidermal placode, a dynamic mini-organ responsible for the development of both teeth and hair [62]. SHH is expressed at the tip of the invaginating hair bud, in the basal keratinocytes [63], and at the tip of the tooth invagination in precursors to ameloblasts [62]. In both structures, loss of SHH leads to stunted growth and morphogenesis but does not prevent differentiation: enamel and dentin secretion occur in the tooth, and hair keratins are made in the hair follicle.

Further highlighting the potential relationship between ameloblastoma and basal cell carcinoma, Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is defined by a germline mutation in PTCH, leading to uninhibited SHH signaling [64]. These patients are prone to develop both multiple basal cell carcinomas and odontogenic keratocysts, another neoplasm of the mandible and maxilla. A recent article actually highlighted the use of a SMO inhibitor, vismodegib, in the treatment of these keratocystic odontogenic tumors, showing a size reduction of the tumor in 4 of 6 patients [65]. A study of loss of heterozygosity (LOH) of PTCH in ameloblastoma showed 40 % of cases ($n = 10$) to harbor LOH for the gene, though these findings did not correlate with downstream levels of GLI (the transcriptional effector of SHH signaling) [66].

In addition to the pathways discussed above, tumor suppressor and anti-apoptotic pathways have been implicated in ameloblastoma pathogenesis. Although immunohistochemical studies have shown p53 and MDM2 to be expressed in a majority of ameloblastomas [67], two studies showed only a minority of ameloblastomas harbor a p53 mutation [68, 69].

Treatment

Surgery

Surgery is the standard treatment for ameloblastomas. Historically, the extent of resection has been controversial, comprising of two surgical options: "conservative" vs. "radical". The former involves enucleation/curettage of the bony cavity, while the latter involves a radical operation with appropriate margins. Advantages of enucleation include the fact that it is an outpatient procedure able to be performed by many different service providers (Oral Surgeons and ENT), since it requires no reconstruction. Historical data on simple enucleation demonstrate recurrence rates 60–90 %, however, and this treatment modality is currently believed to play no role in the management of multicystic ameloblastomas (Table 1) [11, 12, 28, 70–75]. Controversy still exists around the use of this procedure for unicystic ameloblastomas (seen in the pediatric population) because the intraluminal subtype, which requires an open biopsy for diagnosis, does not exhibit an invasive pattern [29]. Furthermore, benign dentigerous cysts can mimic unicystic ameloblastomas and are cured with simple enucleation. To limit recurrence rates of unicystic ameloblastomas, oral surgeons have extended this procedure to include intra-operative adjuvant treatment of the bony margins with cryotherapy [29, 76, 77], tissue fixatives such as Carnoy's solution [28, 73, 75, 78, 79] drilling [77] and cautery [80]. The outcomes of the procedures above demonstrate decreased recurrence rates, but still higher recurrence than compared with the more extensive oncologic operation described below.

The "radical" surgical option is the current standard of care for ameloblastoma and includes en bloc resection with 1–2 cm bone margins [32, 81–84] and immediate bone reconstruction to help with speech and swallowing [81, 85–87].

The bony margin is defined as the distance away from the radiographic margin predicted to be disease free and oncologically safe to perform osteotomies. Data from 82 ameloblastoma specimens showed microscopic tumor extension 2–8 mm (mean of 4.5 mm) beyond the radiographic boundaries of the tumor [88]. Hence, the recommended bone margins are 1–1.5 cm for unicystic and 1.5–2 cm for solid/multicystic histological types, and provides increased cure rates [10, 11, 32, 73, 85, 89]. Ameloblastic carcinoma requires 2–3 cm bone margins [90]. Elective neck dissection is not advocated especially in tumors originating form the maxilla [52, 53].

Surgeons rely on preoperative imaging to correlate the boundaries of the tumor with palpable surgical landmarks. Some use calculations from the CT to determine the proper location for osteotomies, ensuring adequate margins. Several groups have used intra-operative diagnostic assistance to evaluate bony margins, including plain specimen radiography [32, 81–83, 91–94].

Frozen section of the soft tissue (especially overlying cortical perforation) [32, 92, 93, 95–97] and bone marrow margins is strongly advocated [32, 83, 92–99]. Frozen section or touch prep of medullary bone from the mandibular stumps can aid in achieving wider margins and is essential if bone margins are <1 cm [32]. Intra-operative frozen sections demonstrate 95–98 % accuracy with a false negative rate of 3.8 % attributed to inadequate sampling versus misinterpretation by the pathologist [32, 94, 95, 98].

Peripheral ameloblastoma can be removed with 1 cm soft tissue margins and a cuff of the uninvolved alveolar bone (marginal mandibulectomy) to ensure a proper deep margin. For all other WHO-classified mandibular ameloblastomas, a segmental resection which includes at least one adjacent uninvolved anatomic barrier for proper margins is advocated. The healthy mucosa overlying the cortical perforation is often removed as a margin [19, 28]. Segmental resection of the mandible results in discontinuity of the jaw, which is stabilized to its previous position by titanium reconstruction plates to ensure proper occlusion. A fibular free flap is used to restore bone continuity and allow for dental restoration [85, 89, 100–102]. In cases of cortical erosion, there needs to be a 1 cm soft tissue margin along the mucosa of the oral cavity, and the fibular free flap skin paddle is used to line the oral cavity. Reconstructive outcomes show a high rate of success for both esthetic and functional outcomes [103, 104].

Table 1 Reported recurrence rates by type of surgical treatment

Treatment	Patients (*n*)	Recurrence (%)	Reference
Conservative surgery	43	93	Sehdev et al. [70]
Radical surgery	38	13	
Conservative surgery	13	86	Shatkin et al. [71]
Radical surgery	7	14	
Conservative surgery	98	73	Mehlisch et al. [72]
Radical surgery	26	21	
Conservative surgery	51	71	Müller et al. [28]
Radical surgery	33	9	
Radical surgery	229	10	Olaitan et al. [12]
Conservative surgery	68	46	Ueno et al. [73]
Radical surgery	23	9	
Radical surgery	51	22	Eckhardt et al. [74]
Conservative surgery	42	33	Nakamura et al. [75]
Radical surgery	36	7	
Radical surgery	60	0	Becelli et al. [11]
Pooled data			
Conservative surgery	315	65	
Radical surgery	503	11	
Overall	818	31	

This table pools recurrence rates for conservative versus radical resection from a number of ameloblastoma studies. Conservative = enucleation, curettage, or marsupialization. Radical = en bloc resection

For segmental defects of the mandible, vascularized free bone grafts are the standard. The fibular free flap is the most popular in the United States and has the added advantage of reconstructing long segment mandibular defects. In an exceedingly small percentage of patients, a rare vascular pattern to the lower extremity (Bilateral perineal arteria magna) precludes the use of this flap. The iliac crest free flap is also an outstanding reconstructive choice for mandibular defects, allowing for dental restoration with the added advantage of harvesting internal oblique muscle for the reconstruction of the floor of mouth. The iliac crest can be favored for mandibular angle defects eliminating the need for multiple osteotomies as seen with the fibula.

Maxillary lesions are removed through various approaches for partial maxillectomy, with the resultant defect allowing communication among the oral cavity, paranasal sinuses, and/or nasal cavity, causing alterations in speech and swallowing as air and food escape via the fistula during eating and talking [89, 105]. The extent of the soft tissue involvement is demonstrated by preoperative MRI, with the surgical margins limited by potential morbidity from proximity or involvement of vital structures, including the orbit, skull base, cranial nerves and/or carotid artery. Commonly, these defects are not reconstructed with a free flap to avoid covering a potential recurrence site. Instead, a skin graft is used to line the cavity and the patient is fitted with an obturator, allowing for easy access to the resection bed during surveillance.

Radiotherapy and chemotherapy

Prior to the 1980s, it was believed that ameloblastomas were radio resistant. Although several studies have reported on adjuvant radiation for positive margins (gross and microscopic) and for recurrent and unresectable ameloblastomas, the outcomes are poor (Table 2) [70, 71, 106–110]. As these patients are often young, the possible efficacy of radiotherapy must be weighed against the risk for future radiation-induced malignancies and other long-term sequelae of radiation therapy. More work is needed to validate this treatment option [111]. Despite these experiences, some studies advocate for adjuvant radiation in ameloblastic carcinoma, though the data are mixed (Table 3) [16, 43, 44, 46, 112–139]. Complicating matters, there is no animal model of ameloblastoma, making it difficult to determine the biological effects of radiotherapy on ameloblastoma. The closest model is acanthomatous epulis in dogs, which has been hypothesized to

Table 2 Recurrence rates after radiation treatment

Treatment	Patients (*n*)	Recurrence (%)	Reference
XRT	11	100	Sehdev et al. [70]
XRT	2	100	Shatkin et al. [71]
XRT	10	20	Atkinson et al. [109][a, b]
XRT	5	40	Gardner [110][a]
XRT	1	0	Miyamoto et al. [106][a]
XRT	8	50	Pinsolle et al. [107]
XRT	1	0	Ueda et al. [108]
Pooled			
XRT	38	45	

This table details recurrence rates of multiple ameloblastoma studies where radiation treatment was performed. All cases were treated with surgery as well

XRT radiation therapy

[a] Gross disease left post-operatively

[b] Microscopic disease left behind post-operatively

occasionally transform post-radiotherapy [140]. If radiotherapy is to be considered, then more data are needed to better understand its effectiveness.

Systemic chemotherapy has been attempted a number of times, with numerous agents and combinations being employed (Table 4) [40, 141–146]. Reports have suggested that ameloblastoma may be sensitive to platinum-based agents [145], though occasional reports highlight lengthy survival without chemotherapy [147]. Chemotherapy may also have a role in improvement of clinical symptoms in non-surgical patients [147]. Much like radiotherapy, however, only with continuous reporting of empirical case-based data will the role of systemic chemotherapy be evaluable in this rare entity. Furthermore, with advances in the understanding of the molecular pathogenesis of ameloblastoma, targeted agents with fewer systemic side effects may prove more useful than traditional chemotherapeutic regimens.

Prognosis

Prognosis for ameloblastoma depends on the age of the patient, tumor size, extent of disease, location of tumor, and histological type. Recurrence rates are dictated by the adequacy of the surgical margins and extension of maxillary ameloblastoma into vital structures (skull base, orbit, paranasal sinuses). Maxillary ameloblastoma is more aggressive in terms of disease extent and recurrence, with a common hypothesis for this relative difference being that the relative thinness of maxillary cortical bone provides a weaker barrier for loco-regional spread of tumor [8, 105, 148]. Additionally, recurrence and reoperation may lead to increased risk of surgical complications.

Recurrence following conservative treatments is believed to result from persistence of microscopic disease, which grows slowly within a previously evacuated cavity and may take decades to re-present. Standard "radical" surgical resection shows far better outcomes as mentioned

Table 3 Comparison of reported treatment modalities for ameloblastic carcinoma

Treatment	Patients (*n*)	Recurrence (*n*)	Metastasis (*n*)	Average duration of follow-up (month)
Surgery alone	36	44 % (16)	14 % (5)	81.5
Surgery + radiation	20	40 % (8)	35 % (7)	60.3
Surgery + chemotherapy[a]	1	0	0	42
Surgery + radiation + chemotherapy[a]	2	50 % (1)	50 % (1)	30

This table compares various reported treatment regimens for ameloblastic carcinoma [16, 43, 44, 46, 112–139]

[a] Chemotherapy = regimens consisted of (1) cisplatinum, adriamycin, methotrexate, and leucovorin or (2) bleomycin and adriamycin

Table 4 Literature reports of systemic chemotherapy usage in malignant ameloblastoma/ameloblastic carcinoma

Case	Regimen	Response	Reference
1	Cyclophosphamide, methotrexate, 5-fluorouracil	No objective response	Gall et al. [141]
2	Vinblastine, cisplatin, bleomycin	PR	Eliasson et al. [40]
3	Adriamycin, cisplatin, cyclophosphamide	PR	Ramadas et al. [142]
4	1st line: 5-fluorouracil and cisplatin; 2nd line: paclitaxel-carboplatin	PR	Grünwald et al. [143]
5	Cyclophosphamide	No objective response	Campbell et al. [144]
6	Doxorubicin and cisplatin	PR	Amzerin et al. [145]
7	Gemcitabine and carboplatin	PR	Van Dam et al. [146]

earlier (Table 1). Recurrences have been reported from 1 to 45 years after enucleation [149, 150]. For surveillance purposes, patients should have a post-operative baseline CT and lifetime annual clinical exams. In the asymptomatic patient, surveillance CT at increasing intervals over the first 5 years is reasonable.

Ameloblastoma, if untreated, can grow to a very large size and pose an airway risk and metabolic abnormalities [8, 151]. Additionally, reports have documented metastatic ameloblastoma to the lungs associated with a paraneoplastic syndrome causing hypercalcemia. [152, 153] Deaths in patients with multiple recurrences have been reported [72, 105, 154]. For example, death in patients with uncontrolled maxillary ameloblastoma may result from extension into the central nervous system [155]. Recent reports for metastatic ameloblastoma show a mean disease-free survival time of 13 years, though prior reports highlight a poorer reported prognosis for metastatic disease, with median survival after metastasis being 2 years [49, 156].

Conclusions and future directions

Ameloblastoma is a rare tumor of the mandible and maxilla, with a well-documented propensity for loco-regional invasion and risk of recurrence. Therapeutically, simple enucleation has no role in the management of ameloblastoma beyond perhaps the unicystic subtype. Few options exist for treatment beyond wide local excision, which can be associated with significant patient morbidity. Additionally, though radiotherapy has been attempted in recurrent or inoperable cases, studies show its efficacy to be unclear.

Given the rarity of the disease and limited experience with systemic treatments, their role remains undefined, and until recently, little was known about the molecular underpinnings of ameloblastoma. New studies have shed light on two central pathways, MAPK and SHH, that appear to play key roles in ameloblastic oncogenesis, and each of which offers potential new personalized treatment paradigms. Additionally, these discoveries present fertile ground for future work on odontogenic development, and the relationship of ameloblastoma to a number of other epithelial neoplasms.

Most importantly, these recent molecular developments suggest avenues for clinical trial exploration. For example, pre-surgical neo-adjuvant treatment could be considered, such as has been recently reported in keratocystic odontogenic tumors using vismodegib [65]. This approach may also be useful in reducing surgical morbidity, which in ameloblastoma can be significant. Additional approaches may include therapy for advanced/metastatic disease. Some may argue that ameloblastoma may not respond to these targeted approaches, though we believe that much like sarcomas, the uniquely specific causative molecular events may be exquisitely sensitive to targeted therapy [157].

From first being described in 1827 by Cusack, to the recent genetic discoveries, our understanding of ameloblastoma has greatly improved. Moving forward, it will be imperative to further refine our understanding of the disease both clinically and molecularly to improve the precision with which we treat ameloblastoma.

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Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Cusack JW (1827) Report of the amputations of the lower jaw. Dubliln Hop Rec 4:1–38
2. Ivery RH, Churchill HR (1930) The need of a standardized surgical and pathological classification of tumors and anomalies of dental origin. Am Assoc Dent Sch Trans 7:240–245
3. Brazis PW, Miller NR, Lee AG, Holliday MJ (1995) Neuro-ophthalmologic aspects of ameloblastoma. Skull Base Surg 5(4):233–244
4. Lu Y, Xuan M, Takata T, Wang C, He Z, Zhou Z, Mock D, Nikai H (1998) Odontogenic tumors. A demographic study of 759 cases in a Chinese population. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 86(6):707–714
5. Mosadomi A (1975) Odontogenic tumors in an African population. Analysis of twenty-nine cases seen over a 5-year period. Oral Surg Oral Med Oral Pathol 40(4):502–521
6. Barnes L, Everson JW, Reichart P, Sidransky D (eds) (2005) Pathology and genetics of head and neck tumours. IARC Press, Lyon
7. Daley TD, Wysocki GP, Pringle GA (1994) Relative incidence of odontogenic tumors and oral and jaw cysts in a Canadian population. Oral Surg Oral Med Oral Pathol 77(3):276–280
8. Regezi JA, Kerr DA, Courtney RM (1978) Odontogenic tumors: analysis of 706 cases. J Oral Surg 36(10):771–778
9. Larsson A, Almeren H (1978) Ameloblastoma of the jaws. An analysis of a consecutive series of all cases reported to the Swedish Cancer Registry during 1958–1971. Acta Pathol Microbiol Scand A 86A(5):337–349
10. Wenig BM (2007) Atlas of head and neck pathology, 2nd edn. Elsevier Saunders
11. Becelli R, Carboni A, Cerulli G, Perugini M, Iannetti G (2002) Mandibular ameloblastoma: analysis of surgical treatment carried out in 60 patients between 1977 and 1998. J Craniofac Surg 13(3):395–400
12. Olaitan AA, Adeola DS, Adekeye EO (1993) Ameloblastoma: clinical features and management of 315 cases from Kaduna, Nigeria. J Craniomaxillofac Surg 21(8):351–355
13. Schafer DR, Thompson LD, Smith BC, Wenig BM (1998) Primary ameloblastoma of the sinonasal tract: a clinicopathologic study of 24 cases. Cancer 82(4):667–674

14. Reichart PA, Philipsen HP, Sonner S (1995) Ameloblastoma: biological profile of 3677 cases. Eur J Cancer B Oral Oncol 31B(2):86–99
15. Stanley HR, Diehl DL (1965) Ameloblastoma potential of follicular cysts. Oral Surg Oral Med Oral Pathol 20:260–268
16. Slootweg PJ, Muller H (1984) Malignant ameloblastoma or ameloblastic carcinoma. Oral Surg Oral Med Oral Pathol 57(2):168–176
17. Singer SR, Mupparapu M, Philipone E (2009) Cone beam computed tomography findings in a case of plexiform ameloblastoma. Quintessence Int 40(8):627–630
18. Underhill TE, Katz JO, Pope TL Jr, Dunlap CL (1992) Radiologic findings of diseases involving the maxilla and mandible. AJR Am J Roentgenol 159(2):345–350. doi:10.2214/ajr.159.2.1632353
19. Carlson ER (1996) Pathologic facial asymmetries. Atlas Oral Maxillofac Surg Clin N Am 4(1):19–35
20. Cohen MA, Hertzanu Y, Mendelsohn DB (1985) Computed tomography in the diagnosis and treatment of mandibular ameloblastoma: report of cases. J Oral Maxillofac Surg 43(10):796–800
21. Fujita M, Matsuzaki H, Yanagi Y, Hara M, Katase N, Hisatomi M, Unetsubo T, Konouchi H, Nagatsuka H, Asaumi JI (2013) Diagnostic value of MRI for odontogenic tumours. Dentomaxillofac Radiol 42(5):20120265. doi:10.1259/dmfr.20120265
22. Kawai T, Kishino M, Hiranuma H, Sasai T, Ishida T (1999) A unique case of desmoplastic ameloblastoma of the mandible: report of a case and brief review of the English language literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 87(2):258–263
23. Dunfee BL, Sakai O, Pistey R, Gohel A (2006) Radiologic and pathologic characteristics of benign and malignant lesions of the mandible. Radiographics 26(6):1751–1768. doi:10.1148/rg.266055189
24. Chai Y, Jiang X, Ito Y, Bringas P Jr, Han J, Rowitch DH, Soriano P, McMahon AP, Sucov HM (2000) Fate of the mammalian cranial neural crest during tooth and mandibular morphogenesis. Development 127(8):1671–1679
25. Ritchie A (1990) Boyd's text book of pathology, 9th edn. Lea and Febiger, UK
26. Bhasker S (1981) Synopsis of oral pathlogy, 6th edn. The CV Mosby, USA
27. Gardner DG, Corio RL (1984) Plexiform unicystic ameloblastoma. A variant of ameloblastoma with a low-recurrence rate after enucleation. Cancer 53(8):1730–1735
28. Muller H, Slootweg PJ (1985) The ameloblastoma, the controversial approach to therapy. J Maxillofac Surg 13(2):79–84
29. Rosenstein T, Pogrel MA, Smith RA, Regezi JA (2001) Cystic ameloblastoma—behavior and treatment of 21 cases. J Oral Maxillofac Surg 59(11):1311–1316. doi:10.1053/joms.2001.27522
30. Robinson L, Martinez MG (1977) Unicystic ameloblastoma: a prognostically distinct entity. Cancer 40(5):2278–2285
31. Ackermann GL, Altini M, Shear M (1988) The unicystic ameloblastoma: a clinicopathological study of 57 cases. J Oral Pathol 17(9–10):541–546
32. Carlson ER, Marx RE (2006) The ameloblastoma: primary, curative surgical management. J Oral Maxillofac Surg 64(3):484–494. doi:10.1016/j.joms.2005.11.032
33. Waldron CA, el-Mofty SK (1987) A histopathologic study of 116 ameloblastomas with special reference to the desmoplastic variant. Oral Surg Oral Med Oral Pathol 63(4):441–451
34. Philipsen HP, Reichart PA, Takata T (2001) Desmoplastic ameloblastoma (including "hybrid" lesion of ameloblastoma). Biological profile based on 100 cases from the literature and own files. Oral Oncol 37(5):455–460
35. Keszler A, Paparella ML, Dominguez FV (1996) Desmoplastic and non-desmoplastic ameloblastoma: a comparative clinicopathological analysis. Oral Dis 2(3):228–231
36. Takata T, Miyauchi M, Ito H, Ogawa I, Kudo Y, Zhao M, Sato S, Takekoshi T, Nikai H, Tanimoto K (1999) Clinical and histopathological analyses of desmoplastic ameloblastoma. Pathol Res Pract 195(10):669–675. doi:10.1016/S0344-0338(99)80057-0
37. Buchner A, Merrell PW, Carpenter WM (2006) Relative frequency of peripheral odontogenic tumors: a study of 45 new cases and comparison with studies from the literature. J Oral Pathol Med 35(7):385–391. doi:10.1111/j.1600-0714.2006.00437.x
38. Fernandes AM, Duarte EC, Pimenta FJ, Souza LN, Santos VR, Mesquita RA, de Aguiar MC (2005) Odontogenic tumors: a study of 340 cases in a Brazilian population. J Oral Pathol Medicine 34(10):583–587. doi:10.1111/j.1600-0714.2005.00357.x
39. LeCorn DW, Bhattacharyya I, Vertucci FJ (2006) Peripheral ameloblastoma: a case report and review of the literature. J Endod 32(2):152–154. doi:10.1016/j.joen.2005.10.028
40. Eliasson AH, Moser RJ 3rd, Tenholder MF (1989) Diagnosis and treatment of metastatic ameloblastoma. South Med J 82(9):1165–1168
41. Elzay RP (1982) Primary intraosseous carcinoma of the jaws. Review and update of odontogenic carcinomas. Oral Surg Oral Med Oral Pathol 54(3):299–303
42. Kruse AL, Zwahlen RA, Gratz KW (2009) New classification of maxillary ameloblastic carcinoma based on an evidence-based literature review over the last 60 years. Head Neck Oncol 1:31. doi:10.1186/1758-3284-1-31
43. Ward BB, Edlund S, Sciubba J, Helman JI (2007) Ameloblastic carcinoma (primary type) isolated to the anterior maxilla: case report with review of the literature. J Oral Maxillofac Surg 65(9):1800–1803. doi:10.1016/j.joms.2006.06.265
44. Dhir K, Sciubba J, Tufano RP (2003) Ameloblastic carcinoma of the maxilla. Oral Oncol 39(7):736–741
45. Henderson JM, Sonnet JR, Schlesinger C, Ord RA (1999) Pulmonary metastasis of ameloblastoma: case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 88(2):170–176
46. Bruce RA, Jackson IT (1991) Ameloblastic carcinoma. Report of an aggressive case and review of the literature. J Craniomaxillofac Surg 19(6):267–271
47. Clay RP, Weiland LH, Jackson IT (1989) Ameloblastoma metastatic to the lung. Ann Plast Surg 22(2):160–162
48. Kunze E, Donath K, Luhr HG, Engelhardt W, De Vivie R (1985) Biology of metastasizing ameloblastoma. Pathol Res Pract 180(5):526–535. doi:10.1016/S0344-0338(85)80017-0
49. Laughlin EH (1989) Metastasizing ameloblastoma. Cancer 64(3):776–780
50. Kahn MA (1989) Ameloblastoma in young persons: a clinicopathologic analysis and etiologic investigation. Oral Surg Oral Med Oral Pathol 67(6):706–715
51. Correnti M, Rossi M, Avila M, Perrone M, Rivera H (2010) Human papillomavirus in ameloblastoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 110(3):e20–e24. doi:10.1016/j.tripleo.2010.04.030
52. Kahn MA (1992) Demonstration of human papillomavirus DNA in a peripheral ameloblastoma by in situ hybridization. Hum Pathol 23(2):188–191
53. Namin AK, Azad TM, Eslami B, Sarkarat F, Shahrokhi M, Kashanian F (2003) A study of the relationship between ameloblastoma and human papilloma virus. J Oral Maxillofac Surg 61(4):467–470. doi:10.1053/joms.2003.50011
54. Sand L, Jalouli J, Larsson PA, Magnusson B, Hirsch JM (2000) Presence of human papilloma viruses in intraosseous

ameloblastoma. J Oral Maxillofac Surg 58(10):1129–1134. doi:10.1053/joms.2000.9573
55. Migaldi M, Pecorari M, Rossi G, Maiorana A, Bettelli S, Tamassia MG, De Gaetani C, Leocata P, Portolani M (2005) Does HPV play a role in the etiopathogenesis of ameloblastoma? An immunohistochemical, in situ hybridization and polymerase chain reaction study of 18 cases using laser capture microdissection. Mod Pathol 18(2):283–289. doi:10.1038/modpathol.3800241
56. Kurppa KJ, Caton J, Morgan PR, Ristimaki A, Ruhin B, Kellokoski J, Elenius K, Heikinheimo K (2014) High frequency of BRAF V600E mutations in ameloblastoma. J Pathol 232(5):492–498. doi:10.1002/path.4317
57. Sweeney RT, McClary AC, Myers BR, Biscocho J, Neahring L, Kwei KA, Qu K, Gong X, Ng T, Jones CD, Varma S, Odegaard JI, Sugiyama T, Koyota S, Rubin BP, Troxell ML, Pelham RJ, Zehnder JL, Beachy PA, Pollack JR, West RB (2014) Identification of recurrent SMO and BRAF mutations in ameloblastomas. Nat Genet 46(7):722–725. doi:10.1038/ng.2986
58. Brown NA, Rolland DC, McHugh JB, Weigelin HC, Zhao LL, Lim MS, Elenitoba-Johnson KS, Betz BL (2014) Activating FGFR2-RAS-BRAF mutations in ameloblastoma. Clin Cancer Res. doi:10.1158/1078-0432.CCR-14-1069
59. Cobourne MT, Hardcastle Z, Sharpe PT (2001) Sonic hedgehog regulates epithelial proliferation and cell survival in the developing tooth germ. J Dent Res 80(11):1974–1979
60. Heikinheimo K, Jee KJ, Niini T, Aalto Y, Happonen RP, Leivo I, Knuutila S (2002) Gene expression profiling of ameloblastoma and human tooth germ by means of a cDNA microarray. J Dent Res 81(8):525–530
61. Daya-Grosjean L, Couve-Privat S (2005) Sonic hedgehog signaling in basal cell carcinomas. Cancer Lett 225(2):181–192. doi:10.1016/j.canlet.2004.10.003
62. Dassule HR, Lewis P, Bei M, Maas R, McMahon AP (2000) Sonic hedgehog regulates growth and morphogenesis of the tooth. Development 127(22):4775–4785
63. Chiang C, Swan RZ, Grachtchouk M, Bolinger M, Litingtung Y, Robertson EK, Cooper MK, Gaffield W, Westphal H, Beachy PA, Dlugosz AA (1999) Essential role for Sonic hedgehog during hair follicle morphogenesis. Dev Biol 205(1):1–9. doi:10.1006/dbio.1998.9103
64. Gorlin RJ, Goltz RW (1960) Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med 262:908–912. doi:10.1056/NEJM196005052621803
65. Ally MS, Tang JY, Joseph T, Thompson B, Lindgren J, Raphael MA, Ulerio G, Chanana AM, Mackay-Wiggan JM, Bickers DR, Epstein EH Jr (2014) The use of vismodegib to shrink keratocystic odontogenic tumors in patients with basal cell nevus syndrome. JAMA Dermatol 150(5):542–545. doi:10.1001/jamadermatol.2013.7444
66. Farias LC, Gomes CC, Brito JA, Galvao CF, Diniz MG, de Castro WH, Bernardes Vde F, De Marco LA, Gomez RS (2012) Loss of heterozygosity of the PTCH gene in ameloblastoma. Hum Pathol 43(8):1229–1233. doi:10.1016/j.humpath.2011.08.026
67. Carvalhais J, Aguiar M, Araujo V, Araujo N, Gomez R (1999) p53 and MDM2 expression in odontogenic cysts and tumours. Oral Dis 5(3):218–222
68. Appel T, Gath R, Wernert N, Martini M, Berge S (2004) Molecular biological and immunohistochemical analysis of tp53 in human ameloblastomas. Mund Kiefer Gesichtschir 8(3):167–172. doi:10.1007/s10006-004-0539-7
69. Shibata T, Nakata D, Chiba I, Yamashita T, Abiko Y, Tada M, Moriuchi T (2002) Detection of TP53 mutation in ameloblastoma by the use of a yeast functional assay. J Oral Pathol Med 31(9):534–538
70. Sehdev MK, Huvos AG, Strong EW, Gerold FP, Willis GW (1974) Proceedings: Ameloblastoma of maxilla and mandible. Cancer 33(2):324–333
71. Shatkin S, Hoffmeister FS (1965) Ameloblastoma: a rational approach to therapy. Oral Surg Oral Med Oral Pathol 20(4):421–435
72. Mehlisch DR, Dahlin DC, Masson JK (1972) Ameloblastoma: a clinicopathologic report. J Oral Surg 30(1):9–22
73. Ueno S, Mushimoto K, Shirasu R (1989) Prognostic evaluation of ameloblastoma based on histologic and radiographic typing. J Oral Maxillofac Surg 47(1):11–15
74. Eckardt AM, Kokemuller H, Flemming P, Schultze A (2009) Recurrent ameloblastoma following osseous reconstruction—a review of twenty years. J Craniomaxillofac Surg 37(1):36–41. doi:10.1016/j.jcms.2008.07.009
75. Nakamura N, Higuchi Y, Mitsuyasu T, Sandra F, Ohishi M (2002) Comparison of long-term results between different approaches to ameloblastoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93(1):13–20
76. Curi MM, Dib LL, Pinto DS (1997) Management of solid ameloblastoma of the jaws with liquid nitrogen spray cryosurgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84(4):339–344
77. Pogrel MA (1993) The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions. J Oral Maxillofac Surg 51(3):269–273
78. Lau SL, Samman N (2006) Recurrence related to treatment modalities of unicystic ameloblastoma: a systematic review. Int J Oral Maxillofac Surg 35(8):681–690. doi:10.1016/j.ijom.2006.02.016
79. Chapelle KA, Stoelinga PJ, de Wilde PC, Brouns JJ, Voorsmit RA (2004) Rational approach to diagnosis and treatment of ameloblastomas and odontogenic keratocysts. Br J Oral Maxillofac Surg 42(5):381–390. doi:10.1016/j.bjoms.2004.04.005
80. Huffman GG, Thatcher JW (1974) Ameloblastoma—the conservative surgical approach to treatment: report of four cases. J Oral Surg 32(11):850–854
81. Sham E, Leong J, Maher R, Schenberg M, Leung M, Mansour AK (2009) Mandibular ameloblastoma: clinical experience and literature review. ANZ J Surg 79(10):739–744. doi:10.1111/j.1445-2197.2009.05061.x
82. Gardner DG, Pecak AM (1980) The treatment of ameloblastoma based on pathologic and anatomic principles. Cancer 46(11):2514–2519
83. Williams TP (1993) Management of ameloblastoma: a changing perspective. J Oral Maxillofac Surg 51(10):1064–1070
84. Becelli R, Morello R, Renzi G, Matarazzo G, Dominici C (2011) Treatment of recurrent mandibular ameloblastoma with segmental resection and revascularized fibula free flap. J Craniofac Surg 22(3):1163–1165. doi:10.1097/SCS.0b013e318210bc34
85. Vayvada H, Mola F, Menderes A, Yilmaz M (2006) Surgical management of ameloblastoma in the mandible: segmental mandibulectomy and immediate reconstruction with free fibula or deep circumflex iliac artery flap (evaluation of the long-term esthetic and functional results). J Oral Maxillofac Surg 64(10):1532–1539. doi:10.1016/j.joms.2005.11.065
86. Urken ML, Buchbinder D, Weinberg H, Vickery C, Sheiner A, Parker R, Schaefer J, Som P, Shapiro A, Lawson W et al (1991) Functional evaluation following microvascular oromandibular reconstruction of the oral cancer patient: a comparative study of reconstructed and nonreconstructed patients. Laryngoscope 101(9):935–950. doi:10.1288/00005537-199109000-00004
87. Urken ML, Buchbinder D, Costantino PD, Sinha U, Okay D, Lawson W, Biller HF (1998) Oromandibular reconstruction using microvascular composite flaps: report of 210 cases. Arch Otolaryngol Head Neck Surg 124(1):46–55

88. Carlson ER (2000) Ameloblastoma. In: Symposium on odontogenic tumors, AAOMS 82nd annual meeting and scientific sessions, San Francisco, CA, September 23, 2000
89. Zwahlen RA, Gratz KW (2002) Maxillary ameloblastomas: a review of the literature and of a 15-year database. J Craniomaxillofac Surg 30(5):273–279
90. Ndukwe KC, Adebiyi EK, Ugboko VI, Adeyemo WL, Ajayi FO, Ladeinde AL, Okojie VN, Ajike SO, Olasoji HO (2010) Ameloblastic carcinoma: a multicenter Nigerian study. J Oral Maxillofac Surg 68(9):2111–2114. doi:10.1016/j.joms.2009.09.028
91. Gardner DG (1984) A pathologist's approach to the treatment of ameloblastoma. J Oral Maxillofac Surg 42(3):161–166
92. Black CC, Addante RR, Mohila CA (2010) Intraosseous ameloblastoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 110(5):585–592. doi:10.1016/j.tripleo.2010.02.040
93. Marx RE, Smith BH, Smith BR, Fridrich KL (1993) Swelling of the retromolar region and cheek associated with limited opening. J Oral Maxillofac Surg 51(3):304–309
94. Forrest LA, Schuller DE, Karanfilov B, Lucas JG (1997) Update on intraoperative analysis of mandibular margins. Am J Otolaryngol 18(6):396–399
95. Gephardt GN, Zarbo RJ (1996) Interinstitutional comparison of frozen section consultations. A college of American Pathologists Q-Probes study of 90,538 cases in 461 institutions. Arch Pathol Lab Med 120(9):804–809
96. Ueno S, Nakamura S, Mushimoto K, Shirasu R (1986) A clinicopathologic study of ameloblastoma. J Oral Maxillofac Surg 44(5):361–365
97. Gold L, Upton GW, Marx RE (1991) Standardized surgical terminology for the excision of lesions in bone: an argument for accuracy in reporting. J Oral Maxillofac Surg 49(11):1214–1217
98. Winther C, Graem N (2011) Accuracy of frozen section diagnosis: a retrospective analysis of 4785 cases. APMIS 119(4–5): 259–262. doi:10.1111/j.1600-0463.2011.02725.x
99. Guthrie D, Peacock ZS, Sadow P, Dodson TB, August M (2012) Preoperative incisional and intraoperative frozen section biopsy techniques have comparable accuracy in the diagnosis of benign intraosseous jaw pathology. J Oral Maxillofac Surg 70(11): 2566–2572. doi:10.1016/j.joms.2011.11.023
100. Zemann W, Feichtinger M, Kowatsch E, Karcher H (2007) Extensive ameloblastoma of the jaws: surgical management and immediate reconstruction using microvascular flaps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103(2):190–196. doi:10.1016/j.tripleo.2006.05.004
101. Pogrel MA, Podlesh S, Anthony JP, Alexander J (1997) A comparison of vascularized and nonvascularized bone grafts for reconstruction of mandibular continuity defects. J Oral Maxillofac Surg 55(11):1200–1206
102. Chana JS, Chang YM, Wei FC, Shen YF, Chan CP, Lin HN, Tsai CY, Jeng SF (2004) Segmental mandibulectomy and immediate free fibula osteoseptocutaneous flap reconstruction with endosteal implants: an ideal treatment method for mandibular ameloblastoma. Plast Reconstr Surg 113(1):80–87. doi:10.1097/01.PRS.0000097719.69616.29
103. Foster RD, Anthony JP, Sharma A, Pogrel MA (1999) Vascularized bone flaps versus nonvascularized bone grafts for mandibular reconstruction: an outcome analysis of primary bony union and endosseous implant success. Head Neck 21(1):66–71
104. Hidalgo DA, Pusic AL (2002) Free-flap mandibular reconstruction: a 10-year follow-up study. Plastic and reconstructive surgery 110(2):438–449
105. Nastri AL, Wiesenfeld D, Radden BG, Eveson J, Scully C (1995) Maxillary ameloblastoma: a retrospective study of 13 cases. Br J Oral Maxillofac Surg 33(1):28–32
106. Miyamoto CT, Brady LW, Markoe A, Salinger D (1991) Ameloblastoma of the jaw. Treatment with radiation therapy and a case report. Am J Clin Oncol 14(3):225–230
107. Pinsolle J, Michelet V, Coustal B, Siberchicot F, Michelet FX (1995) Treatment of ameloblastoma of the jaws. Arch Otolaryngol Head Neck Surg 121(9):994–996
108. Ueda M, Kaneda T (1991) Combined chemotherapy and radiotherapy for advanced maxillary ameloblastoma. A case report. J Craniomaxillofac surg 19(6):272–274
109. Atkinson CH, Harwood AR, Cummings BJ (1984) Ameloblastoma of the jaw. A reappraisal of the role of megavoltage irradiation. Cancer 53(4):869–873
110. Gardner DG (1988) Radiotherapy in the treatment of ameloblastoma. Int J Oral Maxillofac Surg 17(3):201–205
111. Huvos AG, Woodard HQ, Cahan WG, Higinbotham NL, Stewart FW, Butler A, Bretsky SS (1985) Postradiation osteogenic sarcoma of bone and soft tissues. A clinicopathologic study of 66 patients. Cancer 55(6):1244–1255
112. Philip M, Morris C, Werning J, Mendenhall W (2005) Radiotherapy in the treatment of ameloblastoma and ameloblastic carcinoma. Hong Kong J Radiol 8(3):157
113. Cizmecy O, Aslan A, Onel D, Demiryont M (2004) Ameloblastic carcinoma ex ameloblastoma of the mandible: case report. Otolaryngol Head Neck Surg 130(5):633–634. doi:10.1016/j.otohns.2003.11.012
114. Cox DP, Muller S, Carlson GW, Murray D (2000) Ameloblastic carcinoma ex ameloblastoma of the mandible with malignancy-associated hypercalcemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90(6):716–722. doi:10.1067/moe.2000.109076
115. Akrish S, Buchner A, Shoshani Y, Vered M, Dayan D (2007) Ameloblastic carcinoma: report of a new case, literature review, and comparison to ameloblastoma. J Oral Maxillofac Surg 65(4):777–783. doi:10.1016/j.joms.2005.11.116
116. Corio RL, Goldblatt LI, Edwards PA, Hartman KS (1987) Ameloblastic carcinoma: a clinicopathologic study and assessment of eight cases. Oral Surg Oral Med Oral Pathol 64(5): 570–576
117. Naik V, Kale AD (2007) Ameloblastic carcinoma: a case report. Quintessence Int 38(10):873–879
118. Datta R, Winston JS, Diaz-Reyes G, Loree TR, Myers L, Kuriakose MA, Rigual NR, Hicks WL Jr (2003) Ameloblastic carcinoma: report of an aggressive case with multiple bony metastases. Am J Otolaryngol 24(1):64–69. doi:10.1053/ajot.2003.15
119. Goldenberg D, Sciubba J, Koch W, Tufano RP (2004) Malignant odontogenic tumors: a 22-year experience. Laryngoscope 114(10):1770–1774. doi:10.1097/00005537-200410000-00018
120. Dorner L, Sear AJ, Smith GT (1988) A case of ameloblastic carcinoma with pulmonary metastases. Br J Oral Maxillofac Surg 26(6):503–510
121. McClatchey KD, Sullivan MJ, Paugh DR (1989) Peripheral ameloblastic carcinoma: a case report of a rare neoplasm. J Otolaryngol 18(3):109–111
122. Lee L, Maxymiw WG, Wood RE (1990) Ameloblastic carcinoma of the maxilla metastatic to the mandible. Case report. J Craniomaxillofac surg 18(6):247–250
123. Nagai N, Takeshita N, Nagatsuka H, Inoue M, Nishijima K, Nojima T, Yamasaki M, Hoh C (1991) Ameloblastic carcinoma: case report and review. J Oral Pathol Med 20(9):460–463
124. Gandy SR, Keller EE, Unni KK (1992) Ameloblastic carcinoma: report of two cases. J Oral Maxillofac Surg 50(10):1097–1102
125. Ingram EA, Evans ML, Zitsch RP 3rd (1996) Fine-needle aspiration cytology of ameloblastic carcinoma of the maxilla: a rare tumor. Diagn Cytopathol 14(3):249–252. doi:10.1002/(SICI)1097-0339(199604)14:3<249:AID-DC10>3.0.CO;2-L

126. Lau SK, Tideman H, Wu PC (1998) Ameloblastic carcinoma of the jaws. A report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 85(1):78–81
127. Infante-Cossio P, Hernandez-Guisado JM, Fernandez-Machin P, Garcia-Perla A, Rollon-Mayordomo A, Gutierrez-Perez JL (1998) Ameloblastic carcinoma of the maxilla: a report of 3 cases. J Craniomaxillofac Surg 26(3):159–162
128. Simko EJ, Brannon RB, Eibling DE (1998) Ameloblastic carcinoma of the mandible. Head Neck 20(7):654–659
129. Sastre J, Munoz M, Naval L, Adrados M (2002) Ameloblastic carcinoma of the maxilla: report of a case. J Oral Maxillofac Surg 60(1):102–104
130. Avon SL, McComb J, Clokie C (2003) Ameloblastic carcinoma: case report and literature review. J Can Dent Assoc 69(9):573–576
131. Oginni FO, Ugboko VI, Owotade JF, Adebiyi KE (2003) Ameloblastic carcinoma of the jaws. A report of three Nigerian cases. Odontostomatol Trop 26(104):19–22
132. Carinci F, Palmieri A, Delaiti G, Rubini C, Fioroni M, Martinelli M, Pezzetti F, Scapoli L, Piattelli A (2004) Expression profiling of ameloblastic carcinoma. J Craniofac Surg 15(2):264–269
133. Uzum N, Akyol G, Asal K, Koybasioglu A (2005) Ameloblastic carcinoma containing melanocyte and melanin pigment in the mandible: a case report and review of the literature. J Oral Pathol Med 34(10):618–620. doi:10.1111/j.1600-0714.2005.00306.x
134. Ozlugedik S, Ozcan M, Basturk O, Deren O, Kaptanoglu E, Adanali G, Unal A (2005) Ameloblastic carcinoma arising from anterior skull base. Skull base 15(4):269–272. doi:10.1055/s-2005-918621
135. Suomalainen A, Hietanen J, Robinson S, Peltola JS (2006) Ameloblastic carcinoma of the mandible resembling odontogenic cyst in a panoramic radiograph. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101(5):638–642. doi:10.1016/j.tripleo.2005.07.033
136. Miyake T, Tanaka Y, Kato K, Tanaka M, Sato Y, Ijiri R, Inayama Y, Ito Y, Aoki S, Kawabe R, Tohnai I (2006) Gene mutation analysis and immunohistochemical study of beta-catenin in odontogenic tumors. Pathol Int 56(12):732–737. doi:10.1111/j.1440-1827.2006.02039.x
137. Hall JM, Weathers DR, Unni KK (2007) Ameloblastic carcinoma: an analysis of 14 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103(6):799–807. doi:10.1016/j.tripleo.2006.11.048
138. Benlyazid A, Lacroix-Triki M, Aziza R, Gomez-Brouchet A, Guichard M, Sarini J (2007) Ameloblastic carcinoma of the maxilla: case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104(6):e17–e24. doi:10.1016/j.tripleo.2007.05.026
139. Yazici N, Karagoz B, Varan A, Yilmaz T, Ozturk A, Usubutun A, Buyukpamukcu M (2008) Maxillary ameloblastic carcinoma in a child. Pediatr Blood Cancer 50(1):175–176. doi:10.1002/pbc.20889
140. Gardner DG (1995) Canine acanthomatous epulis. The only common spontaneous ameloblastoma in animals. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 79(5):612–615
141. Gall JA, Sartiano GP, Shreiner DP (1975) Ameloblastoma of the mandible with pulmonary metastasis. Oncology 32(3–4):118–126
142. Ramadas K, Jose C, Subhashini J, Chandi SM, Viswanathan FR (1990) Pulmonary metastases from ameloblastoma of the mandible treated with cisplatin, adriamycin, and cyclophosphamide. Cancer 66(7):1475–1479
143. Grünwald V, Le Blanc S, Karstens JH, Weihkopf T, Kuske M, Ganser A, Schoffski P (2001) Metastatic malignant ameloblastoma responding to chemotherapy with paclitaxel and carboplatin. Ann Oncol 12(10):1489–1491
144. Campbell D, Jeffrey RR, Wallis F, Hulks G, Kerr KM (2003) Metastatic pulmonary ameloblastoma. An unusual case. Br J Oral Maxillofac Surg 41(3):194–196
145. Amzerin M, Fadoukhair Z, Belbaraka R, Iraqui M, Boutayeb S, M'Rabti H, Kebdani T, Hassouni K, Benjaafar N, El Gueddari BK, Errihani H (2011) Metastatic ameloblastoma responding to combination chemotherapy: case report and review of the literature. J Med Case Rep 5:491. doi:10.1186/1752-1947-5-491
146. Van Dam SD, Unni KK, Keller EE (2010) Metastasizing (malignant) ameloblastoma: review of a unique histopathologic entity and report of Mayo Clinic experience. J Oral Maxillofac Surg 68(12):2962–2974. doi:10.1016/j.joms.2010.05.084
147. Ciment LM, Ciment AJ (2002) Malignant ameloblastoma metastatic to the lungs 29 years after primary resection: a case report. Chest 121(4):1359–1361
148. Jackson IT, Callan PP, Forte RA (1996) An anatomical classification of maxillary ameloblastoma as an aid to surgical treatment. J Craniomaxillofac Surg 24(4):230–236
149. Daramola JO, Ajagbe HA, Oluwasanmi JO (1980) Recurrent ameloblastoma of the jaws—a review of 22 cases. Plast Reconstr Surg 65(5):577–579
150. Frantz V, Stix L (1932) Adamantinoma: a case of fifty-one years'duration. Arch Surg 25(5):890–897
151. Nakasato S, Okamura S, Kudo K, Takeda Y (1991) Gigantic ameloblastoma associated with secondary hypoproteinemia. J Oral Maxillofac Surg 49(7):764–767
152. Inoue N, Shimojyo M, Iwai H, Ohtsuki H, Yasumizu R, Shintaku M, Taniguchi N, Inada M, Arika T, Morita S et al (1988) Malignant ameloblastoma with pulmonary metastasis and hypercalcemia. Report of an autopsy case and review of the literature. Am J Clin Pathol 90(4):474–481
153. Harada K, Suda S, Kayano T, Nagura H, Enomoto S (1989) Ameloblastoma with metastasis to the lung and associated hypercalcemia. J Oral Maxillofac Surg 47(10):1083–1087
154. Ramon Y, Mozes M, Buchner A (1964) A fatal case of Ameloblastoma (Adamantinoma). Br J Plast Surg 17:320–324
155. Bredenkamp JK, Zimmerman MC, Mickel RA (1989) Maxillary ameloblastoma. A potentially lethal neoplasm. Arch Otolaryngol Head Neck Surg 115(1):99–104
156. Lin Y, He JF, Li ZY, Liu JH (2013) Ameloblastoma with varied sites of metastasis: report of two cases and literature review. J Craniomaxillofac Surg. doi:10.1016/j.jcms.2013.10.010
157. Nielsen TO, West RB (2010) Translating gene expression into clinical care: sarcomas as a paradigm. J Clin Oncol 28(10):1796–1805. doi:10.1200/JCO.2009.26.1917