Ameloblastoma: Present and Future Concepts of Managing

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Chapter

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Dragana Gabrić, Roko Bjelica, Mato Sušić and Marko Vuletić

Abstract

Ameloblastoma is a benign odontogenic tumor of epithelial origin with locally aggressive behavior. It affects a broad age range of patients and it is most commonly found in the mandible, especially posterior area. The majority of ameloblastomas are conventional (multicystic), which are more difficult to eradicate than the unicystic or peripheral types. Although most of ameloblastoma cases can be treated predictably with radical surgical treatment, the management of recurrent and metastasizing ameloblastomas remains a major challenge. Surgical treatment is standard, but the extent of resection is controversial. Radical resection with segmental and marginal mandibulectomy or curettage and enucleation with better quality of life, but with higher recurrence rate. Besides the conventional surgical treatment, novel therapy options like neoadjuvant molecular targeted therapy and decompression in young patients could make a significant improvement in the management of the disease. The aim of this chapter was to determine the present and future concepts of treatment and discuss significant factors responsible for recurrence.

Keywords: ameloblastoma, odontogenic tumors, surgical procedures, molecular targeted therapy, recurrence

1. Introduction

Odontogenic tumors are considered as relatively rare and destructive neoplasms of the jaw bones. They are derived from the remnants of odontogenic tissue and each odontogenic tumor represents the abnormality in odontogenesis [1].

Ameloblastomas belong to benign odontogenic tumors with locally aggressive behavior. Although the incidence of odontogenic tumors varies from 1% to 32% of all jawbone tumors, ameloblastoma, alongside odontoma, is the most common benign odontogenic tumor [2]. It is predominantly found in the mandible (up to 80%) and most patients diagnosed with ameloblastoma are aged between 30 and 60 years [3].

The current, 5th World Health Organization (WHO) classification from 2022 distinguishes five different types of benign ameloblastoma as described hereafter [4]. They most commonly manifest as slow-growing and asymptomatic swelling with the ability to expand and perforate cortical bone. Slow-growing character and lack of symptoms are considered responsible for delayed diagnosis of the ameloblastoma which is an ongoing problem, especially in developing countries [3].

Throughout history, primary treatment was, and still is, surgical with controversial extent of resection [5]. Taking into consideration severe clinical implications with high recurrence rate it is of utmost importance to provide sufficient guidelines and standardize surgical approach. In addition, recent literature has provided us with breakthrough in the understanding of genetic mutations and signaling pathways crucial in ameloblastoma pathogenesis [6]. Thus, novel therapy options like neoadjuvant molecular targeted therapy could significantly contribute to the management of the disease.

This chapter will address evidence-based treatment options and contemporary concepts of managing ameloblastoma.

2. Etiopathogenesis

The exact etiological factors associated with ameloblastoma are not yet completely understood. Up to 2014, little was known about exact molecular pathogenesis and a variety of etiological factors existed, including trauma, inflammation, dental caries and nutritional deficiencies [3, 7]. Considering ectodermal origin of ameloblastoma and its development from cells of the dental lamina, it is anticipated that enamel organ, cell rests of Malessez, cell rests of Serres and remnants of odontogenic epithelium are linked to etiopathogenesis of ameloblastoma [8].

As the genetic understanding increased, valuable findings have been brought to light regarding molecular pathogenesis of ameloblastoma. In 2014, it was confirmed that recurrent somatic and activating mutations in the mitogen-activated protein kinase (MAPK) plays a prominent role in the pathogenesis of the disease [6, 9, 10]. Additionally, there is evidence that mutations in non-MAPK signaling pathways, especially sonic hedgehog (SHH) pathway are also associated with ameloblastoma [11].

Mutations related to MAPK pathway include BRAF, fibroblast growth factor receptor 2 (FGFR2) and RAS genes [6, 9, 10]. BRAF is a serine/threonine protein kinase which activates the MAPK/ERK signaling pathway with consequential increase in cell proliferation and neoplastic transformation [6]. BRAF V600E mutations were firstly found in ameloblastoma clinical samples by Kurppa et al. [6] using real-time PCR enhanced by Sanger sequencing. These authors observed a high frequency of BRAF V600E mutations (63%). Subsequently, more recent studies described occurrence of the mutations ranging from 43% to 82% [7, 12, 13]. RAS is a protein that normally activates BRAF, therefore acts upstream of BRAF. In addition, the activation of RAS is normally triggered by the activation of FGFR2 which is a membrane-bound activator of MAPK signaling [14]. FGFR2 and RAS mutations were identified in up to 20% ameloblastoma cases [7]. Together, all the mentioned mutations are present in vast majority of ameloblastomas, suggesting that activation of the MAPK signaling pathway represents a critical event in the pathogenesis of ameloblastoma [2].

Several non-MAPK mutations have also been associated with ameloblastoma. The most important is nonclassical G protein-coupled receptor, the smoothened (SMO) gene. It is a signaling receptor that mediates SHH signaling pathway. Frequency rates of SMO mutations are lower than those in MAPK pathways, but these mutations have a greater tendency to appear in the maxillary ameloblastomas. Furthermore, SHH mutations including SMO appear to be associated with higher recurrence of the disease [7, 10].

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3. Classification

WHO has recently provided the 5th edition of Classification of Head and Neck Tumours. Ameloblastoma classification is almost identical to that of 2017, with one new entity that will be mentioned in further text [4].

Ameloblastoma is primarily divided into five types:

- Conventional
- Unicystic
- Extraosseous/Peripheral
- Metastasizing
- Adenoid

Conventional ameloblastoma, earlier known as multicystic or solid ameloblastoma, is the most common type and comprises about 90% of cases. Clinically, it is a slow growing, benign neoplasm with locally aggressive behavior [3]. It is of vital importance to distinguish radiographic features of ameloblastoma to the earlier mentioned term of multicystic ameloblastoma. Multilocular radiographic presentation of ameloblastoma in no way should be considered as the reason why conventional type was named multicystic in the past classifications. On the contrary, it was reported that ameloblastomas appear equally as multilocular or unilocular radiolucencies [15, 16]. However, opinions about radiographic features contradict and radiographic evaluation alone is in no case sufficient for adequate diagnostics (**Figure 1**). Histologically, a decent number of ameloblastoma variants have been found, such as follicular, plexiform, acanthomatous, desmoplastic, basaloid and granular cell. Plexiform and follicular are the two most prevalent histological patterns. It is worth mentioning that ameloblastoma can simultaneously display both histological patterns [3]. Additionally,

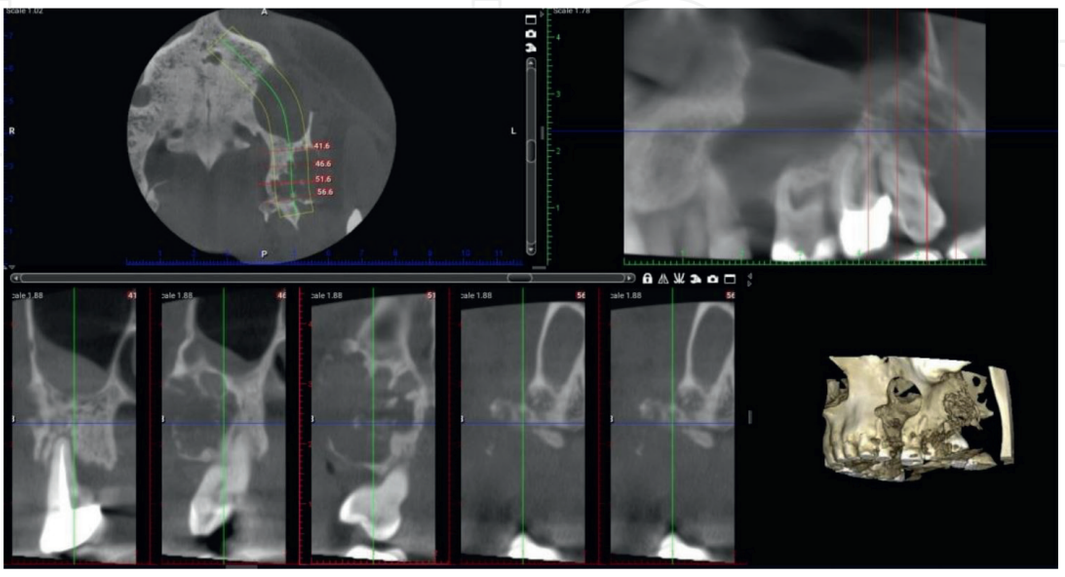

Figure 1.
Conventional ameloblastoma of distal part of maxillae.

desmoplastic ameloblastoma is from 2017 no longer recognized as separate type, but is classified as histological variant because of its distinctive histological appearance. It possesses a pathognomonic histological feature of extensive stromal dysplasia, epithelial islands within a highly collagenous connective tissue, and metaplastic bone formations in some cases [2, 3].

Unicystic type is the second most common ameloblastoma making from 5% to 15% of all cases. This type is most frequently found in younger patients, with different clinical, radiological and histopathological features from conventional type [16]. Unicystic ameloblastomas can be predominantly found in the posterior mandible and are often associatied with an unerupted tooth, resembling dentigerous cyst (**Figure 2**). It is thought to be less aggressive and has a lower recurrence rate, which mainly depends on the histological variant. Luminal and intraluminal variants have a good response to conservative treatment with approximately 10% of recurrence, but conservatively treated mural variant has a high recurrence comparable to that of conventional type [2].

Peripheral or extraosseous ameloblastoma is rare variant that has about 1% ratio among all ameloblastomas [17]. This variant has gone through a terminological

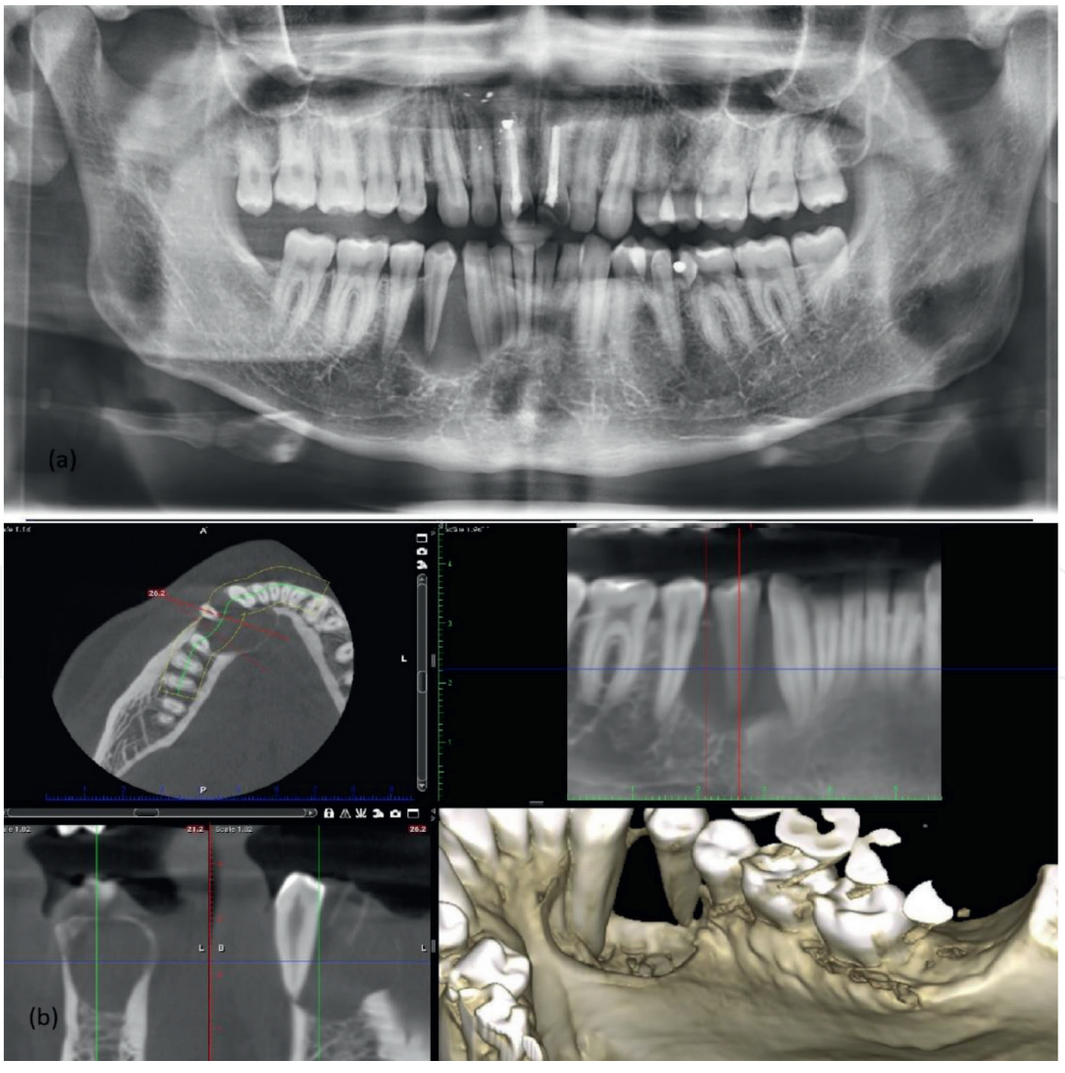

Figure 2.
Radiological features of unicystic ameloblastoma in the mandible: (a) orthopantomographic image; and (b) CBCT image.

evolution from its first appearance in late nineteenth century until 1959, when the term "peripheral ameloblastoma" was used for the first time [18]. Stanley and Krogh [19] introduced this term in their study and from that point on, "epithelial epulis" and "alveolar border ameloblastoma" fell out of favor. This type mostly affects middle-aged patients with higher prevalence in the mandible. It is considered to be amenable to conservative surgical therapy, recurring in a small number of cases [2]. From histological point of view, it has a similar pattern to conventional ameloblastoma consisting of ameloblastic epithelium islands [3].

Metastasizing ameloblastoma was defined as a histologically benign type of ameloblastoma which metastasizes to distant sites by WHO classification from 2017 [14]. It is particularly rare type of ameloblastoma and despite its affiliation with benign tumors, it metastasizes to distant sites and makes treatment unpredictable with a high recurrence rate [20]. It is most commonly found in lungs, but other sites, such as brain and kidneys have also been reported [21].

According to the 5th edition of Classification of Head and Neck Tumors by WHO, adenoid ameloblastoma is introduced as a new entity. It is described as epithelial odontogenic tumor with cribriform architecture, ameloblastoma-like component and presence of duct-like structures. It is also characterized by possible presence of dentinoid, ghost and clear cells [22]. The hybrid histological pattern including both ameloblastoma and adenomatoid odontogenic tumor characteristics was reported in approximately 40 cases in the literature [23]. Moreover, adenoid ameloblastoma is considered as more biologically aggressive type with higher recurrence rate than conventional ameloblastoma. In contrast to other ameloblastoma types, BRAF V600E mutations are not present in the adenoid type [23].

4. Contemporary treatment options

Current management concept of ameloblastoma is still controversial. To date, standard treatment is radical resection with a wide bone margin. However, various treatment methods have been recommended with respect to many factors, such as type and clinical presentation of tumor [5]. Regardless of the type, the management of ameloblastoma is either surgical or non-surgical. Surgical approach can be furtherly divided into radical and conservative surgery. These approaches often intertwine, and conservative methods such as decompression are valuable in preoperative reduction of tumor volume [24]. Non-surgical methods include radiotherapy and/or chemotherapy. Recent advances in signaling pathways and genetic understanding related to pathogenesis of ameloblastoma resulted with the development of molecular targeted therapies as a valuable treatment option in management of the disease [3, 25]. Details on the contemporary surgical approach and aforementioned treatment methods will be provided in the following subchapters.

4.1 Diagnostic protocol

Standard diagnostic protocol of ameloblastoma is by no means different from other odontogenic tumors [26]. Thorough clinical examination combined with adequate radiological imaging and histopathological analysis are mandatory to successful diagnosis and further management. A variety of radiological procedures are available to provide surgeon with precise structural expanse of ameloblastoma. Different methods are often combined, starting with orthopantomogram as a usual starting

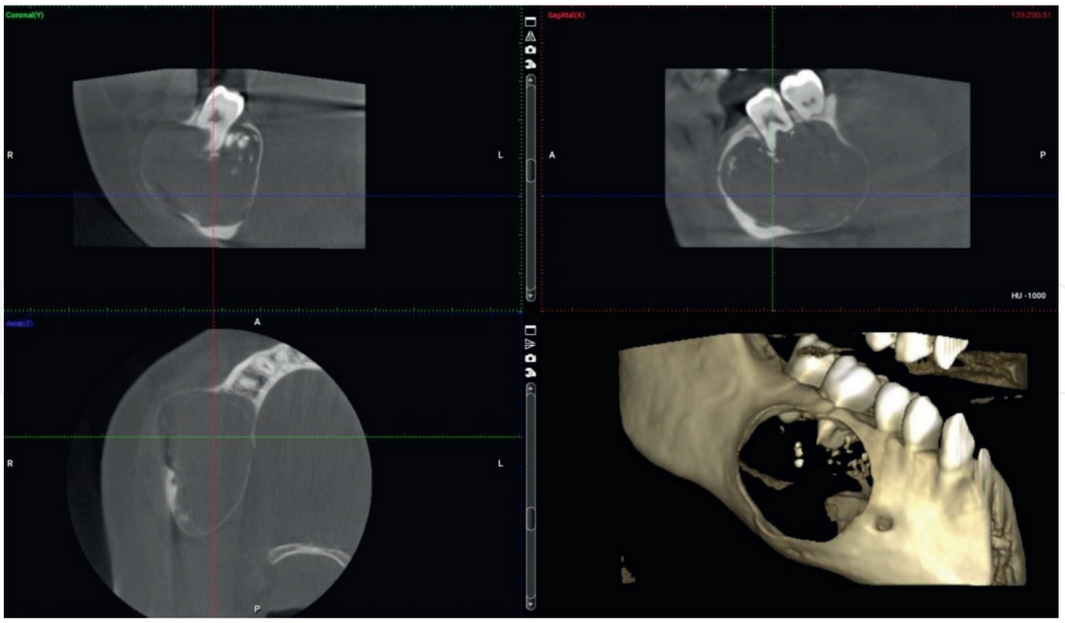

Figure 3.
Preoperative CBCT image of ameloblastoma found on the right side of the mandible.

point. Three-dimensional analysis is further performed by conventional computed tomography (CT), cone-beam computed tomography (CBCT) or magnetic resonance imaging (MRI). Taking into consideration potential malignancy of ameloblastoma, positron emission tomography combined with CT (PET/CT) can be used for diagnosing distant metastasis [3]. CBCT is considered as a standard three-dimensional imaging modality prior to further therapeutic procedures (**Figure 3**). Nevertheless, it is worth pointing out that MRI provides superior soft-tissue contrast, which makes it a useful imaging modality for diagnosing tumors with soft-tissue components [27]. This is especially applicable for depicting the extension of ameloblastoma to adjacent anatomical structures. Finally, definitive diagnosis cannot be made by clinical and/or radiological findings alone, thus it is imperative to obtain a biopsy for histopathological analysis.

4.2 Surgical treatment.

4.2.1 Radical surgical approach

Still a gold standard in ameloblastoma treatment, radical surgery is favored for all aggressive types of primary and recurrent ameloblastomas [3]. Radical resection implies *en bloc* tumor removal with a wide bone margin followed by immediate or delayed bony reconstruction of the defect with tissue grafts and/or prosthetic appliance [28]. In the mandible, resection can be performed through segmental osteotomy which involves the loss of continuity and requires reconstruction or can be marginal preserving the lower border with consequential maintenance of bone continuity [29]. Even though radical treatment is favored according to the contemporary literature [5, 30–32], several factors such as age, clinical presentation and ameloblastoma type should be considered when determining the course of therapy. Surgery can impair facial growth and development of pediatric patients, thus a conservative approach may be preferred [5]. Patient wishes regarding surgically induced facial deformations

and psychological effects affecting the quality of life are also important factors that should not be overlooked.

Relatively high recurrence rate of ameloblastoma presents a major challenge. The recurrence rate of aggressively treated ameloblastomas is approximately 12%, which is significantly lower than that for conservative treatment, with post-treatment recurrence of 30% [33]. In a retrospective review by Ooi et al. [31] patients with conventional and unicystic ameloblastoma treated with segmental mandibulectomy and free fibula flap reconstruction were observed. The treatment showed no recurrence in a 5-year follow-up period with overall patient satisfactory regarding esthetic and functional results. 40% of the patients did not receive any form of prosthodontic rehabilitation and only 3 patients underwent dental implant insertion, showing that low uptake of dental rehabilitation did not adversely affect outcome and patient satisfaction. Another retrospective study by Bianchi et al. [34] confirmed positive outcomes of radical therapy. The study comprised 34 patients with histologically confirmed mandibular ameloblastomas, treated with segmental mandibular resection, fibula or iliac crest free flap reconstruction, and immediate or delayed dental implant placement. The duration of follow-up was from 18 to 120 months and no patient showed radiological or clinical signs of recurrence. Furthermore, recurrence rates up to 80% were reported after enucleation of conventional ameloblastoma, indicating the necessity for segmental resection with at least 1 cm of margin to the bone, including an adjacent soft tissue margin [35]. Moreover, the importance of adequate treatment choice is evident in the study by Hertog et al. [36]. The experience with the treatment of recurrent ameloblastoma previously treated by enucleation over a 40-year period was reported. Of all patients who underwent radical surgery, not a single recurrence was found during 10.5 years follow-up period. The remaining patients treated with conservative approach all developed one or more new recurrences. Observing a localization of tumor alone, it is believed that the best treatment option for maxillary ameloblastoma is radical resection [37]. Maxillary tumors are believed to be more aggressive than those found in the mandible due to the bone histomorphology, which is spongier providing a weak wall of defense against local spread (**Figure 4**). Moreover, the proximity of important anatomical structures such as the orbit, infratemporal fossa,

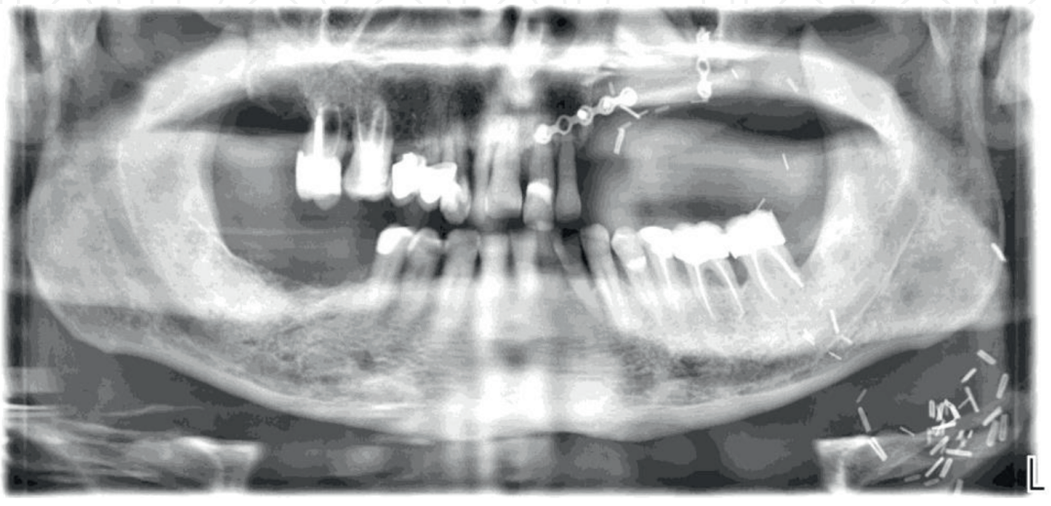

Figure 4.
Postoperative orthopantomographic image after segmental resection of left maxillae.

pterygopalatine fossa, nasal fossa and base of the skull makes the treatment more difficult and mutilating [38]. These tumors can be resected via various midface approaches, resulting with defect that unifies oral cavity, nasal cavity and paranasal sinuses causing alterations in phonation, mastication and deglutition [32]. The remaining defects can be fitted with an obturator, allowing surgeons an easy access for clinical examination [2].

With the development of bone grafting and osteomyocutaneous free flaps, loss of function and esthetics can finally be considered relics of the past. Patients undergoing extensive tumor removals are now enabled to receive improved postoperative course with preserved essential functions such as mastication, deglutition and phonation together with a satisfactory esthetic outcome [39]. Nowadays, the emphasis is increasingly placed on the use of *computer-aided design/computer-aided manufacturing* (CAD/CAM) technology in reconstructive surgery. Virtual surgical planning and 3D printing techniques are used to preoperatively shape free flap dimensions or individually fabricate titanium meshes and fixation plates [40]. In a recent study by Lv et al. [41], guiding plate system for precise mandibular reconstruction was introduced with thorough postoperative evaluation. Mandibular and fibular osteotomy guides for tumor resection and simultaneous donor site bone segment shaping were designed and fabricated using CAD/CAM technology. All patients underwent successful surgery with 100% overall survival rate of flaps. Postoperative esthetic assessment was rated as excellent and quantitative evaluation was performed by measuring different parameters such as discrepancy in osteotomy lines, mandibular resemblance and symmetry. The cohort included patients undergoing traditional resection and reconstruction. There was significant difference between cohort and test group in all the mentioned parameters.

Last but not least important step in surgical management of ameloblastoma is postoperative follow-up. Various examples of recurrences emphasize the inevitable need for prolonged follow-up visits after surgery [42]. Adebayo et al. [42] presented a case of soft tissue recurrence 21 years after radical surgery in the mandible which leads to conclusion that radiological follow-up should be carried out throughout life in ameloblastoma patients.

4.2.2 Conservative surgical approach

Conservative treatment has found its purpose in treating less aggressive types of ameloblastoma [2]. It involves one or more of the following procedures: enucleation, curettage, physicochemical treatment (cryotherapy or Carnoy's solution), marsupialization and decompression (**Figure 5**) [43]. The main advantages of the conservative approach are: preservation of adjacent healthy tissues, avoidance of facial disfiguration and, consequentially, better postoperative quality of life. Pediatric patients are, for instance, very approach sensitive and radical surgery may affect the growth dynamics of the dentition, soft tissues and entire craniofacial skeleton [44]. Therefore, a conservative approach is often the treatment of choice in children. However, ameloblastoma type and histological pattern must be taken into account during the planning and selection of the adequate treatment. These are mandatory factors influencing the surgeon's decision with a primary goal of minimizing the possibility of recurrence and avoiding under- or overtreatment [16].

Considering the high recurrence rate of conservatively treated conventional type of ameloblastoma it is crucial to emphasize the right indication [33]. Firstly, histopathological analysis is necessary to confirm the type of ameloblastoma curable with

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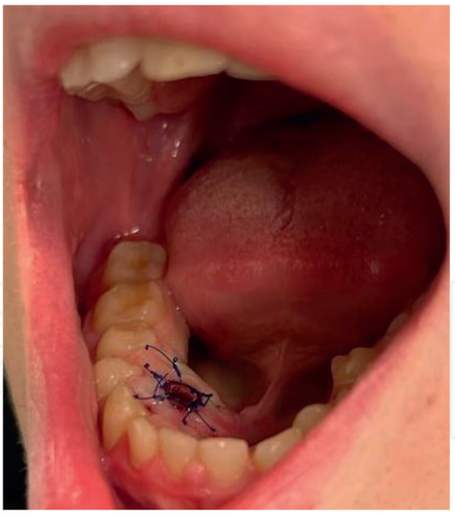

Figure 5.
Preoperative decompression of the unicystic ameloblastoma in the mandible of young patient.

conservative approach. Only less aggressive types such as unicystic or peripheral are suitable to be treated by this type of approach [35]. In a study by Seintou et al. [43], a thorough review of clinical, radiological, and histopathological characteristics of unicystic ameloblastoma in children was presented with findings that treatment is still controversial. However, it was concluded that conservative treatment was preferable due to better postoperative quality of life, despite a slightly higher recurrence rate. Huang et al. [45] also claim that radical treatment should be reserved for recurrent and more aggressive types of ameloblastoma, with important statement that recurrence is probably not a major consideration for pediatric patients and should not be considered as equivalent to failure. On the other hand, some authors [46, 47] believe that radical resection should still be a treatment of choice whenever follow-up examinations are limited. This applies usually to developing countries, but any other limiting factors are not excluded. Even though the radical treatment results with less recurrence, a

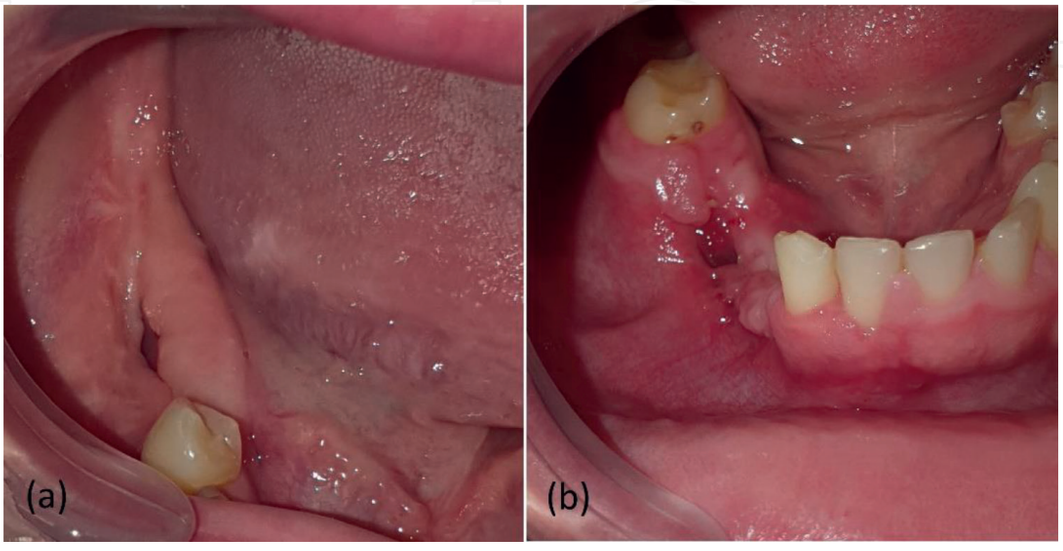

Figure 6.
Postoperative healing after conservative surgical treatment of ameloblastoma in adolescent patient (a), and patient in the middle of 20's (b).

majority of ameloblastoma cases in pediatric patients are unicystic [43, 44]. Less aggressive behavior and lower recurrence rate are factors that furtherly support the conservative treatment of ameloblastoma in these patients (**Figure 6**). In addition, peripheral ameloblastoma is another entity successfully treatable with conservative therapy. It is most frequently present in the gingival tissues and the conservative approach with narrow margins of unaffected tissue is treatment of choice [48].

Altogether, opinions on the treatment of conventional ameloblastoma are still divergent with valid arguments regarding both radical and conservative approaches. It is of vital importance to know the differences between various types of conservative procedures. A simple enucleation is considered as inadequate with unacceptably high recurrence rate of up to 60% in unicystic ameloblastoma and up to 80% in conventional ameloblastoma [35]. Enucleation followed by curettage and/or physicochemical treatment has been suggested as standard conservative approach (**Figures 7** and **8**) [43].

It is necessary to eradicate intraosseous ameloblastoma cells that can be found up to 8 mm from the clinical and radiographic margin of the lesion (**Figure 9**).

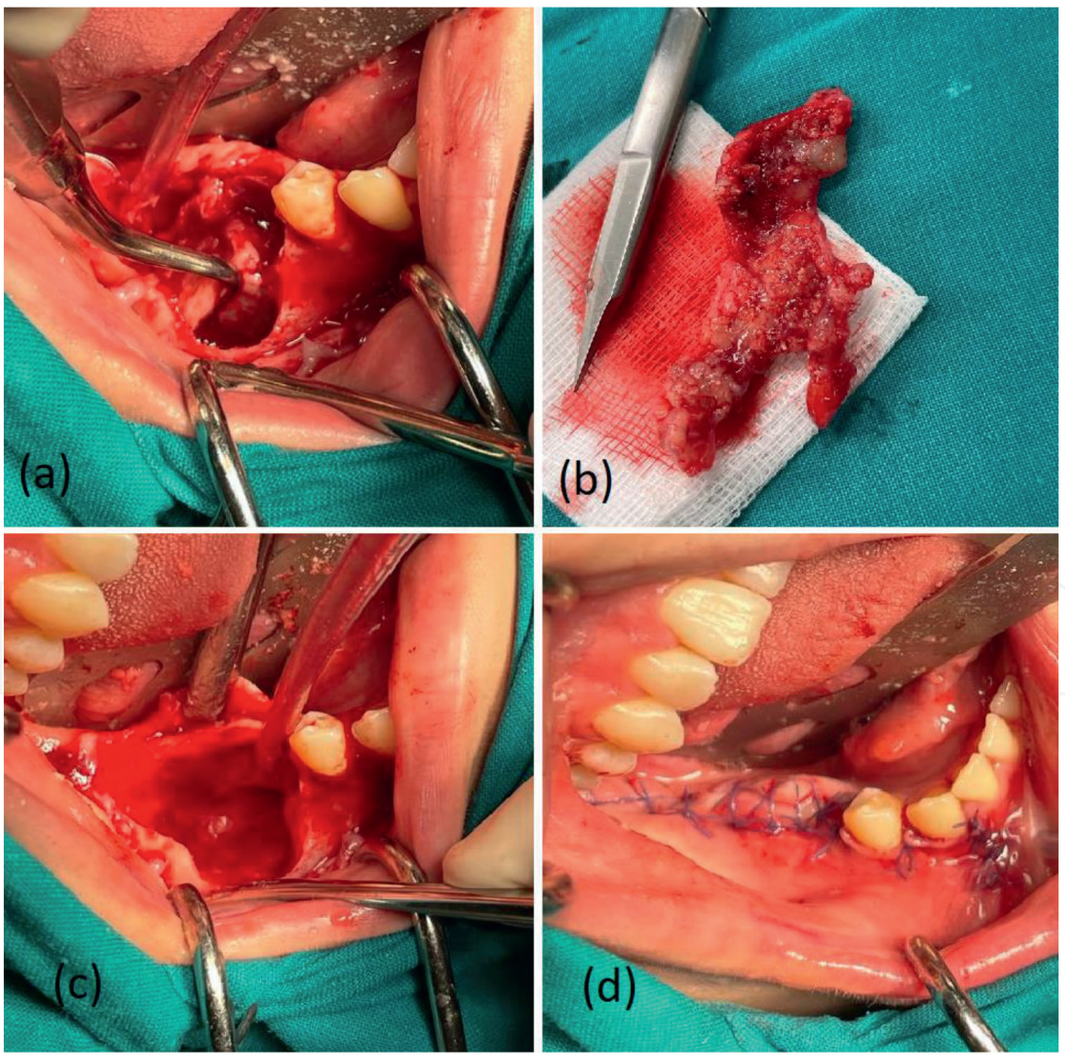

Figure 7.
Conservative surgical treatment of ameloblastoma in an adolescent patient with CBCT image presented in **Figure 3***: (a) enucleation of tumor mass; (b) enucleated ameloblastoma; (c) status post-enucleation and curettage; and (d) primary wound closure.*

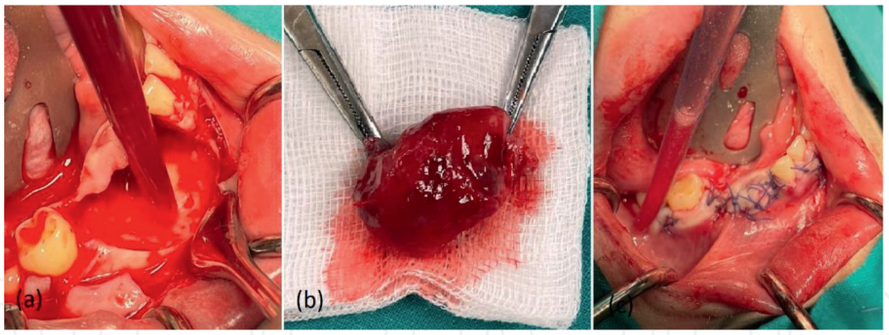

Figure 8.
Conservative surgical treatment of ameloblastoma in patient in the middle 20's with radiological status presented in **Figure 2***: (a) status post enucleation and curettage; (b) enucleated tumor mass; and (c) primary wound closure.*

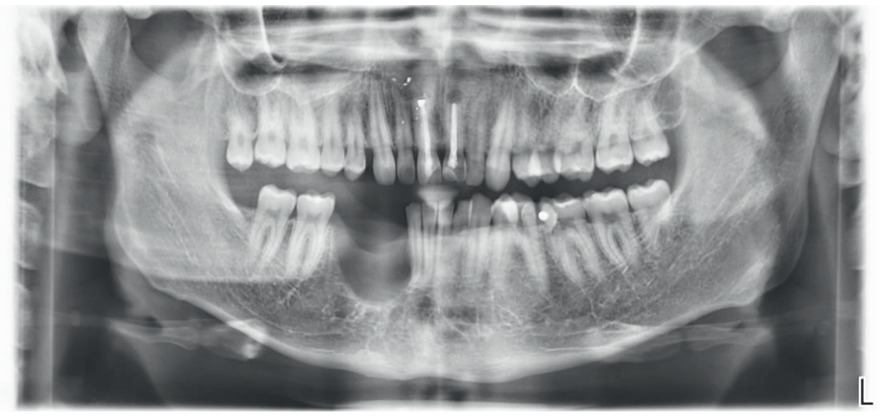

Figure 9.
Orthopantomographic image showing postoperative margins after conservative surgical treatment with decompression and subsequent enucleation and curettage. Preoperative radiological status is presented in **Figure 2***.*

Physicochemical treatment of these cells can be performed with liquid nitrogen cryospray or with Carnoy's solution [30]. Carnoy's solution is a fixative initially proposed by Stoelinga and Bronkhorst [49]. It has ability to penetrate cancellous bone to a depth of 15 mm, so it is ideal for application after enucleation [35].

Decompression is a valuable method most commonly used to preoperatively reduce the size of cysts [50]. The size of the lesion is expected to be reduced by inserting a rubber tube or a stent through a previously created hole in the overlying bone and mucosa [51]. Huang et al. [45] have reported a significant reduction in ameloblastoma size using 6–12 months preoperative decompression. Furthermore, Park et al. [51] reported a 36.7% reduction in size of unicystic ameloblastoma after 13 months of decompression in 5 patients with mean age of 18.6 years (**Figures 10** and **11**). They also highlighted that the patient's age is inversely proportional to the relative velocity of shrinkage. Additionally, contemporary methods including active decompression and distraction osteogenesis have been developed for the treatment of odontogenic cystic entities [52]. Active decompression and distraction osteogenesis involve the use of active negative pressure inside a cyst to increase the velocity of cystic lesion shrinkage and to stimulate the regeneration of bone [52]. There is still no evidence of its clinical use in literature, thus the further research is required to verify the effect of active decompression on pathophysiology of ameloblastoma.

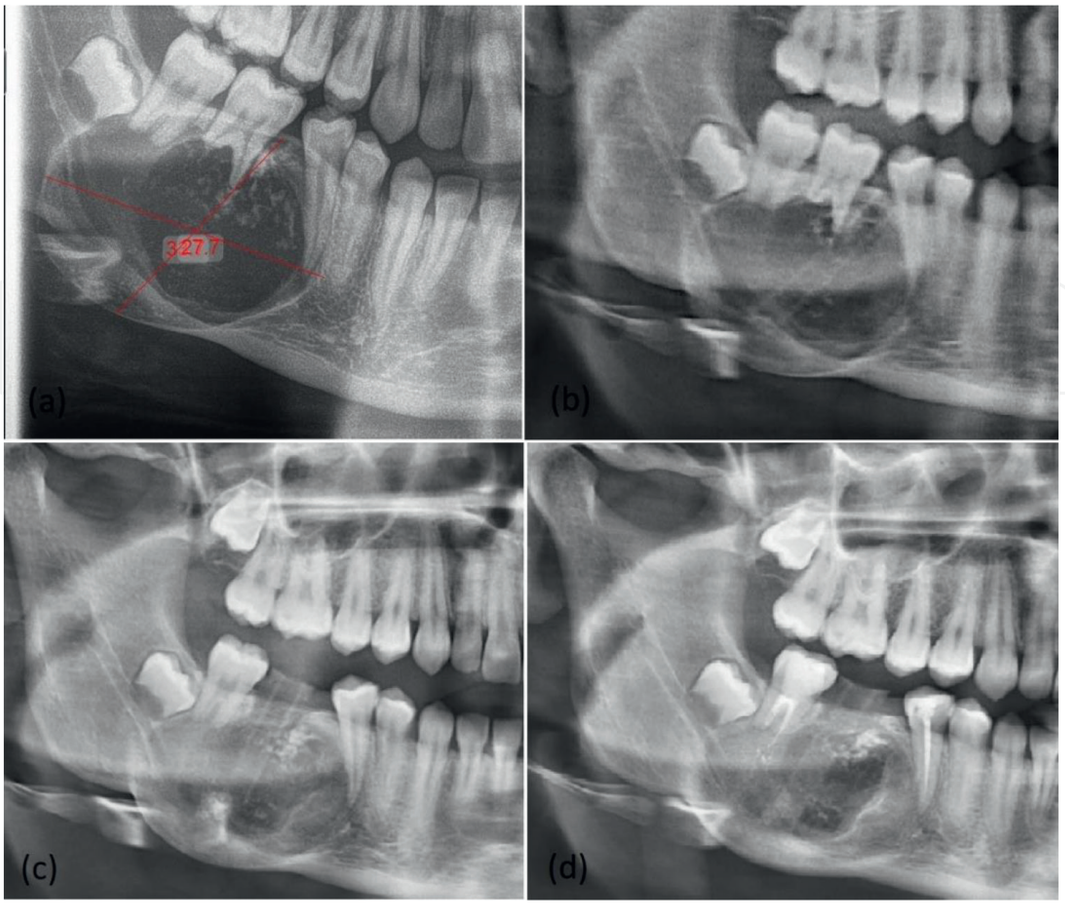

Figure 10.
Decompression in a pediatric patient with unicystic ameloblastoma of the mandible. Preoperative radiographic follow-up (surgical procedure is presented in **Figure 7***: (a) initial situation of a large ameloblastoma; (b) 2 months after rubber tube insertion; (c) 4 months after tube insertion; and (d) 9 months after tube insertion.*

4.3 Non-surgical treatment

4.3.1 Chemotherapy and radiotherapy

Radiation therapy and chemotherapy have played no significant part in the management of ameloblastoma [35]. Ameloblastoma was, together with ameloblastic carcinoma, believed to be radioresistant tumor, as older methods failed to improve outcome of the disease [53]. Nevertheless, more recent literature suggest radiotherapy may be utilized for preventing recurrence in patients with microscopic positive margins or those with inoperable disease [54]. As malignant ameloblastomas or ameloblastic carcinomas are rare, data reporting radiotherapy effects remain scarce. Kennedy et al. [53] achieved local control in 4 of 6 patients treated with radiotherapy alone or postoperatively after radical surgery. Koukourakis et al. [55] concluded that image-guided radiation therapy, intensity-modulated radiation therapy or proton beam irradiation may be beneficial in adjuvant setting after surgical treatment for local control. Results of chemotherapy are also unpredictable with a lack of research [56]. Amzerin et al. [56] used combination of doxorubicin and cisplatin in patient with recurrent ameloblastoma with lung metastases. Pain disappearance, local stabilization and lung lesions shrinkage of 30% were reported. Gall et al. [57] evaluated effectiveness of three chemotherapeutic agents (methotrexate, cyclophosphamide,

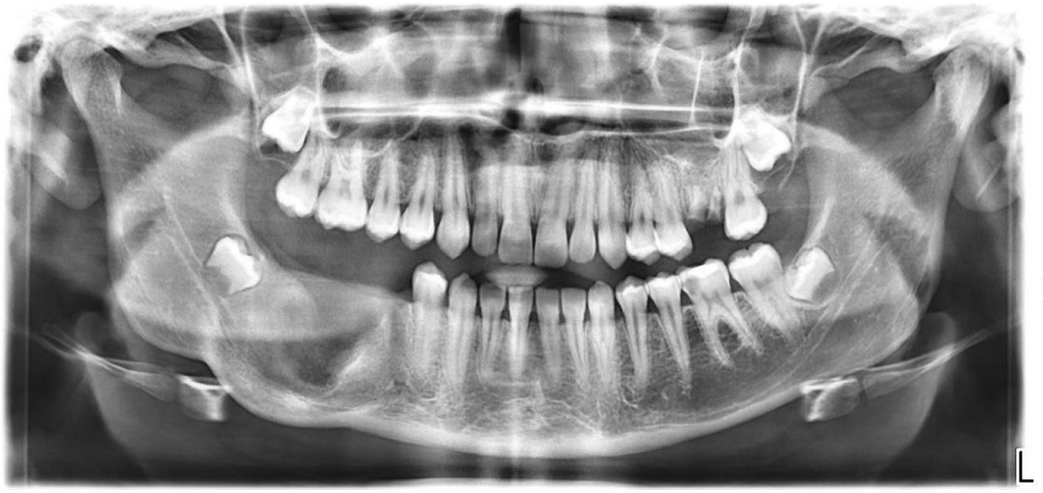

Figure 11.
Postoperative image of the patient presented in **Figure 7**. *Conservative surgery with enucleation and curettage was performed after 12 months of decompression.*

and doxorubicin) with no regression of tumor nodules in the lungs, but with major symptomatic improvements. These data suggest that chemotherapy may improve clinical symptoms in metastatic patients.

4.3.2 Molecular targeted therapy

Over the past decade, novel molecular targeted therapies are evolving alongside with dramatically improved understandings of biological behavior of ameloblastoma [58]. The main identified mutations are found in MAPK and SHH signaling pathways. These include BRAF, RAS and FGFR2 genes from MAPK pathway and SMO gene from SHH signaling pathway [2, 10]. Discovery and clarification of mentioned activated molecular pathways brought out the novel potentional targeted therapies in the management of ameloblastoma.

Drugs approved by US Food and Drug Administration which are predominantly used for treatment of metastasizing, unresectable or recurrent ameloblastoma are vemurafenib, dabrafenib and trametinib [59, 60]. Initially, vemurafenib was approved for use in treatment of metastatic or surgically non-treatable melanoma, while dabrafenib and trametinib for the treatment of metastatic non-small cell lung cancer with BRAF V600E mutations. Vemurafenib and dabrafenib are BRAF inhibitors, while trametinib is MEK inhibitor [59, 60]. Although the available literature is limited with a lack of clinical research, clinical effectiveness of using molecular targeted drugs for patients with ameloblastoma was reported in several case reports [61–66]. Fernandes et al. [61] presented a case of patient with recurrent ameloblastoma with confirmed BRAF V600E mutation. Vemurafenib therapy was prescribed and complete resolution of symptoms together with continuous shrinkage of lesion evidenced on MRI scans after 11 months of therapy were reported. Furthermore, Faden et al. [62] used dabrafenib reduced to a 50% of therapy dose to treat a patient with significant medical comorbidities. MRI analysis showed a 75% reduction in tumor mass after 8 months of therapy. Both authors [61, 62] recommended single agent therapy over dual therapy in ameloblastoma patients. However, adverse reaction to vemurafenib including arthralgia, nausea and rash has been reported after 12 months of therapy [63]. Adverse effects can be controlled by decreasing the dosage without adversely

affecting outcomes of therapy. It has been found that neoadjuvant treatment with dabrafenib significantly reduces size of the primary tumor which could reduce the extent of the subsequent surgery [64]. On the other hand, Kaye et al. [65] reported a case of unresectable locally recurrent ameloblastoma of the mandible with lung metastases treated with dual targeted therapy. They used dabrafenib in combination with trametinib which resulted with significant reduction of tumor and metastases volume and utter resolution of symptoms after 20 weeks. Combination of dabrafenib and trametinib has also proven to have a significant influence resulting with complete remission in a study by Brunet et al. [66].

SMO inhibiting drugs, such as itraconazole and vismodegib, are considered less successful due to the mechanisms of resistance which disable their binding [10]. Cyclopamine is SHH signaling pathway antagonist and is more effective than SMO inhibitors [2]. However, it has ability to inhibit osteoblast proliferation and differentiation with negative effects on bone healing [67].

It is worth mentioning that matrix metalloproteinases (MMPs) have a role in local invasiveness of ameloblastoma [58]. MMPs are zinc-dependent proteinases that are important in extracellular matrix degradation and are associated with tumor growth and invasiveness [68]. MMP-2 and MMP-9 are expressed in various benign and malign tumors, including ameloblastoma. They are mainly involved in angiogenesis and tumor growth [69]. Consequently, invasion of adjacent tissues could be effectively controlled by regulation of MMPs. Still, they have a vital role in tissue remodeling and inhibition of their activity causes major side effects. Thus, further research is needed to reveal potential disease control by MMP inhibitors [58].

5. Conclusions

Despite the great strides that have recently been made in investigation of molecular factors and biological mechanisms responsible for ameloblastoma, the management continues to be the subject of debate among clinicians. Surgeons often empirically decide for radical treatment to reduce the risk of recurrence, affecting postoperative quality of life. Novel conservative surgical methods such as active decompression and distraction osteogenesis have the potential to vastly reduce the extent of surgery. The development of molecular targeted therapies implicates MAPK and SHH pathway inhibition as an effective treatment modality for ameloblastoma. Further clinical research is mandatory for standardization of treatment methods.

Conflict of interest

"The authors declare no conflict of interest."

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