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Establishing the Natural History and Growth Rate of Ameloblastoma with Implications for Management: Systematic Review and Meta-Analysis

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Abstract

Background

Ameloblastoma is the second most common odontogenic tumor, known to be slow-growing, persistent, and locally aggressive. Recent data suggests that ameloblastoma is best treated with wide resection and adequate margins. Following primary excision, bony reconstruction is often necessary for a functional and aesthetically satisfactory outcome, making early diagnosis paramount. Despite earlier diagnosis potentially limiting the extent of resection and reconstruction, an understanding of the growth rate and natural history of ameloblastoma has been notably lacking from the literature.

Method

A systematic review of the literature was conducted by reviewing relevant articles from PubMed and Web of Science databases. Each article's level of evidence was formally appraised according to the Centre of Evidence Based Medicine (CEBM), with data from each utilized in a meta-analysis of growth rates for ameloblastoma.

Results

Literature regarding the natural history of ameloblastoma is limited since the tumor is immediately acted upon at its initial detection, unless the patient voluntarily refuses a surgical intervention. From the limited data, it is derived that the highest estimated growth rate is associated with solid, multicystic type and the lowest rate with peripheral ameloblastomas. After meta-analysis, the calculated mean specific grow rate is 87.84% per year.

Conclusion

The growth rate of ameloblastoma has been demonstrated, offering prognostic and management information, particularly in cases where a delay in management is envisaged.

Introduction

Ameloblastoma is the second most common, benign, but locally aggressive odontogenic tumor [1–3]. Most tumors arise from the mandible or maxilla, and affect between the third and fourth decade of life. Ameloblastoma can be clinically classified into solid, multicystic or unicystic or peripheral subtypes. The solid, multicystic type is the most common, while the unicystic type accounts for 5–15% of the cases, affects a younger population and has 3 variants: simple, luminal and mural. Peripheral ameloblastoma is the least common and has a benign biologic behavior. Ameloblastoma most often presents as a hard painless intraoral swelling or as an incidental finding on routine dental imaging. Although histologically benign, 2–4.5% of all cases have malignant potential and metastasize, most commonly to the lung [4,5]. Hence, the goal of management entails a complete excision with linear margins and early bony reconstruction. Adequate margins can be confirmed histologically postoperatively or radiologically with intraoperative imaging [1,6,7]. Long-term follow-up is critical since recurrences can occur up to 45 years after the initial resection.

Historically, ameloblastoma has been treated with curettage by community dentists or resected by surgeons before a detailed histological work-up is undertaken. In these settings, under-treatment and the persistent biologic behavior of ameloblastoma has resulted in high recurrence rates and morbidity. Given the potential for significant destruction of local anatomy, locoregional recurrences and metastatic potential, a clear understanding of the natural history of ameloblastoma is warranted. Such information can give a guide as to the urgency of management, guide treatment approaches and offer prognostic information. However, this understanding is notably absent from the literature.

In the current study, we have conducted a systematic review of the literature and a meta-analysis of 16 reports, from which the documented tumor dimensions and the duration of symptoms have been used to derive at a quantitative growth rate of ameloblastoma. Such understanding of the growth and natural history of ameloblastoma will be useful when offering treatment options at varying growth phases.

Methods

Search Strategy and Selection Criteria

The current study comprises of a systematic review of the literature and a meta-analysis, aiming to establish the growth and natural history of ameloblastoma. We performed a comprehensive search of the databases including PubMed and Web of Science for eligible studies published between Jan 1, 1950, and May 27, 2014. Search terms were a combination of "ameloblastoma" with "growth", "growth rate", "natural history", "untreated", "declined surgery", "giant", or "extreme". Additional references identified through the reference lists of selected references and bibliographic linkage were included in the review. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for literature attrition is included (Fig. 1) [8]. Only papers published or translated in English were reviewed.

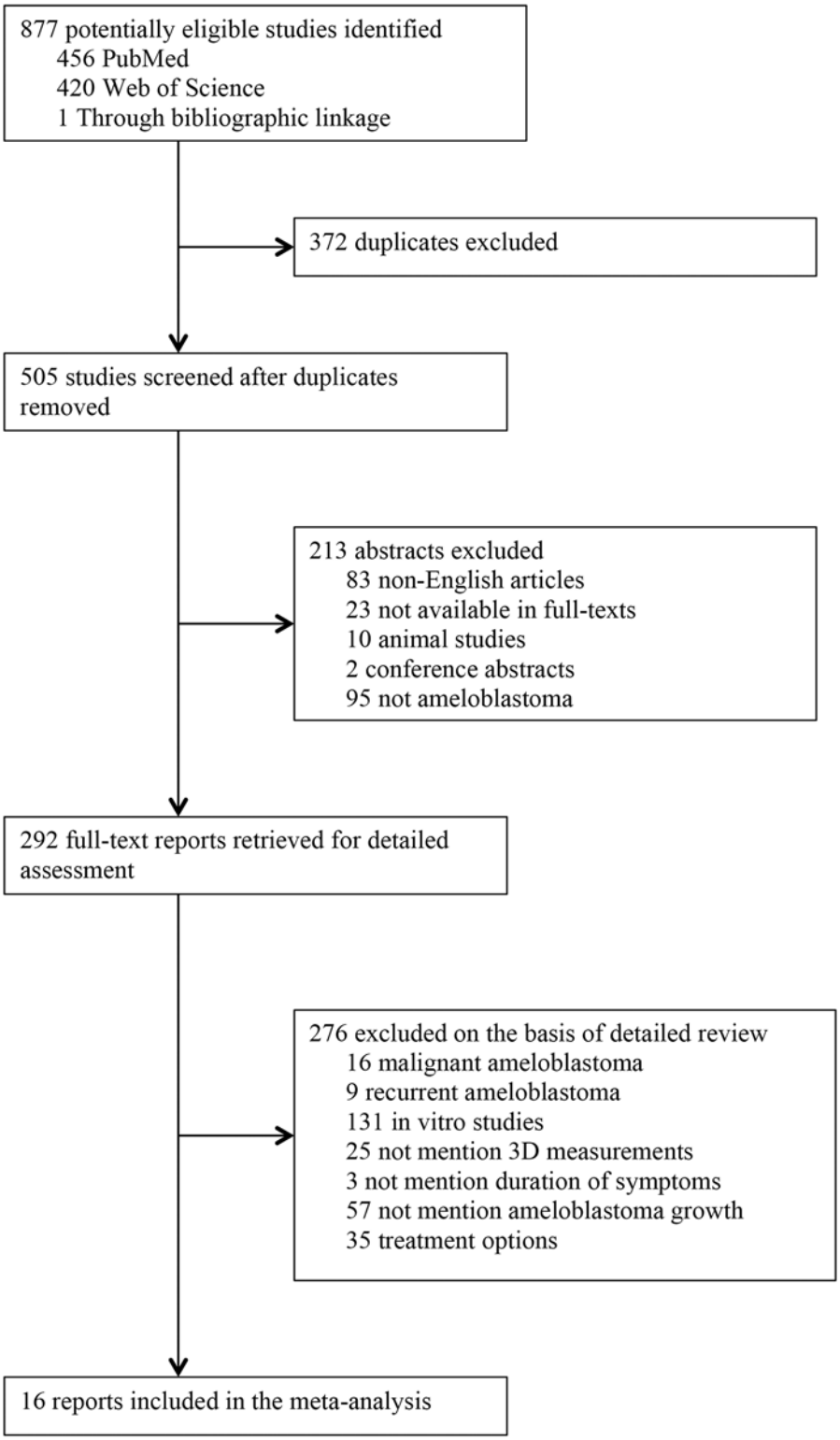

Fig 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for literature attrition in systematic review [8].

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The following inclusion criteria were applied for the meta-analysis: human case reports/series of benign ameloblastoma before the initial surgical intervention and where all three dimensions of the tumor (i.e. length *x* width *x* height) and the duration of symptoms were reported. We excluded studies reporting the growth of ameloblastic carcinoma, malignant ameloblastoma, and recurrent ameloblastoma, in vitro cellular growth or molecular studies, reports where only one or two dimensions of the tumor volume were reported.

Data Extraction

We developed a data abstraction sheet, to record necessary information to establish the level of evidence, study quality, and available outcome and risk factor details. Bias risk was evaluated and the level of evidence was assessed formally according to CEBM (Centre for evidence Based Medicine) evidence level. The CEBM (http://www.cebm.net) attributes standardized levels of evidence, from level 1a (systematic review of randomized control trials) to level 5 (expert opinion), to any research paper. Each of the included studies was thus critically appraised based on their study design and content. For meta-analysis, we recorded patient age, sex, tumor volume, mode of volume measurement, duration of symptoms, and histological subtype.

Data Synthesis and Analysis

Two authors (MPC and WMR) independently screened records and assessed each retrieved full-text articles for inclusion. Disagreements were resolved by a blinded third reviewer (DJHS).

Studies inconsistently documented the tumor volume from either the surgical specimen, the plain radiograph, or from clinical examination. We considered the direct measurement from a surgical specimen the most accurate, then radiographs, and clinical examination in descending order. Hence, where the tumor volume was mentioned multiple times in a report, we would select the most accurate volume.

We extracted tumor volume dimensions from each study and the duration of symptoms in order to derive the specific growth rate (SGR; growth % per year) of each case. SGR was calculated using a formula previously described to quantify the tumor response to anti-cancer treatment [9]. Mehrara *et al* [9] mentions a logarithm of the ratio of post-treatment tumor volume (V_2) to the pre-treatment tumor volume (V_1) divided by the duration of treatment (T_2-T_1) (Equation 1).

$$SGR = \frac{\ln(V_2/V_1)}{T_2 - T_1} \quad (1)$$

For appropriate calculation in our study, V_1 was considered "1" and T_1 as "0".

Statistical Analysis

Statistical software, STATA (Version 13; StataCorp; College Station, TX, USA) was used for analysis. Initially, we treated SGR as a continuous variable and utilized Kruskal-Wallis equality-of-populations rank test. We calculated the statistical association between SGR and gender or three age groups (0–20, 21–40, 41 years and older). Then, we divided SGR into two groups: less than 100% per year and equal to or more than 100%. Using Pearson's chi-squared test, we compared SGR against different histological subtypes (plexiform and follicular versus the rest), the three age groups, and gender. In all analyses, a p value lower than 0.05 was used as the level of statistical significance.

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There was no funding source for this study. All authors had full access to the data included in the study and had final responsibility for the decision to submit for publication.

Results

Literature Review

Systematic review of the literature identified 2 formal papers that discuss the natural history and growth rate of ameloblastoma. In a retrospective review of 100 cases of ameloblastoma, Odukoya *et al* report a superior average growth rate in the solid, multicystic subtype, compared to the peripheral subtype (0.81 vs 0.17 cm^3/month respectively) [10]. In a similar study, the same authors have retrospectively analyzed the maximal tumor diameter from 330 biopsy specimens and found that the solid, multicystic type grows more aggressively than desmoplastic ameloblastomas (0.71 vs 0.36 cm/month respectively) [11].

Through rigorous assessment (Fig. 1), we also identified 16 published reports where the tumor volume and the duration of symptoms before receiving any treatment were known. They were utilized for the subsequent meta-analysis and to derive the SGR [12–27].

Natural History and Growth Rate of Ameloblastoma

Throughout the literature, cases have been reported where patients with ameloblastoma did not receive immediate primary surgical interventions for various reasons—economic, fear of surgery, ignorance—and presented with a large solid, multicystic ameloblastoma [12–27]. Using the inclusion and exclusion criteria mentioned previously, we have identified and analyzed 16 published cases to calculate SGR of benign ameloblastoma (Table 1). The average age is 41 year-old (range: 10–62) and females are more frequently reported (2.67:1). There are six plexiform, two follicular, and one acanthomatous histological subtypes, and two are unknown. Mean duration of symptoms is 9.04 years (range: 0.17–23).

We have only perused reports where all three dimensions of the tumor volume are known in order to attain the most accurate estimate of the volume for calculating SGR. We excluded studies of ameloblastoma carcinoma or malignant ameloblastoma since they display significantly different biological behaviors [4]. Ameloblastic carcinoma histologically exhibits malignant features. Even though histologically appear benign, malignant ameloblastoma tend to metastasize to distant sites in contrast to benign ameloblastomas. Furthermore, we have limited our search to the clinical cases and omitted studies of in vitro growth rate or expression of proliferative cell markers. They do not adequately account for the complex multi-factorial in vivo environmental elements contributing to the tumor growth.

Using the formula devised by Mehrara *et al* [28] for our meta-analysis, the mean SGR was initially calculated as 298% per year (range: 37.37–3356.83). Interestingly, once the outlier (3356.83% [14]) is removed, the mean SGR decreases significantly to a more reasonable 87.84% (range: 37.37–169.98). Pramulio *et al* [14] acknowledge that the patient's history may have been unreliable and the duration of symptom may have been much longer.

Factors Associated with More Rapid Growth

The calculated growth rates as above are based on averages from the reported series. This is clearly not a reflection of the tumor biology nor the intrinsic growth of ameloblastoma and its subtypes, but of the average calculated rates. We have analyzed our findings to identify factors that would be potentially associated with a higher SGR. Interestingly, none of the factors—gender, age groups, and histological subtypes—have shown statistical significance with SGR

Table 1. Characteristics of large ameloblastoma cases reported in the literature.

	Age (year)	Sex	Volume (cm)	Weight (gram)	Mode of measurement	Duration of Symptoms (years)	SGR (%/year)	Histological Type	Level of Evidence and Study Quality
Hunasgi[23]	39	F	12.0 *x* 10.0 *x* 9.0	1200	Surgical	10	69.85	Granular cell	4
Catherine[24]	48	F	30.0 *x* 18.0 *x* 10.0	N/A	Radiographic	23	37.37	Follicular & plexiform	4
Mijiti[25]	40	M	25.0 *x* 20.0 *x* 15.0	N/A	Radiographic	15	59.48	Desmoplastic	4
Ota[22]	32	F	27.2 *x* 20.3 *x* 15.1	1600	Surgical	10	90.28	Acanthomatous	4
Chauhan[21]	42	F	15.0 *x* 14.0 *x* 10.0	N/A	Surgical	4.5	169.98	Plexiform	4
Acharya[26]	35	F	15.0 *x* 12.0 *x* 10.0	1350	Surgical	10	74.95	Plexiform	4
Hata[20]	53	M	14.0 *x* 11.0 *x* 10.0	N/A	Clinical	11	66.72	Follicular	4
Mukhopadhyay [27]	32	M	25.0 *x* 15.0 *x* 10.0	N/A	Surgical	7	117.56	N/A	4
Hughes[19]	53	F	15.2 *x* 11.4 *x* 12.0	1280	Surgical	6	127.32	Plexiform	4
Dunn[18]	62	F	17.0 *x* 15.0 *x* 13.0	1282	Radiographic	6	135.10	Plexiform	4
Gordy[17]	19	F	8.0 *x* 6.0 *x* 6.0	N/A	Surgical	5	113.19	Follicular	4
Ueyama[16]	73	M	10.0 *x* 9.0 *x* 7.5	435	Surgical	10	65.13	Plexiform	4
Nakasato[15]	39	F	11.0 *x* 10.0 *x* 6.0	386	Clinical	6	108.18	Plexiform	4
Pramulio[14]	10	M	9.0 *x* 6.0 *x* 5.0	N/A	Clinical	0.17	3356.83	Unknown	4
Osaki[13]	30	F	14.0 *x* 13.0 *x* 12.0	936	Surgical	7	109.84	Plexiform	4
Rambo[12]	41	F	21.0 *x* 15.0 *x* 15.0	N/A	Surgical	14	60.43	Unknown	4

Abbreviations: N/A: not applicable; SGR: specific growth rate.

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(Table 2). The most statistical significance is found where histological subtypes divided into two subgroups—plexiform and follicular versus the rest—are correlated to SGR also divided into two subgroups—less than 100% versus equal to or more than 100% (p = 0.14). This discrepancy is most likely due to the small sample size (n = 16). Unfortunately given the fact that most cases of ameloblastoma are almost universally treated immediately upon detection, it may be difficult to perform a study like this in a large scale.

Notwithstanding, in the literature, there are other factors that have established a clear correlation with more rapid growth and a poorer outcome. These include maxillary ameloblastoma when compared to the mandible [29], the solid, multicystic histological subtype, unicystic subtype invading the fibrous wall [30], older age (as young age is associated with unicystic ameloblastoma, and hence, better outcome) [31], malignant ameloblastoma, and suboptimal treatment (e.g. curettage, enucleation).

Table 2. Summary of statistical analysis of patient factors against the specific growth rate of the tumor.

P values	Gender	Age group	Plexiform and follicular vs other histological subtypes
SGR as a continuous variable	0.24	0.68	N/A
SGR in 2 groups	0.31	0.25	0.14

Abbreviations: SGR: specific growth rate; vs: versus; N/A: not applicable.

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Discussion

Background

An understanding of the growth of ameloblastoma mandates a "control group" of ameloblastoma from which its natural history can be derived. For decades, ameloblastoma has been treated primarily surgically, either conservatively or radically, at the time of its first presentation without confirmatory histological diagnosis. This has meant that few studies offer any information about the untreated growth of these tumors. Furthermore, due to its rare nature, most reports have been limited to small-scale case studies. By combining data from all eligible published reports, we have derived at a quantitative growth rate of benign ameloblastoma. Despite the relatively small sample size (n = 16), the information will be useful for planning management, especially in the early stages of tumor growth.

While most authors would simply describe ameloblastoma as a slow growing tumor, a group in Nigeria has quantified its growth rate [10,11]. Odukoya *et al* [10] report a level 4 retrospective analysis of 100 ameloblastoma cases treated in a single center. They have calculated estimated monthly growth rate of the tumors in order to predict the "biologic aggression" of individual subtypes by dividing the average tumor volume at presentation to the duration of symptoms. Consistent with the literature, the solid, multicystic ameloblastoma has the fastest growth rate and the peripheral subtype the slowest (0.81 versus 0.17 cm^3/month, respectively). Limitations of this study include the assumption that ameloblastoma follows linear growth. Furthermore, the mechanism of tumor volume measurement (e.g. clinically versus radiologically) and the reasoning behind the selection of 100 cases are not clarified. Moreover, the authors acknowledge their reliance on the patients to provide accurate history. Interestingly, the same authors [11] would later use the largest tumor diameter to compare the estimated growth rate of desmoplastic ameloblastoma and the conventional solid, multicystic type in another level 4 retrospective study of 330 biopsy specimens. The limitations are similar to the previous study but, in addition, the latter analyses only a small sample size of desmoplastic specimens (n = 14). They conclude that desmoplastic ameloblastoma may be less biologically aggressive compared to the solid, multicystic type (0.36 versus 0.71 cm/month, respectively) due to the desmoplasia acting as a tumor-limiting barrier.

For meta-analysis, we have used the formula mentioned by Mehrara *et al* [9]. In contrast to the more traditional tumor doubling time, SGR (Equation 1) more accurately reflects the natural exponential growth of the tumour [9]. Odukoya *et al* [10] and Effiom *et al* [11] simply divide the tumor volume or diameter by the symptom duration to arrive at an estimated monthly growth rate, which falsely assumes a linear growth pattern. In fact, evidences show that ameloblastoma initially exhibits slow growth, but later its growth accelerates [13,14,32]. Pramulio *et al* [14] reports a 10 year-old boy with a 2 month history of right jaw swelling that grows substantially in the few weeks prior to the presentation. Osaki *et al* [13] mentions a 30 year-old female with a 7 year history of left mandibular swelling that accelerates to the lower jaw 3 years before presentation. Rajaonarison Ny Ony *et al* [32] describes a case of maxillary ameloblastoma in a 23 year-old female growing slowly for 15 years before exhibiting accelerated growth in the 5 weeks preceding to the presentation.

Symptomatically, patients with ameloblastoma initially present with painless intraoral swelling. Early complications include generalized edema and anemia secondary to selective hypoproteinemia from transudation through the semipermeable cyst wall and bleeding from the ulcerations respectively. These are resistant to aggressive medical treatment. Later complications are associated with obstruction leading to small mouth opening, such as difficulty with mastication, deglutition, phonation and airway obstruction, as well as the loss of dentition on

the ipsilateral side. It is worth noting that all of the metabolic derangements improved dramatically after radical tumor resection.

Management of Benign Ameloblastoma

Despite its benign histology, ameloblastoma is associated with significant morbidities and is fatal if suboptimally treated [33,34]. Complete surgical removal of tumor and restoration of function and appearance are the main goal of therapy [6,35]. Surgical intervention is popularly classified into conservative resection with or without adjunctive therapy, and radical resection. Tumor excision is ideally followed by reconstruction with a bone graft or flap, distraction osteogenesis and dental prostheses [36]. Reconstruction is easier if done earlier due to absence of scarring or contracture, and it can be beneficial psychologically. Radiotherapy and chemotherapy have no role in ameloblastoma management. Radiation used alone is associated with 100% failure rate and serious complications, such as osteomyelitis leading to death and sarcoma development [37].

Conservative Resection

Conservative surgical approach, such as curettage and enucleation, is frequently used for the treatment of unicystic ameloblastoma, except in the mural variant where the epithelium invades the cyst wall [3,38,39]. Although technically straightforward, curettage or enucleation can be associated with high recurrence rates (30–90%) when used against more aggressive solid, multicystic ameloblastomas [2,40–43]. Moreover, curettage or enucleation may not be able to remove the tumor tissue from within the cancellous bone beyond the macroscopic appearance and radiographic boundary. Hence, conservative resection has widely only been advocated in solid, multicystic ameloblastomas for patients of less than 10 years of age or smaller tumors [44]. Interestingly, evidence has also been offered that even for unicystic ameloblastomas, curettage or enucleation may still be associated recurrence rates (35–60%) higher than radical excision [35,45–48]. Furthermore, the luminal and intraluminal variants of unicystic ameloblastoma are difficult to differentiate from the mural type preoperatively, leading to the risk of "under-treatment" [49].

In order to improve its efficacy, curettage or enucleation can be paired with cryotherapy [50], electrocautery [51] or application of cauterizing agents like Carnoy's solution [52]. Despite encouraging early results [53–55], the combination of curettage and cryotherapy has a recurrence rate (31%) higher than radical resection and is also associated with pathological fracture (11%) and wound dehiscence (30%) [50]. Hence, this is not appropriate where soft tissue extension and cortical thinning or perforations are present. The results are similarly unremarkable with electrocautery and Carnoy's solution.

Radical Resection

A radical approach—either marginal or segmental resection with adequate margin—ensures maximal removal of solid, multicystic ameloblastoma, minimizing the recurrence rate (0–10%) and the risk of metastasis [41,56–60]. Some literature suggests that ameloblastoma can extend into cancellous bone histologically at a mean of 4.5 mm (range: 2.3–8 mm) beyond the radiographic boundary [61] and currently, the literature recommends the use of 1–1.5 cm resection margin [48]. Satisfactory margins can be achieved by the application of new specialized imaging techniques, such as flat panel volumetric CT (fpvCT) [1], which can provide accurate anatomical details for intraoperative margin assessment.

In maxillary ameloblastoma, early radical resection is especially beneficial. Although less common and histologically similar to mandibular ameloblastoma, maxillary ameloblastoma acts clinically more aggressive. Maxilla lacks the thick cortical bone found in mandible that can

slow down the tumor growth. Furthermore, maxillary ameloblastoma can potentially invade the central nervous system [29,40,62] and the rate of surgical cure decreases significantly once the tumor has extended beyond the confines of the maxillary bone [63]. In contrast, peripheral ameloblastomas are relatively innocuous with no bone involvement and can be sufficiently managed with a local excision and a long-term follow-up of the surgical site [64].

Marginal resection for solid, multicystic ameloblastoma is advantageous since it preserves the inferior margin of the mandible and prevents the necessity of a complex bone reconstruction [65]. However, where radical marginal resection may result in jaw instability and an increased risk of pathological fractures, segmental resection with bony reconstruction is the preferred option [6]. Furthermore, the unexcised inferior margin of mandible may present a source of tumor recurrence [65]. Jaw reconstruction techniques with a bone graft or a flap are now well described in the literature and are associated with relatively low morbidity [66].

Bony Reconstruction

An understanding of the natural history of ameloblastoma can potentially limit the extent of resection and reconstruction. Conservative resection through enucleation or marginal resection can facilitate a limited reconstruction, with either no reconstruction at all, or bone graft reconstruction. In this setting, either autologous or alloplastic options are available, which can each fill the resection defect and provide form and/or strength to the remaining facial skeleton.

Where a segmental alveolar defect exists, in either mandible or maxilla, a bone graft can be used for smaller defects, particularly those less than 5 cm in length. A bone graft in this setting can be derived from the iliac crest (most commonly) [67,68], fibula [69], scapula [70], rib [71] or the radius [72]. A bone graft can be broadly classified as non-vascularized or vascularized. A non-vascularized bone graft heals by 'creeping substitution', in which there is a combination of osteoblast migration and bony scaffold graft take, while the framework maintains structural integrity during this process. Compared to alloplastic or vascularized options, bone grafts can provide a better bulk of bone for the placement of dental implants, a superior contour, undergoes remodeling upon placement and is associated with shorter hospital stays and decreased number of subsequent operations. Hence, a non-vascularized bone graft is indicated where the bony defect is shorter and an adequate amount of soft tissue is available. Handschel *et al* [73] recommends non-vascularized iliac crest graft for mandibular defects up to 5–6 cm in length. Since the average length of defect experienced by the author was 4.9 cm, the graft is suitable for most cases. Increased graft length is associated with an increased graft failure rate [74]. Pogrel *et al* [75] reports 75% failure rate for grafts longer than 12 cm and recommends extreme caution when using grafts longer than 9 cm. Additional advantages of a bone graft include being able to prepare and insert one in the same operation with the primary resection [76]. In addition, it provides a superior function in regard to mastication and deglutition [77]. Successful graft uptake is assessed by the maintenance of bone continuity, complete consolidation with the absence of infection examined clinically in the operating theatre or on imaging [78]. Potential complications are infection, fracture and plate exposure [73]. In addition, a variable degree of bony resorption is associated with bone grafts [56].

For a larger bony defect or where inadequate soft tissue is available, a free flap (vascularized bone graft) is suggested instead. The ability to vascularize a bone based on its intrinsic vasculature has meant that large segments, large enough to reconstruct the entire alveolus, can be transferred safely in a single stage. As for bone grafts, the iliac crest, fibula, scapula, rib and radius have all been described in this setting. These flaps can be transferred as pedicled or free flaps, and can also be transferred as bone only, or composite flaps. While useful in complex situations, these flaps mandate lengthy operative times, increased length of hospital stays and patient morbidity.

Length of Follow-Up

Given the biologic behavior of ameloblastomas, a long-term follow-up is mandatory. More than 50% of recurrences occur within 5 years of the primary surgical intervention [3]. However, sporadic reports of recurrences at 20, 30 and 45 years have been reported in the literature [79–82]. Of note, higher recurrence rate is reported in granular and follicular histological subtypes [3]. Inadequately short follow-up may give physicians a false indication of cure and a potential to miss metastatic ameloblastoma [3].

Conclusion

Current meta-analysis has produced a mean SGR of 87.84% growth per year for benign ameloblastoma, after removing outliers, which offers prognostic and management information, particularly in cases where a delay in management is envisaged. The greatest growth rate may be associated with plexiform and follicular histological subtypes, but this did not reach statistical significance. Early intervention can limit subsequent growth and facilitate more conservative reconstructive options.

Supporting Information

S1 PRISMA Checklist.
(PDF)

Acknowledgments

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Author Contributions

Conceived and designed the experiments: MPC DHS WMR. Performed the experiments: MPC DHS WMR. Analyzed the data: MPC DHS WMR. Contributed reagents/materials/analysis tools: MPC NRS DHS WMR. Wrote the paper: MPC WMR.

References

1. De Silva I, Rozen WM, Ramakrishnan A, Mirkazemi M, Baillieu C et al. (2012) Achieving adequate margins in ameloblastoma resection: the role for intra-operative specimen imaging. Clinical report and systematic review. PLoS One 7: e47897. doi: 10.1371/journal.pone.0047897 PMID: 23094099
2. Gardner DG, Pecak AM (1980) The treatment of ameloblastoma based on pathologic and anatomic principles. Cancer 46: 2514–2519. PMID: 7438024
3. Reichart PA, Philipsen HP, Sonner S (1995) Ameloblastoma: biological profile of 3677 cases. Eur J Cancer B Oral Oncol 31B: 86–99. PMID: 7633291
4. Kunze E, Donath K, Luhr HG, Engelhardt W, De Vivie R (1985) Biology of metastasizing ameloblastoma. Pathol Res Pract 180: 526–535. PMID: 4080638
5. Galetta D, Petrella F, Leo F, Pelosi G, Spaggiari L (2006) Treatment of pulmonary metastases from primary intraosseous odontogenic carcinoma. Lancet Oncol 7: 272–273. PMID: 16510338
6. Carlson ER, Marx RE (2006) The ameloblastoma: primary, curative surgical management. J Oral Maxillofac Surg 64: 484–494. PMID: 16487813
7. Forrest LA, Schuller DE, Karanfilov B, Lucas JG (1997) Update on intraoperative analysis of mandibular margins. Am J Otolaryngol 18: 396–399. PMID: 9395016
8. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6: e1000097. doi: 10.1371/journal.pmed.1000097 PMID: 19621072

9. Mehrara E, Forssell-Aronsson E, Bernhardt P (2011) Objective assessment of tumour response to therapy based on tumour growth kinetics. Br J Cancer 105: 682–686. doi: 10.1038/bjc.2011.276 PMID: 21792200
10. Odukoya O, Effiom OA (2008) Clinicopathological study of 100 Nigerian cases of ameloblastoma. Niger Postgrad Med J 15: 1–5. PMID: 18408774
11. Effiom OA, Odukoya O (2011) Desmoplastic ameloblastoma: analysis of 17 Nigerian cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 111: e27–31. doi: 10.1016/j.tripleo.2010.09.076 PMID: 21237425
12. Rambo VB, Davies NE (1977) Giant ameloblastomas. JAMA 238: 418–420. PMID: 577557
13. Osaki T, Ryoke K, Nagami T, Ogawa T, Hamada T (1985) Ameloblastoma with hypoproteinemia due to protein leakage. Int J Oral Surg 14: 302–306. PMID: 3926678
14. Pramulio TH, Said HM, Kozlowski K (1985) Huge ameloblastoma of the jaw (report of three cases). Australas Radiol 29: 308–310. PMID: 3835963
15. Nakasato S, Okamura S, Kudo K, Takeda Y (1991) Gigantic ameloblastoma associated with secondary hypoproteinemia. J Oral Maxillofac Surg 49: 764–767. PMID: 2056379
16. Ueyama Y, Tsukamoto G, Matsumura T (1995) Gigantic ameloblastoma of the mandible complicating hypoproteinemia: case report. J Craniomaxillofac Surg 23: 47–49. PMID: 7699084
17. Gordy FM, Holder R, O'Carroll MK, Krolls SO (1996) Growth of an ameloblastoma during pregnancy: opportunity lost? Spec Care Dentist 16: 199–203. PMID: 9582721
18. Dunn JL, Olan WJ, Bank WO, Narang AK, Schwartz AM (1997) Giant ameloblastoma: radiologic diagnosis and treatment. Radiographics 17: 531–536. PMID: 9084089
19. Hughes CA, Wilson WR, Olding M (1999) Giant ameloblastoma: report of an extreme case and a description of its treatment. Ear Nose Throat J 78: 568, 570–562, 574. PMID: 10485149
20. Hata H, Ebihara M, Onitsuka T, Nakagawa M, Kitagawa Y et al. (2008) Large ameloblastoma of the mandible with hypoproteinemia. Int J Oral Maxillofac Surg 37: 866–869. doi: 10.1016/j.ijom.2008.04.001 PMID: 18554869
21. Chauhan DS, Guruprasad Y (2011) Plexiform ameloblastoma of the mandible. J Clin Imaging Sci 1: 61. doi: 10.4103/2156-7514.91134 PMID: 22267996
22. Ota Y, Aoki T, Otsuru M, Hirabayashi K, Nakamura N et al. (2012) Huge ameloblastoma associated with hypercalcemia, leukocytosis, and elevated tumor markers via production of parathyroid hormone-related protein and granulocyte colony-stimulating factor. J Oral Maxillofac Surg 70: 1380–1385. doi: 10.1016/j.joms.2011.06.003 PMID: 21824706
23. Hunasgi S, Koneru A, Chauhan DS, Guruprasad Y (2013) Rare giant granular cell ameloblastoma: a case report and an immunohistochemical study. Case Rep Dent 2013: 372781. doi: 10.1155/2013/372781 PMID: 23533826
24. Catherine Z, Isaac S, Cotton F, Roch J, Rousset M et al. (2013) [Giant ameloblastoma of the mandible]. Rev Stomatol Chir Maxillofac Chir Orale 114: 97–101. doi: 10.1016/j.revsto.2013.01.005 PMID: 23838249
25. Mijiti A, Ling W, Maimaiti A, Moming A (2013) Single-stage management of huge desmoplastic ameloblastoma of the anterior mandible. J Plast Reconstr Aesthet Surg 66: 1440–1441. doi: 10.1016/j.bjps.2013.04.051 PMID: 23664801
26. Acharya S, Joshi A, Tayaar AS, Gopalkrishnan K (2011) Extreme ameloblastoma of the mandible with hypoproteinemia. A case report and review of clinicopathological features. J Clin Exp Dent 3: e343–347.
27. Mukhopadhyay S, Raha K, Mondal SC (2005) Huge ameloblastoma of jaw-A case report. Indian J Otolaryngol Head Neck Surg 57: 247–248. doi: 10.1007/BF03008023 PMID: 23120181
28. Mehrara E, Forssell-Aronsson E, Ahlman H, Bernhardt P (2007) Specific growth rate versus doubling time for quantitative characterization of tumor growth rate. Cancer Res 67: 3970–3975. PMID: 17440113
29. Bredenkamp JK, Zimmerman MC, Mickel RA (1989) Maxillary ameloblastoma. A potentially lethal neoplasm. Arch Otolaryngol Head Neck Surg 115: 99–104. PMID: 2642382
30. Li TJ, Wu YT, Yu SF, Yu GY (2000) Unicystic ameloblastoma: a clinicopathologic study of 33 Chinese patients. Am J Surg Pathol 24: 1385–1392. PMID: 11023100
31. Kahn MA (1989) Ameloblastoma in young persons: a clinicopathologic analysis and etiologic investigation. Oral Surg Oral Med Oral Pathol 67: 706–715. PMID: 2544844
32. Rajaonarison Ny Ony N, Randriamarolahy A, Randrianjanahary OM, Ahmad A, Bruneton JN (2012) Giant ameloblastoma. Clin Imaging 36: 146–148. doi: 10.1016/j.clinimag.2011.06.009 PMID: 22370136

33. Mehlisch DR, Dahlin DC, Masson JK (1972) Ameloblastoma: a clinicopathologic report. J Oral Surg 30: 9–22. PMID: 4500335

34. Oka K, Fukui M, Yamashita M, Takeshita I, Fujii K et al. (1986) Mandibular ameloblastoma with intracranial extension and distant metastasis. Clin Neurol Neurosurg 88: 303–309. PMID: 3802688

35. 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: 13–20. PMID: 11805772

36. Ruiz Valero CA, Duran-Rodriguez G, Solano-Parra N, Castro-Nunez J (2013) Immediate Total Temporomandibular Joint Replacement With TMJ Concepts Prosthesis as an Alternative for Ameloblastoma Cases. J Oral Maxillofac Surg. doi: 10.1016/j.joms.2013.11.012 PMID: 24831938

37. Huvos AG, Woodard HQ, Cahan WG, Higinbotham NL, Stewart FW et al. (1985) Postradiation osteogenic sarcoma of bone and soft tissues. A clinicopathologic study of 66 patients. Cancer 55: 1244–1255. PMID: 3855683

38. Sampson DE, Pogrel MA (1999) Management of mandibular ameloblastoma: the clinical basis for a treatment algorithm. J Oral Maxillofac Surg 57: 1074–1077; discussion 1078–1079 PMID: 10484108

39. Escande C, Chaine A, Menard P, Ernenwein D, Ghoul S et al. (2009) A treatment algorithm for adult ameloblastomas according to the Pitie-Salpetriere Hospital experience. J Craniomaxillofac Surg 37: 363–369. doi: 10.1016/j.jcms.2009.05.001 PMID: 19559625

40. Sehdev MK, Huvos AG, Strong EW, Gerold FP, Willis GW (1974) Proceedings: Ameloblastoma of maxilla and mandible. Cancer 33: 324–333. PMID: 4812754

41. Muller H, Slootweg PJ (1985) The ameloblastoma, the controversial approach to therapy. J Maxillofac Surg 13: 79–84. PMID: 3858399

42. Gardner DG (1996) Some current concepts on the pathology of ameloblastomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 82: 660–669. PMID: 8974139

43. Luo DY, Feng CJ, Guo JB (2012) Pulmonary metastases from an Ameloblastoma: case report and review of the literature. J Craniomaxillofac Surg 40: e470–474. doi: 10.1016/j.jcms.2012.03.006 PMID: 22507293

44. Hong J, Yun PY, Chung IH, Myoung H, Suh JD et al. (2007) Long-term follow up on recurrence of 305 ameloblastoma cases. Int J Oral Maxillofac Surg 36: 283–288. PMID: 17222535

45. Robinson L, Martinez MG (1977) Unicystic ameloblastoma: a prognostically distinct entity. Cancer 40: 2278–2285. PMID: 922668

46. Ackermann GL, Altini M, Shear M (1988) The unicystic ameloblastoma: a clinicopathological study of 57 cases. J Oral Pathol 17: 541–546. PMID: 3150441

47. Ueno S, Mushimoto K, Shirasu R (1989) Prognostic evaluation of ameloblastoma based on histologic and radiographic typing. J Oral Maxillofac Surg 47: 11–15. PMID: 2911052

48. Pogrel MA, Montes DM (2009) Is there a role for enucleation in the management of ameloblastoma? Int J Oral Maxillofac Surg 38: 807–812. doi: 10.1016/j.ijom.2009.02.018 PMID: 19297131

49. Philipsen HP, Reichart PA (1998) Unicystic ameloblastoma. A review of 193 cases from the literature. Oral Oncol 34: 317–325. PMID: 9861335

50. 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: 339–344. PMID: 9347494

51. Huffman GG, Thatcher JW (1974) Ameloblastoma—the conservative surgical approach to treatment: report of four cases. J Oral Surg 32: 850–854. PMID: 4530076

52. Stoelinga PJ (2005) The treatment of odontogenic keratocysts by excision of the overlying, attached mucosa, enucleation, and treatment of the bony defect with carnoy solution. J Oral Maxillofac Surg 63: 1662–1666. PMID: 16243184

53. Holland PS, Mellor WC (1981) The conservative treatment of ameloblastoma, using diathermy or cryosurgery. A 29-year review. Int J Oral Surg 10: 32–36. PMID: 6807902

54. Pogrel MA (1993) The use of liquid nitrogen cryotherapy in the management of locally aggressive bone lesions. J Oral Maxillofac Surg 51: 269–273; discussion 274 PMID: 8445469

55. Salmassy DA, Pogrel MA (1995) Liquid nitrogen cryosurgery and immediate bone grafting in the management of aggressive primary jaw lesions. J Oral Maxillofac Surg 53: 784–790. PMID: 7595793

56. Simon EN, Merkx MA, Kalyanyama BM, Shubi FM, Stoelinga PJ (2013) Immediate reconstruction of the mandible after resection for aggressive odontogenic tumours: a cohort study. Int J Oral Maxillofac Surg 42: 106–112. doi: 10.1016/j.ijom.2012.07.010 PMID: 22898314

57. Mendenhall WM, Werning JW, Fernandes R, Malyapa RS, Mendenhall NP (2007) Ameloblastoma. Am J Clin Oncol 30: 645–648. PMID: 18091060

58. Yilmaz M, Vayvada H, Menderes A, Demirdover C, Kizilkaya A (2008) A comparison of vascularized fibular flap and iliac crest flap for mandibular reconstruction. J Craniofac Surg 19: 227–234. doi: 10.1097/scs.0b013e31815c942c PMID: 18216693

59. Dandriyal R, Gupta A, Pant S, Baweja HH (2011) Surgical management of ameloblastoma: Conservative or radical approach. Natl J Maxillofac Surg 2: 22–27. doi: 10.4103/0975-5950.85849 PMID: 22442605

60. Hertog D, Schulten EA, Leemans CR, Winters HA, Van der Waal I (2011) Management of recurrent ameloblastoma of the jaws; a 40-year single institution experience. Oral Oncol 47: 145–146. doi: 10.1016/j.oraloncology.2010.11.008 PMID: 21159544

61. 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: 304–309. PMID: 8445473

62. 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: 28–32. PMID: 7718524

63. Komisar A (1984) Plexiform ameloblastoma of the maxilla with extension to the skull base. Head Neck Surg 7: 172–175. PMID: 6511439

64. Gardner DG (1977) Peripheral ameloblastoma: a study of 21 cases, including 5 reported as basal cell carcinoma of the gingiva. Cancer 39: 1625–1633. PMID: 856447

65. Feinberg SE, Steinberg B (1996) Surgical management of ameloblastoma. Current status of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81: 383–388. PMID: 8705582

66. Carlson ER, Monteleone K (2004) An analysis of inadvertent perforations of mucosa and skin concurrent with mandibular reconstruction. J Oral Maxillofac Surg 62: 1103–1107. PMID: 15346361

67. Taylor GI (1982) Reconstruction of the mandible with free composite iliac bone grafts. Ann Plast Surg 9: 361–376. PMID: 6758673

68. David DJ, Tan E, Katsaros J, Sheen R (1988) Mandibular reconstruction with vascularized iliac crest: a 10-year experience. Plast Reconstr Surg 82: 792–803. PMID: 3174869

69. Hidalgo DA, Rekow A (1995) A review of 60 consecutive fibula free flap mandible reconstructions. Plast Reconstr Surg 96: 585–596; discussion 597–602 PMID: 7638283

70. Sullivan MJ, Baker SR, Crompton R, Smith-Wheelock M (1989) Free scapular osteocutaneous flap for mandibular reconstruction. Arch Otolaryngol Head Neck Surg 115: 1334–1340. PMID: 2803713

71. Serafin D, Villarreal-Rios A, Georgiade NG (1977) A rib-containing free flap to reconstruct mandibular defects. Br J Plast Surg 30: 263–266. PMID: 588790

72. Vaughan ED (1994) The radial forearm flap in orofacial reconstruction. Int J Oral Maxillofac Surg 23: 194–204. PMID: 7798689

73. Handschel J, Hassanyar H, Depprich RA, Ommerborn MA, Sproll KC et al. (2011) Nonvascularized iliac bone grafts for mandibular reconstruction—requirements and limitations. In Vivo 25: 795–799. PMID: 21753136

74. Millard DR, Campbell RC, Stokley P, Garst W (1969) Interim report on immediate mandibular repair. Am J Surg 118: 726–731. PMID: 4899746

75. 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: 1200–1206. PMID: 9371107

76. Hayter JP, Cawood JI (1996) Oral rehabilitation with endosteal implants and free flaps. Int J Oral Maxillofac Surg 25: 3–12. PMID: 8833293

77. Vu DD, Schmidt BL (2008) Quality of life evaluation for patients receiving vascularized versus nonvascularized bone graft reconstruction of segmental mandibular defects. J Oral Maxillofac Surg 66: 1856–1863. doi: 10.1016/j.joms.2008.04.021 PMID: 18718392

78. van Gemert JT, van Es RJ, Van Cann EM, Koole R (2009) Nonvascularized bone grafts for segmental reconstruction of the mandible—a reappraisal. J Oral Maxillofac Surg 67: 1446–1452. doi: 10.1016/j.joms.2008.12.052 PMID: 19531416

79. Daramola JO, Ajagbe HA, Oluwasanmi JO (1980) Recurrent ameloblastoma of the jaws—a review of 22 cases. Plast Reconstr Surg 65: 577–579. PMID: 7367497

80. Adekeye EO, Lavery KM (1986) Recurrent ameloblastoma of the maxillo-facial region. Clinical features and treatment. J Maxillofac Surg 14: 153–157. PMID: 3459793

81. Hayward JR (1973) Recurrent ameloblastoma 30 years after surgical treatment. J Oral Surg 31: 368–370. PMID: 4512196

82. Frantz VK, Stix L (1932) Adamantinoma: a case of fifty-one years' duration. Arch Surg 25: 890–897.