REVIEW ARTICLE

AMELOBLASTOMAS AND THEIR MANAGEMENT: A REVIEW

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ABSTRACT

Objective — *To review the pertinent literature and determine the most appropriate method of treatment for ameloblastomas.*

Methodology — *A computerized literature search using Medline was conducted for published articles on treatment of ameloblastomas. MeSH phrases used in the search were ameloblastoma AND treatment; ameloblastoma AND surgical management. An attempt was made to conduct a systematic review on the subject, but due to inconsistency in terminology, treatment protocol, lack of randomised controlled trial and inadequate follow-up and assessment in most of the articles studied, a narrative critical review of selected relevant literature regarding treatment of ameloblastoma was undertaken.*

Results — *It is widely reported that the recurrence of an ameloblastoma in large part reflects the inadequacy or failure of the primary surgical procedure. Recent studies have unequivocally showed that when a diagnosis of ameloblastoma is made, the treatment must be aggressive and radical to avoid recurrence. The recurrence rates of 55% to 90% for solid or multicystic lesions treated by conservative approach (enucleation or curettage) and even metastases have been reported. Regarding unicystic ameloblastoma, systematic review of the literature has shown that radical approach to treatment resulted in lowest recurrence rate. For ameloblastomas, the first surgery (especially radical) affords the best chance for cure.*

Conclusions — *There is a lack of consensus on the most appropriate treatment modality for ameloblastomas. However, a more radical approach (whenever possible) appears to be the best method for the management of these benign, but locally aggressive, lesions with propensity for multiple recurrences.*

Key words — *Ameloblastoma, Meta-analysis.*

INTRODUCTION:

Ameloblastoma is reported to constitute about 1-3% of tumours and cysts of the jaws.[1-3] The tumour is by far more common in the mandible than in the maxilla and shows predilection for various parts of the mandible in different racial groups.[4] The relative frequency of the mandible to maxilla is reported as varying from 80–20% to 99–1%.[2,3] It often presents as a slow growing, painless swelling, causing expansion of the cortical bone, perforation of the lingual and/or buccal plates and infiltration of soft tissue. There is often delay in the diagnosis because of its slow-growing nature.[5] Ameloblastoma of the jaws is the most commonly encountered odontogenic tumour in Africa [6–9] and Asia,[10,11] but the second most common odontogenic tumour in North and South America.[12–14] The aim of the present study was to critically review the pertinent literature and determine the most appropriate method of treatment for ameloblastomas.

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METHODOLOGY

A computerized literature search using Medline was conducted for published articles on treatment of ameloblastomas. MeSH phrases used in the search

were: ameloblastoma AND treatment; ameloblastoma AND surgical management. The Boolean operator 'AND' was used to combine and narrow the searches. The full-texts of all these articles were thoroughly examined by 2 of the authors. Most of the articles were case reports, retrospective case series and nonrandomised controlled studies. Only one case of systematic review of retrospective case series regarding treatment of unicystic ameloblastoma was found in the literature. An attempt was made to conduct a systematic review on the subject. However, there was inconsistency in terminology, patients' characteristics, extent of tumour, treatment protocol and follow-up period. Meta-analysis is only possible if there is sufficient similarity in variable studied including patients' characteristics, treatment given, outcome measure and follow-up period. Therefore, a narrative critical review of selected relevant literature regarding treatment (conservative or radical) of ameloblastoma was undertaken. The following treatment modalities were identified in the literature: enucleation with or without application of carnoyl solution, curettage, surgery with adjuvant cryotherapy, marsupialisation, and resection (marginal, segmental, hemi- and total resection).

MANAGEMENT:

Growth Potential and Behaviour of Ameloblastomas

Ameloblastomas are aggressive benign tumours of epithelial origin that may arise from the enamel organ, remnants of dental lamina, the lining of an odontogenic (dentigerous) cyst, or possibly from the basal epithelial cells of the oral mucosa.[5] The clinicopathological features are benign with a slow-growing pattern, but locally invasive. The clinical behaviour may be regarded as lying somewhere between benign and malignant, and the high recurrence is a problem for clinicians.[15] They may show various biologic behaviours, ranging from cystic expansion to more aggressive infiltration of adjacent tissue.[16] Unlike carcinomas, ameloblastomas are circumferentially delineated by a continuous basement membrane, and they tend to spread into tissue spaces by expanding their compartment volumes.[17] The architectural pattern of the ameloblastoma is such that the border of the tumour within cancellous bone lies beyond the apparent macroscopic surface and the radiographic boundaries of the lesion.[5] There are conflicting reports in the literature regarding the growth characteristics of ameloblastomas and its relationship to the inferior alveolar nerve.[16,18] According to Tingchun et al a tumour that lies adjacent to, or is contained within, the mandibular canal may destroy and grow into the canal.[18] In contrast however, Nakamura et al detected neither invasion into the nerve sheath nor invasion into the nerve itself by ameloblastomas.[16]

The classification of ameloblastoma in the past was poorly defined. The current concept is to classify ameloblastomas as solid/multicystic, classical intraosseous; peripheral; or unicystic subtypes.[5] This classification has a direct bearing on the pathologic behaviour of these variants. Solid or multicystic variants of ameloblastomas are locally aggressive, and recur if inadequately excised. However, unicystic ameloblastoma was identified as a prognostically distinct entity with less aggressive behaviour.[19] The most common histologic subtypes of ameloblastomas are follicular, plexiform, acanthomatous, granular and desmoplastic.[15,20] Hong et al recently showed that the histopathology of an ameloblastoma is significantly associated with a recurrence.[15] It was shown that the follicular, granular cell and acanthomatous types have a relatively high likelihood of recurrence. In contrast, the desmoplastic, plexiform and unicystic types show a relatively low potential for recurrence.

Treatment

Treatment of ameloblastomas is primarily surgical. There has been some debate regarding the most appropriate method for surgical removal of ameloblastomas. These range from conservative to radical modes of treatment. The conservative modalities include curettage, enucleation and cryosurgery; while the radical modalities are marginal, segmental and composite resections. There is a lack of consensus over the most appropriate treatment modality.

Proponents of conservative approach believe that ameloblastomas though, locally invasive, are essentially benign in nature, therefore, they should be treated as such.[21–23] Ueno et al suggested that that 'excessive resection' of the mandible constituted excessive treatment,[21] and Feinberg and Steinberg noted that this might be particularly true in young patients, in whom an interruption in growth and development could interfere with future function and aesthetics.[22] Sammartino et al also advocated for conservative treatment of large ameloblastoma due to 'low morbidity' associated with these procedures. According to the authors radical treatment is associated with serious cosmetic, functional and

aesthetic problems.[22] Sammartino et al also advocated for conservative treatment of large ameloblastoma due to 'low morbidity' associated with these procedures. According to the authors radical treatment is associated with serious cosmetic, functional and reconstructive problems.[23] Others have also advocated for enucleation for the treatment of ameloblastomas with preservation of the healthy periosteum which is important for bone regeneration especially in children.[24] Several authors have also recommended enucleation rather than partial or complete jaw resection to treat unicystic ameloblastoma, believed to occur predominantly in paediatric population.[19,22,25]

Proponents of radical approach to the treatment of ameloblastomas are of the opinion that, although, these tumours are histologically benign in nature, they are locally aggressive and the clinical behaviour may be regarded as lying somewhere between benign and malignant lesions. Enucleation and curettage of ameloblastoma result in unacceptable recurrence rates.[26] The recurrence rates of 55% to 90% for solid or multicystic lesions treated by enucleation or curettage have been reported.[27] Metastases following conservative management have also been reported.[28]

DISCUSSION:

Current opinion regarding treatment of ameloblastomas is essentially based on case reports, anecdotal evidence, retrospective reviews, and histological evidence. There are not many large-scale studies with long-term follow-up results. The benign nature of these lesions often leads the surgeons to perform simpler extirpative procedures to avoid the potential morbidity associated with large resections. This approach is still commonly practiced, despite reported recurrence rates of 55% to 90% for solid multicystic treated by enucleation or curettage and even occasional metastases.[15,26,28] Sammartino et al recently proposed a new treatment algorithm to assist surgeons to develop a 'rational' diagnostic protocol and establish effective conservative surgical management in patients with mandibular ameloblastomas based on a ten year experience in their institution. According to the authors small ameloblastomas were treated by wide resection which includes at least 1cm of normal bone at the tumour margin. Large lesions without perforation of the cortex were treated conservatively (curettage), while those with cortical perforation were treated by resection with overlying soft tissues.[23] Accordingly, close follow-up was deemed necessary in cases treated conservatively in order to identify subsequent recurrences early and treat them more aggressively. The authors treated 15 cases of ameloblastoma, including 10 solid multicystic ameloblastoma and 5 unicystic ameloblastoma. Of the 15 cases, 7 (46.7%) recurred after the first operation, all but one of which was within 5 years of surgery. The peak period of recurrence was 3 years. Of the 7 cases that recurred, 6 of them were solid multicystic type. Despite the obvious high recurrence rate in their study, the authors recommended that large ameloblastoma with no cortical perforation be treated by curettage with 0.5–1 cm of clinically uninvolved surround bone.[23]

The rationale behind treatment of small ameloblastoma with resection and large ones (no bone perforation) with less than radical approach; only to wait for recurrence before radical treatment is instituted may not be clinically justifiable in view of the aggressive nature and overwhelming evidence regarding high recurrence rate if ameloblastomas were treated conservatively. One reason given by Sammartino et al for conservative treatment of large ameloblastoma was 'low morbidity'. According to the them, radical treatment is associated with serious cosmetic, functional and reconstructive problems. Despite the 'radical' nature of a surgical resection, it may actually involve less morbidity than extensive hard and soft tissue resection with associated extensive morbidity that may be warranted in case of recurrence following inadequate primary treatment.[26] In fact, with modern day reconstructive options, the need for reconstruction after surgical resection should not be a sole reason for treating ameloblastomas with a less than radical approach.

The cost-benefit analysis of the conservative management is another topical issue. Treatment of large ameloblastoma with less than radical approach, only to wait for recurrence before radical treatment is instituted is expensive in terms of cost to the patient and extensive follow-up required. It has been reported that the recurrence of an ameloblastoma in large part reflects the inadequacy or failure of the primary surgical procedure.[15,29] Satkin and Hoffmeister in looking at early data from 1918 onward showed that continued under-treatment of ameloblastoma can lead to extensive and at that time unresectable recurrences.[30] They reported a mortality of 30% from recurrent ameloblastoma in an early series of 13 cases. Hong et al in a retrospective analysis of 239 patients with ameloblastomas of the jaws reported recurrences of 4.5% in patients treated by segmental resection or maxillectomy, 11.6% in patient treated

by resection with bone margin and 29.3% treated with conservative treatment (enucleation, curettage and marsupialization).[15] Disease-free survival with respect to treatment modalities showed a statistically significant difference (p = 0.01) when 'segmental resection or maxillectomy' and 'resection with bone margin are compared with 'conservative' treatment. The difference between the 'resection with bone margin' and 'segmental resection or maxillectomy' groups was not statistically significant (*p*=0.05).[15]

Disease-Free survival is usually used to analyze results of treatment for localized disease which renders the patient apparently disease free, such as surgery or surgery and adjuvant therapy. In disease free survival, the event is relapse rather than death. In another recent report by Ghandhi et al, primary management by conservative approach led to a recurrence in approximately 80% of cases and this included cases of unicystic ameloblastoma. Of the 41 cases of solid/multicystic ameloblastoma, 20 were treated radically and 21 conservatively. There were no recurrences in the radically treated group. Among the conservative group, 16 (76.2%) out of 21 cases had recurrence. All the recurrent cases were treated with radical surgery. Two cases had second recurrence; one of which showed spread to the base of the skull. With secondary radical surgery there was a well-recognised recurrence rate. Segmental or composite resection produces good results especially when carried out as a primary treatment.[26] Once the tumour infiltrates the surrounding soft tissues, the rate of recurrence increases. This is mainly because of the difficulty in identifying the tumour boundary. Even extensive surgery cannot guarantee complete excision once this occurs. Satkin and Hoffmeister also reviewed 20 cases of ameloblastoma and found a recurrence rate of 19% when treated with resection versus 86% for curettage. The propensity for high recurrence of ameloblastoma was also attested to by 60% recurrence rate for solid or multicystic treated by enucleation/curettage by proponents of conservative management.[23]

Sampson and Pogrel reviewed the records of 26 consecutive patients with mandibular ameloblastomas.[26] Of the 26 cases, 10 were referred with recurrence after failed treatment (curettage) elsewhere, and 16 were referred for primary treatment. In total, 11 patients had recurrences all originally treated primarily by curettage alone. Some of these patients had been treated with multiple attempts at curettage, with all lesions recurring. In two instances, patients required more than one secondary operation to eradicate the disease. Six of the 11 patients had recurrence with soft tissue involvement and were treated with resection. Two of the 6 patients developed secondary soft tissue recurrences. These 2 patients each underwent multiple secondary procedures to eradicate the disease, including neck dissections and skull base resections.

Multiple recurrences after conservative treatment of ameloblastomas have also been reported by other authors.[5,15,31] Reports from Africa have also corroborated the fact that resection with bone margin is the treatment of choice for ameloblastomas.[3,4,8,29,32]

Chidzonga stated that the recommended treatment for ameloblastoma in children should be radical resection 0.5 to 1 cm past what appears to be normal bone.[32] Radical treatment was also the method of choice employed by Arotiba et al.[33] Other studies have also shown that when a diagnosis of ameloblastoma is made, the treatment must be aggressive and radical.[5,15,29] For solid-multicystic ameloblastomaof the mandible, a resection of the jaw should be approximately 1.5–2 cm beyond the radiological limit, in order to ensure that all the 'microcysts' and 'daughter cysts' are removed.[15,29]

The unicystic ameloblastoma deserves special consideration on the basis of its clinical and radiologic appearance, its histopathology, and its response to treatment.[19] In 1977, Robinson and Martinez identified a subset of ameloblastoma, called unicystic ameloblastoma, regarded as a separate entity.[19] These tumours often occur as a painless swelling involving the posterior region of the mandible. Radiographically, they present primarily as a unilocular radiolucency and diagnosis is often made following histologic study of the enucleated specimen. This variant of ameloblastoma was reported to have shown less aggressive behaviour than the conventional ameloblastoma. Robinson and Martinez initially recommended conservative treatment for unicystic ameloblastoma because its behaviour was thought to be different from solid or multicystic type. However, recent emerging clinical evidence have indicated the aggressive nature of the so-called unicystic ameloblastoma.[34,35]

Ghandhi et al reported a recurrence rate of 80% for unicystic ameloblastoma treated conservatively.[5] In a recent study, Hong et al reported a recurrence rate of 15.5% (11 out of 77) of unicystic ameloblastoma

treated conservatively, as against 9% (1 out of 11) recurrence for resection with bone margin.[15] A review of the English-language literature taken from cases reports and reviews from 1977 to 2006 disclosed a total of 128 cases of unicystic ameloblastoma, of which 18 (14.6%) had recurred. In addition, a recent systematic review (considered the best level of evidence) showed that enucleation of unicystic ameloblastoma resulted in the highest recurrence rate; and the lowest recurrence rate was associated with resection of the tumour.[34]

Enucleation alone yielded 30.5% recurrence rate, followed by recurrence rate of 18% for marsupialization, 16% for enucleation with application Carnoy's solution, and 3.6% for resection. The explanation is 2-fold, firstly, the cystic lining of the tumour is inadequately removed. Sometimes, especially in posterior maxillary ameloblastomas, the tumour is not perfectly rounded or oval in shape so the enucleation may not be as simple as expected, and remnants can be left behind in complex anatomical structures without being noticed. Secondly, the ameloblastic tumour cells can invade the cancellous bone to a certain extent.[34]

Marx et al demonstrated that ameloblastoma tumour cells can extend from 2.3 to 8 mm beyond radiographic margin of the tumour, thus, by enucleation alone, the ameloblastic cells will be left behind despite the tumour being enucleated whole.[36] Three histologic variants of unicystic ameloblastoma are described in the literature.[37,38] In the first type, luminal ameloblastoma; the tumour is confined to the luminal surface of the cyst. In the second type, intraluminal ameloblastoma, tumour nodules project from the cystic lining into the lumen of the cyst. In the third type, mural ameloblastoma, the fibrous wall of the cyst is infiltrated with tumour nodules. The third type is considered the most aggressive, with a recurrence rate as high 35.7% reported in the literature for mural unicystic ameloblastomas.[35] Different proliferating potentials have been reported between different areas of the unicystic ameloblastoma, in the form of a higher PCNA and Ki-67 labelling index, especially in the tumour nodules within the cystic wall.[39] This discovery provided a biologic basis to recommend a more radical surgical excision as the treatment of choice for unicystic ameloblastoma.

CONCLUSIONS:

Ameloblastoma is considered to be a benign, but locally invasive odontogenic tumour with a high rate of recurrence. Essentially, most studies showed that the prognosis for ameloblastoma is more dependent on the method of surgical treatment rather the histologic type of tumour. Resection with some safe margin (marginal, segmental or composite resection depending on the site and size of the lesion) is the best primary method for treating solid/multicystic ameloblastomas to avoid recurrence.

In view of the emerging unacceptable recurrence rate of unicystic ameloblastoma, marginal resection should be the minimum standard for the treatment of unicystic ameloblastoma of the mandible. Despite the 'radical' nature of a surgical resection, it may actually involve less morbidity than extensive hard and soft tissue resection with associated extensive morbidity that may be warranted in case of recurrence following inadequate primary treatment. However, a conservative (curettage, not enucleation) method may be considered in case of unicystic ameloblastoma of the anterior mandible without soft tissue involvement, for patients in their first decade of life. In this case, patient compliance and careful follow-up is important. In the event of a recurrence, resection with normal bone margin is advocated. Finally, in view of the fact that there is a lack of consensus on the most appropriate treatment modality for ameloblastomas, there is a need to conduct more evidence-based clinical studies for clinical practice guidelines in the management of ameloblastomas of the jaws.

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