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Conservative vs radical treatment of ameloblastoma : A 14-year study in Kedah

Investigator names and affiliation:

Ling Xiao Feng, BDS(Mal), MDS(OMFS)(HK), MFDSRCS(Eng), FIBCSOMS

Sumairi bin Ismail, BDSc(UWA), MClinDent(OMOP)(Mal)

Marzuki bin Zainal Abidin, BDS(Adelaide), MClinDent(OMFS)(Mal)

Nurfitri Atirah bt Amran, BDS(UiTM)

Mohammad Azrin bin Abd Samad, BDS(UiTM)

Mei Mei Tew, BPharm(Hons)(AIMST), MBA(USM)

Noratikah binti Awang Hasyim, BDS(Malaya), MClinDent(OMOP)(Mal)

Chief investigator :

Ling Xiao Feng,

Tel : +604-4457333

Email : drxfling@hotmail.com

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Introduction and Literature Review

Ameloblastoma is a locally aggressive benign odontogenic tumour of the jaws, representing 2-3% of all lesions of the jaws. [1] It is often diagnosed around the age of 36 years and it affects both sexes equally.[2] Despite its benign histological appearance, if left untreated, it is clinically persistent, causing facial disfiguration and can kill from invasion of vital structures, super-infection, or distant metastases.[3] The tumour is usually symptomless at the early stage, but may later cause pain, loosening of teeth, malocclusion or bulging of jaws.[4]

In 2022, the World Health Organization (WHO) classification of ameloblastoma was updated to include five subtypes namely: unicystic, extraosseous, conventional, adenoid and metastasizing ameloblastoma.[5] The unicystic variant can be further divided into three subtypes depending on mural involvement. Subtype 1 cysts are lined by variable epithelium with no infiltration into the cystic wall. Those in subtype 2 show intraluminal, plexiform, epithelial proliferation without infiltration, and those in subtype 3 show either a follicular or plexiform pattern of invasion by epithelium into the cystic wall.[6] Extraosseous or peripheral ameloblastomas, comprising only 1% to 5% of all ameloblastomas, and they feature more benign behaviour than other types with minimal bony involvement.[7] Conventional ameloblastoma (solid/multicystic type) is the most common variant and it invades the bone marrow spaces.[8] Adenoid ameloblastoma is the only new entity added in the odontogenic lesions and it is defined as an epithelial odontogenic neoplasm composed of cribriform architecture and duct-like structures and frequently includes dentinoid.[9] Metastasizing ameloblastoma is defined as ameloblastoma that has metastasized despite its benign histopathological appearance.[9] The main histological types of ameloblastoma are follicular and plexiform with subtypes acanthomatous, spindle cell, granular cell, basal cell and desmoplastic. [3]

The treatment regimens for ameloblastoma are controversial, and typically grouped into: radical resection of the jaw, and conservative treatment.[10] Traditionally, treatment has depended on the histological features. The conventional ameloblastoma, and the subtype 3 unicystic ameloblastoma are considered aggressive with a high potential recurrence rate, therefore the approach has been to resect the lesion and repair the defect with a microvascular graft.[11] Simple tumour enucleation can preserve mandibular continuity which

is crucial to the postoperative appearance and function. However, due to the feature of local infiltration, this may result in a high recurrence rate of up to 60% in the unicystic variant, and 60-80% in the conventional ameloblastoma.[12] While surgical treatment is the acceptable form of treatment, study shows that opinions vary as to how radical it should be. However, adequate therapy necessitates a compromise between the least destructive treatment possible for a benign tumour and a suitable radical method for preventing a recurrence.[13] Many previous studies have focused on elucidating the treatment regimens for ameloblastoma, but the result remain controversial.[10]

Objectives

To evaluate the epidemiological data of ameloblastoma in Kedah

To identify the clinicopathological characteristics that predict the outcome of the treatment and recurrence rate

To identify the various treatment outcomes for ameloblastoma

To identify the factors that associated with the frequency of recurrence following treatment of these lesions.

To establish a rational treatment regimen for specific lesion

Methodology

A retrospective cohort study was conducted for patients who underwent treatment for ameloblastoma at the Department of Oral & Maxillofacial Surgery, Sultan Abdul Halim Hospital and Department of Oral & Maxillofacial Surgery, Sultanah Bahiyah Hospital, from 2007 to 2021. All patients with histopathologically proven ameloblastoma and undergo at least 2 years of follow-up were included in the study. The exclusion criteria were patients with incomplete records and those with a disputed histopathologic finding. Demographic variables included age and gender, social history like smoking habits were collected via electronic Health Information System (e-HIS). The records were examined by two investigators (NA, MA) and the following information sought: site of lesion, size of lesion (greatest radiographic dimension), presence of bony expansion, presence of tooth displacement, presence of numbness, radiological finding, various type of treatments (conservative treatment, radical treatment), follow up duration, and presence of recurrence. Conservative treatment included enucleation with application Carnoy's solution, enucleation with peripheral ostestomy,

enucleation with peripheral ostectomy and application of Carnoy's solution; on the other hand, radical treatment included marginal resection and segmental resection. Histopathology slides retrieved from the laboratory was examined by the oral pathologist (SI).

Data analysis

A descriptive analysis was performed based on mean +/- standard deviation (SD) for continuous data and number and percentage for categorical data. The Independent t-Test was performed to compare the differences in age and tumour size for both recurrent and non-recurrent groups. Pearson Chi Square test or Fisher's exact test was used to test for the association between other categorical variables with the outcome. The level of statistical significance was set at $P < 0.05$. All data will be analysed using IBM SPSS Statistics version 26.

Result

Review of the e-HIS records yielded 60 patients with histopathologically proven ameloblastoma from 2007-2021. 51 patients met the study's inclusion criteria and were selected for further review. There were 26 male patients and 25 female patients. The mean age was 39.8 +/- 18.8 years old. The mean follow up period was 77.4 +/- 29.8 months, with the maximum follow up period of 156 months, and the mean tumour size was 4.6 cm +/- 3.6 cm, median size was 4.2 cm, and maximum 14.0 cm. A recurrence was observed in 10 patients out of 51 patients (19.6%). The mean duration for recurrence was 32.8 months. There was no significant association between treatment modalities and tumour recurrence ($p>0.05$), although there were trends toward lesser recurrence rate among patients undergoing radical treatment. The risk estimation revealed that the patient underwent conservative treatment was 4.17-fold higher risk of recurrence than those who underwent radical treatment, with a 95% confidence interval ranging from 0.478 to 36.530. None of the variables, sex, race, site of tumour, and treatment modalities, were found to lead to the increase of recurrence rates ($p > 0.05$). Patient demographics, site of tumour, WHO classification, and treatment modalities were summarized in Table 1. Imaging data (panoramic radiograph) was available on 51 patients. Eleven patients (21.5%) showed unilocular radiolucency, thirty-five patients (68.6%) showed multilocular radiolucency, and five patients (9.8%) showed mixed radiolucent and radiopaque lesions. One patient with unilocular radiolucency showed recurrence and nine patients with multilocular radiolucency showed recurrence. There was no significant

association between histologic pattern and tumor recurrence (p>0.05), although there were trends toward higher recurrence rate in follicular ameloblastoma. The radiological-pathological characteristics was summarized in Table 2.

Discussion

The prevalence according to gender showed a female to male ratio of 1:1.04 at an average age of 39.8 years old. Most previous studies showed almost equal gender distribution at the average age of 36 years old.[2,8,14] Distribution of ameloblastoma among Caucasian (24.8%), Blacks (34.4%), and people of Asian descent (Chinese, Indians, Japanese, Malays and Thai)(38.4%) was reported by Reichart et al.[2], who analysed the available literature on 3677 patients with ameloblastoma. Ninety percent of the ameloblastoma in our study affected the mandible. Studies showed, ameloblastoma most presented as swelling over the mandible. (80.0%-91.8%).[2,8,14,15] Maxillary ameloblastoma on the other hand, had been shown to occur at an older age with male predilection.[16] Mean tumour size varies considerably (3.9cm – 4.3cm)[2,15] In Asians, the average tumour size was 4.8 cm.[2] The same study also reported that the average size of tumour in developing countries was larger than those from developed countries and ameloblastoma in women was statistically significant larger than in men.[2] The recurrence rate in our study, 19.6% during the average of 6.45 years follow up was in line with other studies. (17.2% - 24.0%)[8,15,16] The mean duration for recurrence in our study was shorter, other study showed that the period of recurrence after conservative surgery was significantly shorter (4.8 years) than after radical surgery (11.1 years).[2]

In the present study, follicular subtype was found to be the most prevalent subtype (90.2%), in agreement with the literature.[15] Follicular and plexiform ameloblastomas occured in younger patients and more frequently in the posterior part of the jaws, whereas the desmoplastic type was seen more frequently in the maxillary sinus and the anterior segments of the jaw.[2]

Although ameloblastoma was essentially benign, it was locally invasive.[17] The recurrence rate of ameloblastoma ranged widely according to its treatment and histological subtype.[6] A recent systematic review and meta-analysis showed that, the pooled recurrence rate for conventional ameloblastoma was 8% after radical treatment and 41% after conservative

treatment.[17] For unicystic ameloblastoma, these values were 3% and 21% respectively.[17] In the present study, our recurrence rate for conventional ameloblastoma was 7.1% after radical treatment and 21.6% after conservative treatment. The recurrence rate after conservative treatment in our study was surprisingly low compared to other study, 60%-80% in conventional ameloblastoma and 60% in unicystic ameloblastoma.[12] Six cases of unicystic ameloblastoma were conservatively treated in our study and there was only 1 case of recurrence. No doubt, radical treatment adequately removed the tumour and minimized the risk of recurrence, it was bound to cause a large bone defect, severe facial deformity, malocclusion, lip numbness and poor mastication.[18] Most studies did not report on the post operative quality of life after undergoing radical treatment. Although radical treatment can lower the recurrence rate, it jeopardized functional and cosmetic outcomes of the jaws.[8] The ameloblastoma affected a relatively young population, and radical treatment with its attendant facial deformity can have a considerable impact on one's life.[6]

Enucleation with peripheral ostectomy ensured the postoperative quality of life and at the same time keep the risk of recurrence low.[4] In our study, the recurrence rate for enucleation with peripheral ostectomy was 26.7% in conventional ameloblastoma, which was lower than the reported rates, 33.3%.[4] Before enucleation, teeth directly related to the tumour would be extracted. The additional procedure of peripheral ostectomy was aimed at removing the infiltrative tumour islands that might exist in the residual bone walls after simple enucleation.[4] The bone trimming procedure should be done under vigorous saline irrigation, to maintain the bone regeneration capacity. Preservation of the periosteum was vital, even in area of bone perforation.[4] Bismuth iodoform paraffin paste (BIPP) impregnated ribbon gauze was inserted into the bony defect and would be replaced every 10 days with a shortened ribbon gauze until the bony defect epithelized. By using this method, the continuity of mandible was preserved, and following bone regeneration, the paper thin plates thickened significantly.[4]

Tissue fixatives like Carnoy's solution (chloroform 3ml, absolute alcohol 6ml, glacial acetic acid 1ml, ferric chloride 1g)[19] was also used to kill residual infiltrative tumour islands in bone walls.[4] In our study, the recurrence rate for enucleation with application of Carnoy's solution was 16.67% in conventional ameloblastoma and 1 case of recurrence in unicystic ameloblastoma. Recurrence rate of 11.1% had been reported by using this method though

the duration of follow up was inadequate.(mean period of follow up 38 months)[6] All efforts should be aimed at proper enucleation and elimination of possible remnants and elimination of the bony septae as to assure proper treatment of the whole bony cavity with Carnoy's solution.[20] Application of Carnoy's solution was limited to 3 minutes using cotton applicators and it was followed by copious irrigation using normal saline.[19] Application of Carnoy's solution may damage the capacity for bone regeneration[4], and was restricted in certain countries due to the carcinogenic effect of chloroform.

The relationship between tumour site and recurrence risk has been controversial.[16] In our study, all ameloblastoma involving the maxilla underwent radical treatment and we recorded no recurrence. That was the reason why we did not find a significant difference in proportion of recurrent maxillary and mandibular ameloblastomas. We were more aggressive at the initial surgical intervention in maxillary ameloblastoma because maxillary ameloblastoma demonstrated propensity for multiple recurrences and regionally aggressive behaviour.[16] Maxilla consisted of medullary bone, which made maxilla easily invaded by tumours and facilitated the spread of the tumour.[2,21] The proximity of maxilla with the nasal cavity, paranasal sinuses, orbits, parapharyngeal tissues and skull base, made obvious the totally different growth pattern of maxillary ameloblastomas.[21]

Regular follow up was mandatory regardless the choice of treatment.[15] We would recommend follow up for close monitoring of ameloblastoma twice a year the first 5 years postoperatively. Radiographic examination was valuable in detecting recurrence at the earliest stage,[4] and we would recommend panoramic radiograph for all patients annually for the first 5 years. Diagnosis of symptomless recurrence had been considerably improved with the periodically usage of computer tomography (CT).[2] Although most tumours recured within 5 years of original diagnosis[2,22], study showed that ameloblastoma was a lifelong disease, where late recurrences were seen in 23% of the study population.[16]

Our recommended treatment for recurrences was radical surgery, particularly with maxillary ameloblastoma where spread can occur to structures posterosuperior to the maxilla.[22] Enucleation played no part in the management of the recurrent ameloblastoma.[12] Special attention must be given to any soft tissue extension present in the recurrence.

Conclusion

Our data indicate that the conservative treatment can preserve the appearance and function well, at the same time keeping the risk of recurrence lower than currently published figures. The management of ameloblastoma should be aimed to reduce the risk of recurrence, at the same time, minimising morbidity for the patient. Therefore, we would suggest conservative treatment for primary tumour and young patients while radical treatment was reserved for recurrence, very large lesion with substantial cortical perforation and maxillary ameloblastoma.

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Table 1. **Patient demographics, site of tumour, The 2022 WHO classification[5], and treatment modalities.**

Variables	Total	Recurrences , n(%)	p-value
Sex			
Male	26 (51.0)	6 (23.1)	**0.525[a]**
Female	25 (49.0)	4 (16.0)	
Race			
Malay	40 (78.4)	8 (20.0)	**0.727[b]**
Chinese	6 (11.8)	2 (33.3)	
Indian	4 (7.8)	0 (0.0)	
Others	1 (2.0)	0 (0.0)	
Site of tumour			
Anterior maxilla	4 (7.8)	0 (0.0)	**0.895[b]**
Posterior maxilla	1 (2.0)	0 (0.0)	
Anterior mandible	4 (7.8)	1 (25.0)	
Posterior mandible	42 (82.4)	9 (21.4)	
The 2022 WHO classification[5]			
Ameloblastoma, unicystic	6 (11.8)	1 16.6)	**>0.99[b]**
Ameloblastoma, extraosseous	0 (0.0)	0 (0.0)	
Ameloblastoma, conventional	45 (88.2)	9 (20.0)	
Adenoid ameloblastoma	0 (0.0)	0 (0.0)	
Metastasizing ameloblastoma	0 (0.0)	0 (0.0)	
Treatment			
Conservative treatment Enucleation / Enucleation with peripheral ostectomy / Enucleation with application of Carnoy's solution	37	9 (24.3)	**0.168[b]**
Radical treatment Segmental resection / Marginal resection	14	1 (7.1)	

Note: [a] Chi Square Test, [b]Fischer Exact Test.

Abbreviation: WHO, World Health Organization

Table 2. **Clinical, radiological, and histopathological characteristics**

Variables	Total	Recurrences , n(%)	p-value
Bony expansion			
Yes	50 (98.0)	10 (20.0)	**>0.99[b]**
No	1 (2.0)	0 (0.0)	
Tooth displacement			
Yes	25 (49.0)	5 (9.8)	**0.95[a]**
No	26 (51.0)	5 (19.2)	
Root resorption			
Yes	16 (31.4)	2 (12.5)	**0.387[a]**
No	35 (68.6)	8 (22.9)	
Radiological characteristics			
Unilocular	11 (21.6)	1 (9.1)	**0.391[b]**
Multilocular	35 (68.6)	9 (25.7	
Mixed	5 (9.8)	0 (0.0)	
Histopathological characteristics			
Follicular	45 (88.2)	10 (22.2)	**0.653[b]**
Desmoplastic	5 (9.8)	0 (0.0)	
Granular	1 (2.0)	0 (0.0)	

Note: [a] Chi Square Test, [b]Fischer Exact Test.

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