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Review Article

AMELOBLASTOMA - MANAGEMENT AND ROLE OF BRAF INHIBITORS: A REVIEW ARTICLE

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A B S T R A C T

Abstract Ameloblastoma is a rare odontogenic neoplasm involving the mandible and maxilla, with multiple histologic variations , and high chances of recurrence rates if treated improperly. The current standard of treatment is wide local excision with appropriate margins and immediate reconstruction. Here we have reviewed the ameloblastoma literature, using the available evidences to highlight the changes in management over the past several years. Additionaly, we explore the recent molecular characterization of these tumors which may direct towards new potential avenues of personalized treatment.

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 in literature by Cusack in the year 1827[1].

Etymologically, the name is derived from the old French word ‘‘amel,’’ which means enamel, and the Greek word ‘‘blastos,’’ meaning germ or bud. Over time, this tumor has been denoted to by many different names which includes ‘‘cystosarcoma,’’ ‘‘adamantine epithelioma,’’ ‘‘adamantinoma,’’ and finally ‘‘ameloblastoma’’ [2,3].

Ameloblastoma displays variable geographic prevalence, being the most common benign odontogenic tumor in Africa and China[3,4,5], while it is the second most common in the United States and Canada after odontoma[6,7,8]. African Americans have an overall fivefold increased risk of disease as compared to Caucasians. Global incidence has been estimated to be 0.5 cases per million person years, and most cases are diagnosed in patients 30–60 years of age[9].

In this review article, we have summarized the natural history and clinicopathological variants of ameloblastoma. The Diagnostic evaluation and surgical management of the various histologic variants of ameloblastoma will also be discussed. As controversy has existed for some time now with respect to enucleation/curettage versus resection with wide margins, we will also highlight the evidence supporting adequate surgical bony margins. Furthermore, the potential role of adjuvant radiation and chemotherapy will be addressed. This discussion is complicated due to the lack of a staging system and the absence of prospective studies for this rare disease, both of which make it difficult to compare and evaluate the treatment outcomes, especially when recurrences can occur even decades after initial treatment. Also, emerging molecular data are refining our understanding of the pathogenesis of ameloblastoma and may have treatment implications.

Patient presentation and diagnostics

Ameloblastoma is usually presented as 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 discovery on imaging [11]. Pain is usually uncommon but can occur due to hemorrhage, especially following a fine needle aspiration (FNA)[12]. Pain with rapid growth may indicate rare malignant ameloblastoma. Tooth displacement and root resorption are uncommon but have been reported in up to 25 % of desmoplastic ameloblastomas[13]. Paresthesiais also uncommon, with rare reported cases of perineural invasion. Up to 80 % of ameloblastoma cases occur in the mandible, with a higher chance of occurrence in the posterior mandibular region [14]. Rare cases have also been reported as primary to the sinonasal cavities[13]. Ameloblastoma can also be associated with unerupted third molar teeth[11,15], chiefly in the unicystic type. Desmoplastic ameloblastomas often occur in the anterior or premolar regions of the mandible or maxilla. Ameloblastic carcinomas also favor the mandible (*2/3) over the maxilla[16].

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Maxillary ameloblastomas also mostly occur in the posterior molar region. Preoperative diagnostic evaluation comprises of imaging and possible biopsy. Ameloblastomas originate from within the 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 observed 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 beneficial diagnostic imaging modality, typically demonstrating well-defined radiolucent uni/multilocular expansile lesions (Fig.2). CT is also useful for the evaluation of cortical destruction (revealing a window for biopsy) and soft tissue extension, recognizing the full extent of the tumor to support surgical planning[19]. MRI provides potentially more complete information than CT about soft tissue extension and marrow extension beyond the lytic bone cavity. MRI is particularly valuable 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 can be often misdiagnosed as a fibro-osseous lesion[20,21]. PET-CT is generally reserved for metastatic ameloblastoma, where it may aid with staging of the distant metastasis[22]. Imaging findings are distinguishing but not pathognomonic, and the diagnosis is classically established by histology. Biopsy can 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[23]. Biopsy is also helpful for proper preoperative staging in malignant ameloblastomas. Furthermore, over-treatment of benign dentigerous cysts that cannot be differentiated from some unicystic ameloblastomas and hence must be avoided; these cannot be diagnosed on FNA and need open biopsy in the form of curettage. A biopsy should be performed 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 should be acquired via a window of cortical erosion as identified by imaging or from the dental socket.

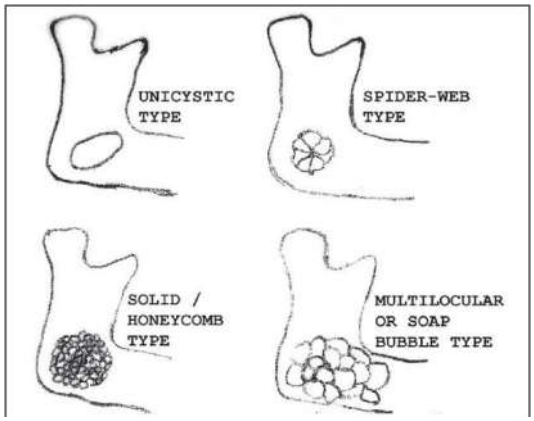

Fig 1 Types of Ameloblastoma

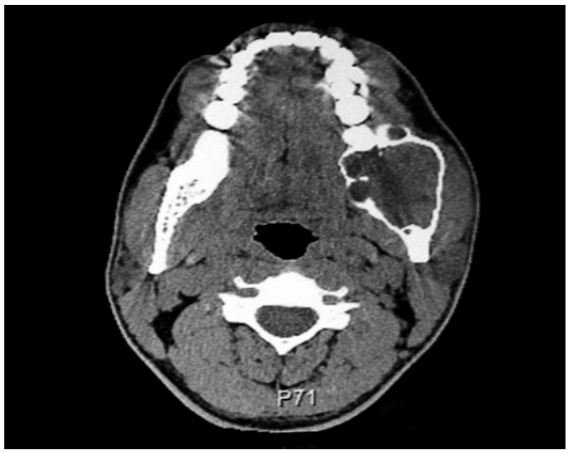

Fig 2 CT scan showing the extent of ameloblastoma

Incisional biopsy will provide a more accurate diagnosis but requires disruption of the mucosa which will ultimately need to be removed at surgery. Peripheral ameloblastomas are not covered by bone and can be biopsied without any difficulty.

Histopathology profile

Histopathologically, ameloblastoma bear a resemblance to normal odontogenic/enamel epithelium and ectomesenchyme. Odontogenesis consists of chronographic and reciprocal interactions between the ectomesenchyme cells, which are derived from the neural crestand the oral cavity lining epithelium[24]. Ameloblastic epithelium has been hypothesized to arise from cells from the rests of enamel organand alsofrom cells of the sheet of Hertwig's or epithelial cell rest of Malassez, epithelial boundary of an odontogenic cyst, particularly a dentigerous cyst, basal cells of the oral mucosa, heterotopic epithelial from other parts of the body, perhaps pituitary [26,26]. The 2005 WHO classification for ameloblastomas comprises of four subtypes. The solid/multicystic is the most common type, comprising 91 % of the ameloblastomas in the largest series. 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 linked 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 display 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[29,30,31,32]. Conflicting 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 has reported lower recurrence rates with this subtype, though other reports have demonstrated aggressive biologic behavior with higher recurrence rates [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 which do not involve the underlying bone [27,38,39,40,41]. 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 [42,43,44]. Cellular atypia and mitotic activity are

hardly present in any histologic subtype of ameloblastoma, and any increase in either parameter[46,47,48]. Additionally, microscopic patterns of ameloblastoma include follicular, plexiform, acanthomatous, spindle, basal cell-like, desmoplastic, and granular cell (Fig. 3). 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[49,50].

Of diagnostic relevance, expression of BRAFV600E was readily demonstrable by immunohistochemistry The studies by Sweeney *et al*. and Brown *et al*. also described 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)[57,58].

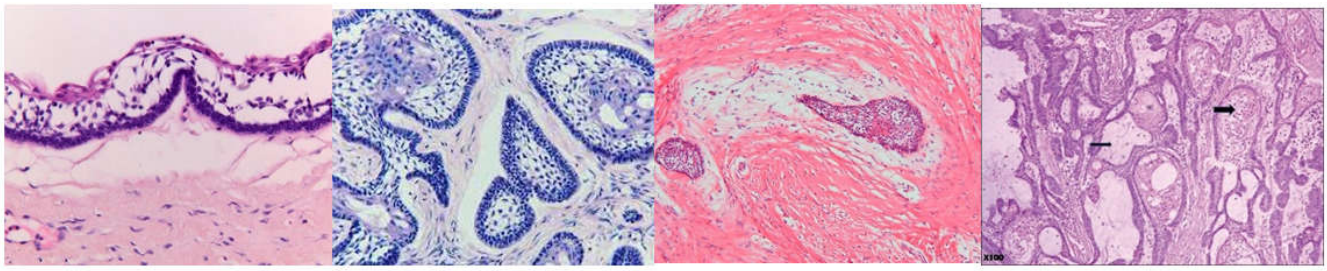

Fig 3 Showing Various Histologic Types OF Ameloblastoma a) Unicystic b) Follicular c) Desmoplastic d) Plexiform

Molecular Biology Aspects

A specific etiology for ameloblastoma has yet to be explained. A study by Kahn *et al* showed three of ten cases of ameloblastoma in persons under the age of 19 to be positive for the 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[51,52,53,54], the most commonly being HPV 6, though a large study (n = 18) using laser capture micro dissection hasshowed 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 now, little was known about the molecular aberrations driving ameloblastoma, due to the tumor's rarity and to the fact that technologies to query the tumor genome does not work as efficiently in formalin-fixed paraffin-embedded tissue. In 2014, however, three separate reports, 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 and BRAF) that controls cell proliferation[56,57,58].

In particular, all three studies specified 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. Additionally, two of the three reports went on to depict 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 containing the BRAF-V600E mutation, was exquisitely sensitive to vemurafenib at concentrations similar to BRAFV600E mutated melanoma and colorectal cancer cell lines. In addition to the functional profile, Brown *et al*. also reported a statistically significant association of BRAF-mutated ameloblastomas recurring later than their wild type (non-mutated) counterparts, signifying a better prognosis[57,58].

Furthermore, the effect of the activated SMO mutation could be blocked by select pharmacologic inhibitors of SHH signaling, including KAAD cyclopamine and arsenic trioxide[59]. Current evidence proposes that the SHH pathway is instrumental in the formation of the tooth bud. A microarray study performed earlier by Heikinheimo *et al*. exhibited both SHH and PTCH (Patched-also in the SHH pathway) to be under expressed 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[60]. Of note, both recent genomic studies also found that most SMO-mutated ameloblastomas contained an additional mutation in either fibroblast growth factor receptor 2 (FGFR2) or Ras (KRAS, HRAS or NRAS. Nevertheless, SMO and BRAF mutations were nearly always mutually exclusive, occurring mainly in tumors of the maxilla and mandible, respectively[57,58]. 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*. also describedfewer common mutations in ameloblastomas, including in PIK3CA (in the PI3-kinase pathway that controls cell survival), CTNNB1 (b-catenin, in the Wnt signaling pathway), and SMARCB1 (involved in chromatin remodeling). Ameloblastoma also shows many resemblances to basal cell carcinoma at the developmental stage[58]. 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, and at the tip of the tooth invagination in precursors to ameloblasts[63]. 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[62].

Further stressing the possible 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 predisposed to to develop both multiple basal cell carcinomas and odontogenic keratocysts, another neoplasm of the mandible and maxilla. A recent article actually emphasized 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 associate 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 modalities

Surgery

Surgery is the standard line of action for ameloblastomas. Historically, the extent of resection has been controversial, including 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 comprise 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 presently believed to play no role in the management of multicystic ameloblastomas (Table 1) [70,71,727,73,74,75]. 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].Also, benign dentigerous cysts can mimic unicystic ameloblastomas and aretreated 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 cryosurgery, tissue fixatives such as Carnoy’s solution, drilling and cautery[29,76,77,78,79,80]. The results of the procedures abovedemonstrate diminished 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 and immediate bone reconstruction to help with speech and swallowing (Fig 4)[81,82,83,84,85]. The bony margin is demarcated as the distance away from the radiographic margin predicted to be disease free and oncologically safe to perform osteotomies[86,87]. 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 necessitates 2–3 cm bone margins[90]. Elective neck dissection is not encouraged especially in tumors originating from the maxilla[52,53]. Surgeons depend on on preoperative imaging to correlate the boundaries of the tumor with palpable surgical landmarks. Some use CT to determine the proper location for osteotomies, ensuring adequate margins. Several groups have utilized intra-operative diagnostic assistance to assess bony margins, including plain specimen radiography[91,92,93,94]. Frozen section of the soft tissue and bone marrow margins is strongly advocated[95.96,97,98,99]. Frozen section or touch prep of medullary bone from the mandibular stumps can help in achieving wider margins and is essential if bone margins are1 cm[32]. Intra-operative frozen sections establish 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 comprises at least one adjacent uninvolved anatomic barrier for proper margins is encouraged. 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 a proper occlusion. A fibular free flap is used to restore bone continuity and allow for dental restoration[100,101,102]. 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 depict a high rate of success for both esthetic and functional outcomes[103,104]. 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 benefit of reconstructing long segment mandibular defects. In a very 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 excellent 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 preferred for mandibular angle defects eliminating the necessity 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].

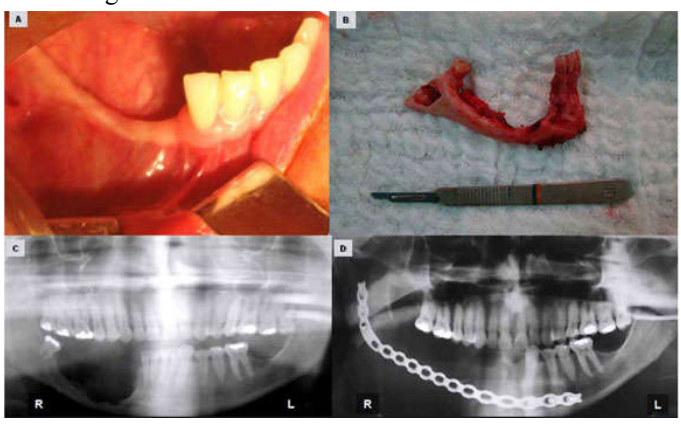

Fig 4 Resection and reconstruction of Mandible

The extent of the soft tissue involvement is verified 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. As an alternative, 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.

Table 1 Reported recurrence rates by type of surgical

Treatment	Patients (n)	Recurrence (%)	Reference
Conservative surgery	44	93	Sehdev al[70]
Radical surgery	38	13	
Conservative surgery	13	0	Shaktin *et al*[71]
Radical surgery	7	14	
Conservative surgery	98	73	Mehlisch *et al*[72]
Radical surgery	26	21	
Conservative surgery	51	71	Muller *et al*[28]
Radical surgery	33	9	
Radical surgery	229	10	Olatian *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]

Radiotherapy and chemotherapy

Prior to the 1980s, it was thought that ameloblastomas are radio resistant. Although numerous studies have stated on adjuvant radiation for positive margins (gross and microscopic) and for recurrent and unresectable ameloblastomas, the outcomes are poor (Table 2)[106,107,108,109,110]. As these patients are often young, the possible value of radiotherapy must be evaluated against the risk for future radiation-induced malignancies and other long-term sequelae of radiation therapy. More work is required to validate this treatment option[111]. In spite of these experiences, some studies support for adjuvant radiation in Ameloblastic carcinoma, though the data are mixed (Table 3) [112-139]. Complicating matters, there are no animal model for ameloblastoma, making it problematic to determine the biological effects of radiotherapy on ameloblastoma. The closest model is acanthomatous epulis in dogs, which has been hypothesized to occasionally transform post-radiotherapy[140]. If radiotherapy is to be considered, then more data are required to better comprehend its effectiveness. Systemic chemotherapy has been attempted a number of times using numerous agents and combinations being employed (Table 4)[141-146]. Reports have proposed that ameloblastoma may be sensitive to platinum-based agents, though occasional reports highlight lengthy survival without chemotherapy[145.147]. 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.

Table 2 Reoccurrence rates after radiation treatment

Treatment	Patients(n)	Recurrence(%)	Reference
XRT	*11*	100	Sehdev *et al*[70]
XRT	2	100	Shakin *et al*[71]
XRT	10	20	Atkinson *et al*[109]
XRT	5	40	Gardner *et al*[110]
XRT	1	0	Miyamoto *et al*[106]
XRT	8	50	Pinsolle *et al*[107]
XRT	*1*	0	Ueda *et al*[108]
XRT- radiation therapy			

Table 3 Comparison of reported treatment modalities for Ameloblastic carcinoma[112-139]

Treatment	Patients(n)	Recurrence (n)	Metastasis	Average duration of follow-up in months
Surgery alone	*36*	44%	14%	81.5
Surgery + radiation	20	40%	35%	60.3
Surgery + chemotherapy	1	0	0	42
Surgery + radiation + chemotherapy	2	50%	50%	30
Chemotherapy regimen consisted of	cisplatinum	Adriamycin	methotrexate	Leucovorin and bleomycin

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

Case	Regimen	Response	Reference
1	*Cyclophosphamide,methotrexate ,5-fluorouracil*	No response	Gall *et al*[141]
2	*Vinblastine,cisplastin,* bleomycin	PR	Eliasson *et al*[40]
3	Adriamycin, cisplatin, cyclophosphamide	PR	Ramadas *et al*[142]
4	Cyclophosphamide	No response	Campbell *et al*[144]
5	Doxorubicin and cisplatin	PR	Amzerin *et al*[145]
6	Gemcitabine and carboplatin	PR	Van Dam *et al*[146]

BRAF inhibition as a treatment modality

Although little has been known about genetic anomalies in this tumor until recently, a highly recurrent somatic mutation was recognized in the mitogen-activated protein kinase (MAPK) pathway: V600E mutations in the BRAF gene (BRAFV600E). Amazingly, 57% of ameloblastomas were found to harbor BRAFV600E and almost all ameloblastomas with the mutations were found in the mandible (96%). This finding suggested the need of targeted therapy for patients with ameloblastoma. After the identification of the highly frequent BRAFV600E mutation, two case reports indicated the efficacy of BRAF inhibitor therapy for multiply recurrent large ameloblastomas with BRAFV600E mutations in the mandible [158]. In one of the case reports, both the primary and metastatic recurrent ameloblastomas responded significantly to therapy with dual BRAF/MEK inhibition (dabrafenib/trametinib). In another report, therapy with a single BRAF inhibition (dabrafenib) demonstrated noticeable volume reduction of recurrent ameloblastoma; and an ongoing response was recorded even after 12 months of therapy, in spite of a 50% reduction in the dose of dabrafenib compared with the dose for metastatic melanoma [158]. Along with the notable reduction of tumor volume, the BRAF inhibitor therapies also improved the associated facial deformities. In melanoma, the clinical outcomes have been mainly improved after the application of BRAF inhibitor therapy[152,158]. Taking that result into account, BRAF inhibitor therapy is a promising for treatment of large ameloblastomas with BRAFV600E mutation, though clinical

trials are necessary to validate the efficacy of the therapy for clinical application. Recent developments in molecular medicine signify the effectiveness of personalized targeted therapy in ameloblastoma. However, for completelycuring of large ameloblastoma, additional therapies are considered feasible.

Prognosis

Prognosis for ameloblastoma rest on 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 the vital structures (skull base, orbit, paranasal sinuses). Maxillary ameloblastoma is generallymore 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 local regional spread of tumor[8,105,148].Furthermore, recurrence and reoperation may cause increased risk of surgical complications. Recurrence following conservative treatments is thought 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 (Table 1). Recurrences have been reported from 1 to 45 years after enucleation[149,150]. For follow up 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 rational. Ameloblastoma, if untreated, can grow to a very large size and may 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

Ameloblastoma is a rare tumor of the mandible and maxilla, with a well-documented tendency for local regional invasion and risk of recurrence. Therapeutically, simple enucleation has little or no role in the management of ameloblastoma beyond perhaps the unicystic subtype. Few other options exist for treatment beyond wide local excision, which can be associated with significant patient morbidity. Furthermore, though radiotherapy has been performed 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 indefinite, and until recently, little was known about the molecular underpinnings of ameloblastoma. Newer 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 finely 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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