Systematic Review

Ameloblastomas vs recurrent ameloblastomas: a systematic review

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Abstract – Introduction: Ameloblastoma is an odontogenic tumour with high recurrence rate. The objective of the present study was to evaluate existing literature regarding clinical, radiographic, histopathologic features, treatment, and recurrence rate of ameloblastomas and compare it with features of recurrent ameloblastomas. **Materials and methods:** A systematic review was done based on the PRISMA statement. Search was performed in “Pubmed” database with search terminology “recurrent ameloblastoma”, “ameloblastoma recurrence” for articles published between 2010 and 2020. Data were extracted from full-text articles and discussed. **Results:** Out of 515 articles, 16 articles fulfilled the inclusion and exclusion criteria. Data was analysed in two sections. The first with 10 publications assessed features of ameloblastoma in general and their recurrence rate while the second section evaluated features of only recurrent ameloblastomas in 6 publications. There were 234 recurrences in 936 cases with recurrence rate of 23.50%. Male predominance was noted and mandible was commonly affected. Solid/multicystic ameloblastomas formed 74.5% of the tumours and unicystic formed 23.3%. The recurrence rate after conservative treatment was 64.9% and after radical treatment was 12%. **Conclusions:** The main factors for recurrence were multilobular ameloblastomas, follicular histopathology and conservative treatment.

Introduction

Ameloblastoma is a benign, locally aggressive, odontogenic tumor of epithelial origin [1]. Among the odontogenic tumours it accounts for the second most common tumour [2]. The incidence of ameloblastoma per year is 0.5 cases per million persons globally [3]. According to the proposed WHO (2017) classification, ameloblastoma is classified as conventional, unicystic, peripheral and metastasising types [2]. Ameloblastoma has high recurrence rate due to which opinions regarding the management of ameloblastoma have always been controversial [1,4].

Existing literature suggest recurrences of 55–90% with conservative treatment and 15–25% following a radical approach [4]. Patients present with serious aesthetic and functional impairment and need to undergo reconstructive surgeries with radical approach [4]. The reasons for recurrence can be multifactorial such as local invasiveness of the tumour, histological type, tissue components and the treatment approach [1,3]. The objective of the present study was to evaluate the literature regarding clinical, radiographic,

histopathologic features; treatment and recurrence rate of ameloblastomas and compare it to features of recurrent ameloblastomas.

Materials and methods

The present systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement which was shown in Figure 1. Literature search was carried out in “Pubmed” database with search terminology “recurrent ameloblastoma”, “ameloblastoma recurrence”. Data available from 2010 to 2020 was selected. English-language articles and human studies were chosen for the study. In addition to this, manual searches were performed of the reference lists of the articles and similar articles shown in the Pubmed database. This manual search was done in order to find other eligible articles for the review which was not available in the electronic database. Reviews, systematic reviews, meta-analysis, original research articles were selected for the present review. Case reports were excluded. Our search criteria resulted in 59 articles. As a first step (screening) studies which did not report on clinicopathological details of the ameloblastomas, management and

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Fig. 1. Flowchart of the study selection process.

recurrence of ameloblastoma were excluded by screening the titles and abstracts from the search results. The article selection for the present review was done by two independent reviewers. Any disagreements regarding the inclusion of articles between the reviewers were resolved by discussion. Studies included in other review articles or meta-analyses which were already selected for our review were excluded to avoid doubling of data. In the second step, authors evaluated 16 full-text articles meeting the inclusion and exclusion criteria. The following data were extracted from full-text articles: author, publication year, number of cases reported, age, gender, location, radiographic features, tumour type, treatment type, recurrence rate, time period of recurrence after treatment and contributing factors for recurrence. The data was tabulated and the results recorded.

Data obtained was discussed under two different sections. The first section includes clinical, radiographic, histopathological, management details and recurrence rate of the ameloblastomas in general. In the second section authors specifically analysed recurrent ameloblastomas.

Results

Our search resulted in a total of 515 articles, out of which only 479 articles were available with full text. After exclusion of case reports, a total of 59 articles were identified. Of these, 43 articles were excluded from the present review due to missing information regarding clinical features, radiographic features, histological type, treatment and recurrence. We further categorised selected 16 articles into two sections. First section assessed features of ameloblastoma in general with their recurrence rate and included 10 publications with a total of 1206 cases of ameloblastoma while the second section evaluated features of only recurrent ameloblastomas and consisted of six publications with 1115 ameloblastoma cases.

Section 1: Clinicopathological features of ameloblastoma and recurrence rate

A total of 1206 cases of ameloblastoma were identified in 10 publications. Summary of studies included in the review regarding ameloblastoma in general and the recurrence rate is shown in [Table I \[4–14\]](#).

Among the reported cases there were 234 recurrences in 936 cases with a recurrence rate of 23.50%. The average age was 43.34 ± 8.5 years. Since three of the studies (Zhang *et al.* [6], Seintou *et al.* [9], Bansal *et al.* [10] included subjects exclusively below the age of 18, they were excluded from average age calculation. Male predominance was noted with a male: female ratio of 1.2:1. The mandible had 89% (999) cases while the maxilla had 11% (121) cases. The mandible had 8-times more cases than the maxilla. Data regarding radiographic features was available in 494 cases. Multilocular cases accounted for 33.6% (166) while 62.7% (310) cases were unilocular. In the histopathological analysis, solid/multicystic ameloblastomas formed 74.5% (898) of the tumours and unicystic formed 23.3% (281). Among the data available for histopathological variant of solid/ multicystic ameloblastomas, 47.3% (98/207) were follicular and 28.5% (59/207) were plexiform ameloblastomas. Conservative treatment was done in 64.4% (421/654) and radical treatment in 35.6% (233/654). The studies had an average follow up of 6.2 years. The recurrence rate after conservative treatment was 64.9% (148/228) and after radical treatment was 12% (25/207). Comparison of clinicopathological features of ameloblastoma and recurrent ameloblastomas is presented in [Figure 2](#).

Section 2: Clinicopathological features of recurrent ameloblastoma

Six publications with 1115 ameloblastoma cases were identified reporting a total of 180 cases of recurrence. Summary

Table I. Clinicopathological features of ameloblastoma and recurrence rate.

Sl No	Author	No of cases	Avg Age in years	Gender	Location	Radiographic features	Diagnosis	Treatment	Avg time after T/t	Contributing Factors For Recurrence	Recurrence Rate
1	Hertog (2010) [5]	25 8/20 (5 year follow up)	34.4	Males-14 Females-11	Mandible-20 Maxilla-5		Follicular- 10 Plexiform- 7	Conservative- 17 Radical-8	5 years		53% Conservative-8/15 Radical-None
2	Zhang <i>et al.</i> (2010) [6]	Males –23 Females- 14 (all < 18)	14.8		Mandible (100%)	Multilocular 16 cases (16/37, 43.2%), Unilocular- 21 (56.8%)	Unicyclic –9 Solid-28 Follicular- 18 cases (48.7%), Plexiform – 4	Conservative –29 (78.4%, 7 unicyclic, 22 solid type) Radical –8 (21.6%, 6 solid and 2 unicyclic type) Enucleation (n 42/92, 45.7%)	3 months to 6 years	Conservative treatment	27% (9 –solid type, 1 – unicyclic type.)
3	Siar <i>et al.</i> (2012) [7]	340 18/135		Male-197 Female- 143	Mandible- (n 311/340, -91.5%), Maxilla 29	Multilocular radiolucencies (36.8%)	Unicyclic ameloblastomas- 95 (28%) SMA- 221 (65%) Desmoplastic ameloblastoma, 22 (6.4%) and peripheral ameloblastomas-2 (0.6%) Multicyclic –129 Unicyclic –98				18 /135 cases (13.3%) 6 UAs (26.1%) and 17 SMAs (73.9%)
4	Antonoglou (2014) [8]	35/229		NA	Mandible – 141 Maxilla-2 NA-86					Unicyclic- Radical-4% Conservative-17% Solid or multicystic Radical –8% Conservative-38% Conservative approach with enucleation or excision	
5	Seintou <i>et al.</i> (2014) [9]	15/ 51	12.7 (<16)	Males –25 Females-26	44(86.3%) Mandible	Root resorption, 36 (70.6%) were unilocular, three (5.9%) were multilocular,	Unicyclic ameloblastoma	Enucleation or enucleation- curettage- 31/51, 60.8%. Margin resection-3 (5.9%)	4.4 years		Recurrence: 29.4% (All cases were treated with enucleation or excision)
6	Bansal <i>et al.</i> (2015) [10]	1/39	13.6 (<18)	Males –26 Females-13	Mandible (97.4%);	Multilocular radiolucencies in 12/ 39 cases (30.7%) and unilocular radiolucencies in 23 (59.0%); one case (2.6%) showed a mixed radio-opaque/ radiolucent lesion	Solid variant-20 of 39 cases (51.3%) Unicyclic- 19 (48.7%) Follicular –4 Plexiform –16	Conservative surgical treatment (enucleation plus peripheral ostectomy) 18 (5 solid, 13 unicyclic) Resection (segmental or hemi-mandibulectomy and bone graft/ surgical plates) 15 (12 solid, 3 unicyclic) SMA-30(85.3%) radical treatment (surgical resection), 4 14.7% treated conservatively UA- cons 4(66.7%) rather than with surgical resection 2(33.3%).	11 years	Conservative treatment	2.6%
7	Singh T <i>et al.</i> (2015) [11]	6/41	43	Males –26 Females- 15	Mandible 33 (80.5%) compared to the maxilla- 8 (19.5%)		SMA most common subtype (34 cases), followed by the UA (6 cases).		8.5 years		SMA: 14.7% Conservative T/t –60% Radical T/t- 6.9% UA- 33.3%(2)

Table I. (continued).

Sl No	Author	No of cases	Avg Age in years	Gender	Location	Radiographic features	Diagnosis	Treatment	Avg time after T/t	Contributing Factors For Recurrence	Recurrence Rate
8	Almeida (2016) [4]	116/394	37	Males -179 Females-215	Mandible (90%)		Multicystic 66/116 were follicular ameloblastoma, 21/116 were plexiform ameloblastoma	Cons -245 Rad-149	Within 5 years		29.4% Conservative T/t - 98 (40%) Radical T/t-18(12%)
9	Milman (2016) [12]	16/23	56	Males-19 Females-4	Maxilla with orbital extension		Follicular (45%) and plexiform(41%) Basal cell like(9%) and mixed (4.5%)	Conservative T/t -14 Radical T/t -7	3.8 years		Recurrence-70% Conservative T/t-57% Radical T/t-29%
10	Laborde A et al. (2017) [13]	9/27	46.3 ± 17.4	17 Males-17 Females-7	Mandible: 20 patients (74.1%) Maxilla 7	-	Follicular (29.6%) and plexiform (22.2%) MC-10 UC-15	Recurrence: Conservative treatment 22 and Radical treatment 14 case	--	Conservative treatment	33%

Avg: Average; T/t: treatment; UA: Unicystic ameloblastoma; SMA: Solid multicystic ameloblastoma; MC: Multicystic; UC: Unicystic; M:F-Male:Female; NA: Not available.

of studies included in the review regarding the recurrent ameloblastoma is shown in Table II [14–19]. The average age was 36.18 ± 5.47 years. Male predilection was noted with the Male: Female ratio being 1.2:1. The mandible had 84.7% (148) cases while the maxilla had 15.3% (27) cases. Around 6 fold higher cases in the mandible when compared to the maxilla with a ratio of 5.6:1 was observed. Radiographic features were reported in only three publications (total cases 120) and were predominantly multilocular (70%) while unilocular cases accounted for 30%. Solid or multicystic ameloblastomas were more common with 82.7% (125) cases while unicystic ameloblastomas made up 17.2% (26) cases. Among the solid/multicystic ameloblastomas, 65.3% were of the follicular variant. Conservative management was adopted in 61.2% cases and 38.8% cases underwent radical management. The main contributing factors identified were conservative treatment, tumour size larger than 6 cm with invasion of soft tissues or adjacent anatomical structures, rupture of basal cortical bone, radiographically multilocular lesions and histologically follicular tumours. Unicystic ameloblastomas with intramural proliferation had higher incidence of recurrence. The reported recurrence rates in the studies ranged from 9.78% to 29%.

Discussion

Management of ameloblastoma has always been a difficult decision for the surgeon with both conservative and radical methods having their advantages and disadvantages [3,20]. Conservative surgery preserves tissues and decreases morbidity and is preferred in younger individuals but is associated with higher recurrence rate. Radical surgery involves tumor resection with wide bone margin and is associated with decreased recurrence but higher morbidity and need for surgical grafts and prosthetic rehabilitation [3].

In the analysis of recurrent ameloblastomas, we found that multilocular radiographic appearance, follicular histopathology and conservative treatment were risk factors for recurrent ameloblastoma. Among the analysed cases of ameloblastoma, conservative management was associated with significantly increased recurrence. Multilocular lesions were associated with higher recurrence rate although majority (62%) of analysed cases were unilocular ameloblastomas.

The mean age of subjects in the study was 43.34 ± 8.5 years. This is higher than that reported in previous studies. Krishnapillai *et al.* [15] reported a mean of 30 years with highest cases in 3rd decade while More *et al.* reported a similar mean age of 43.5 years. Hasegawa *et al.* [21] reported a mean age of 28.2 years. Almeida *et al.* [4] reported a mean age of 38 years which is similar to the present study. The mean age is reported as different in different parts of the world where the fifth and sixth decades have higher incidence in Europe and North America while the peak incidence in Asia is between third and sixth decades [22]. Overall prevalence worldwide is in the third decade [22]. One reason for the higher reported age of the present study could be because we excluded those manuscripts

AMELOBLASTOMA VS RECURRENT AMELOBLASTOMA

Section 1: Clinicopathological features of Ameloblastoma and Recurrence Rate

Clinical features	Radiographic features	Histopathological features	Treatment and recurrent rate
<ul style="list-style-type: none"> • Average age - 41 years • Male: female ratio of 1.2:1 • Mandible 89%, Maxilla 11% 	<ul style="list-style-type: none"> • Multilocular 33.6% • Unilocular 62.7% 	<ul style="list-style-type: none"> • Solid/Multicystic 74.5% • Unicystic 23.3% 	<ul style="list-style-type: none"> • Conservative treatment 64.4% • Radical treatment 35.6% • Recurrence rate after conservative treatment -64.9% and after radical treatment - 12%

Section 2: Clinicopathological features of Recurrent Ameloblastoma

Clinical features	Radiographic features	Histopathological features	Treatment
<ul style="list-style-type: none"> • Average age - 35 years • Male: female ratio of 1.2:1 • Mandible 84.7% • Maxilla 15.3% 	<ul style="list-style-type: none"> • Multilocular 70% • Unilocular 30% 	<ul style="list-style-type: none"> • Solid/Multicystic 82.7% • Unicystic 17.2% 	<ul style="list-style-type: none"> • Conservative management - 61.2% cases • Radical management- 38.8% cases

Fig. 2. Comparison of clinicopathological features of ameloblastoma and recurrent ameloblastomas.

which only included subjects below 20 years of age. Slight male predilection was noted in the current study which is similar to that reported by Krishnapillai *et al.* [15] and Hendra *et al.* [23].

In the analysis of recurrent cases, the average age was 36.18 ± 5.47 years. This is similar to the average age of occurrence of ameloblastomas and implies that recurrences occur within a few years of treatment. Arotiba *et al.* [17] and Milman *et al.* [12] reported highest recurrence in the third and fourth decade. Recurrent cases showed male predilection with male female ratio similar to that of ameloblastomas.

Mandibular predominance has been noted in most studies similar to ours where the mandible was involved eight times as often as the maxilla. This is similar to the results by Fregnani *et al.* [14] and Hong *et al.* [24].

Among the recurrent ameloblastomas, cases were 6 times higher in the mandible. This is probably because ameloblastomas occur mainly in the mandible.

In the present analysis, we found higher proportion of unilocular ameloblastomas when compared to multilocular. This is in contrast to Cadavid *et al.* [25] and More *et al.* [26] who

reported higher incidence of multilocularity. This difference might be due to the fact that not all included manuscripts mentioned the radiographic features.

Among recurrent ameloblastomas, 70% had multilocular appearance while unilocular appearance was seen in 30%. Thus, recurrences appear to be higher in multilocular lesions. This may be due to incomplete surgical removal of microcysts and daughter cysts.

Approximately three fourth cases were of the solid/multicystic variant with the follicular type being the commonest followed by plexiform variant. Fregnani *et al.* [14] reported that solid ameloblastomas were more prevalent than unicystic. Cadavid *et al.* [25] mention that the plexiform and follicular variants are the most common while Arotiba *et al.* [17] reported that the follicular type was commonest.

Among the recurrent ameloblastomas, solid/multicystic ameloblastomas predominated with 82% and the follicular variant was the most common histopathologic type followed by unicystic ameloblastomas. This suggests that multicystic ameloblastomas are more aggressive than unicystic. Similar

Table II. Clinicopathological features of recurrent ameloblastoma.

Sl No	Author	No of cases	Avg Age in years	Gender	Location	Radiographic features	Diagnosis	Initial Treatment	Avg time after Treatment	Contributing Factors for Recurrence	Recurrence Rate
1	Fregmani <i>et al.</i> (2010) [14]	27/ 121	33.2	Males- 10 (18.5%) Females –15 (25.4%)	Mandible 24 (23.5%) Maxilla 1 (9.1)2-not known	Multilocular 18 (29.0) Unilocular 6(13.3%)	Follicular in 12 cases (31.5%); Unicystic with mural infiltration in 2 cases (28%)	Bone curettage + cryotherapy 15 (31.2%) Bone curettage 4 cases (20%) Segmental resection 8 cases (17%)	9.7 years	Radiographically multilocular lesions, ruptured basal cortical bone and histologically follicular tumours	22.3%
2	Krishnapillai R <i>et al.</i> (2010) [15]	9/73	43.3	Males (55.55%)	Molar ramus mandible (66.66%)	Multilocular (55.55%)	Follicular (66.66%) followed by unicystic ameloblastoma (22.22%) Unicystic- 5	Data not available	between 10 months and 16 years	Unicystic cases- intramural proliferation Conservative treatment	13.3%
3	Hertog <i>et al.</i> (2011) [16]	18	26.5 (range 12–53)	Male:8 Female: 10	Mandible 15 Maxilla 3	-	Follicular ameloblastoma	Enucleation 18	10.5 year follow up	Inadequate Surgical removal ; seeding of tumour cells during surgery	-
4	Arotiba GT <i>et al.</i> (2012) [17]	30	37±13.1	18 Males (60%) Females12 (40%)	Mandible 24(80%) and maxilla 6(20%)	-	Follicular ameloblastoma	Enucleation 9 cases (30%) Hemimandibulectomy and surgical resection 6 cases each –20%	8.12±5.29 years	Not reported	
5	Infante-Cossio P <i>et al.</i> (2013) [18]	9/31	36.1	2 Male and 7 Female	Mandible	--	Multicystic –6 Unicystic –3	Curettage in 5 cases, and enucleation and curettage in 4 cases	32 months	Conservative Treatment	29%
6	Yang R <i>et al.</i> (2017) [19]	87/890	35	54 Males (62%) 33 Female (37.93%)	Maxilla –17, Mandible- 70	Unilocular-29% Multilocular-70%	Unicystic –14 Desmoplastic-10 Multicystic-57 Peripheral-6	Aggressive curettage-49, Resected with margin –38	34.0 months	Tumor larger than 6 cm and invasion to soft tissues or adjacent anatomical structures	9.78%

results were reported by Hendra *et al.* [22,23]. Hong *et al.* [24] mention that follicular, granular cell and acanthomatous ameloblastomas are associated with the highest recurrence and need more radical treatment while plexiform and desmoplastic types have low recurrence. This is similar to the present results. Follicular types are more often multilocular ameloblastomas while unicystic ameloblastomas tend to be unilocular [24].

Conservative treatment includes enucleation, marsupialization followed by enucleation, enucleation with bone curettage without a safety margin while radical treatment includes resection with a bone margin, en bloc resection, marginal mandibulectomy and segmental resection or maxillectomy [21].

Conservative management was done in 64.4% cases in the present study. The recurrence rate after conservative treatment was 64.9% and after radical treatment was 12%. Thus, recurrence after conservative treatment was markedly higher than after radical treatment. This is similar to the study by Laborde *et al.* [13] where conservative treatment was associated with a recurrence rate of 90.9%. Other studies have also reported similar results [5,24]. Thus our results support the hypothesis that radical treatment is associated with lower risk of recurrence. Fregnani *et al.* [14] reported that a ruptured basal cortical bone was associated with three times increased risk of recurrence. A systematic review of treatment of unicystic ameloblastomas found that resection was associated with the lowest risk for recurrence followed by enucleation and Carnoy's solution and simple enucleation [27].

The average period of follow up was 6.2 years. Recurrences in ameloblastoma can occur as long as 10–15 years after treatment [16]. Our results showed that most recurrences occurred within 5 years. The reported recurrence rates in the studies ranged from 9.78% [6] to 29% [18]. Among the evaluated studies, we found a recurrence rate of 23.5%.

Hong *et al.* [24] suggest that resection with safety margin is the best management for ameloblastomas with conservative management reserved for patients below 10 years and unicystic or plexiform ameloblastomas. Hendra *et al.* [22] and Bansal *et al.* [10] recommended conservative management only to avoid functional psychological and esthetic side effects in children. Antonoglou *et al.* [8] in an analysis of conservative versus radical treatment found that radical surgery was associated with decreased recurrence in a 5-year follow up. Almeida *et al.* [4] recommend bone resection for all cases diagnosed with multicystic ameloblastoma.

There were a few limitations in the present study. Data was extracted from a single database only. This could have led to selection bias. Further, all articles did not report all clinical and radiographic features thereby limiting the data availability.

Prospects: In the present study, ameloblastoma recurrence was associated with multilocular ameloblastomas, follicular histopathology and conservative treatment. Future research should concentrate on management strategies for these specific types of ameloblastoma in order to reduce the incidence of tumour recurrence and its associated morbidities.

Conclusion

Highlight of present review is features of ameloblastomas in general and recurrent ameloblastomas being analysed and presented separately. Our study concluded that the clinico-pathologic features of ameloblastomas in general were similar to recurrent ameloblastomas. The main contributing factors identified for recurrence were multilocular ameloblastomas, follicular histopathology and conservative treatment methods. Based on the present systematic review, radical management is recommended for solid/multicystic ameloblastomas in order to decrease the recurrences. However, various factors such as age of the patient, size of lesion, soft tissue involvement and histological parameters have to be taken into consideration when deciding management of ameloblastomas. In such cases, regular follow up is mandatory.

Conflicts of interest

The authors declare no conflict of interest.

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Ethical approval

Ethical approval was not required.

Informed consent

This article does not contain any studies involving human subjects.

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