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Ameloblastoma: Biological Profile of 3677 Cases

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Available literature on ameloblastoma of the jaw was reviewed, including publications from 1960 to 1993, and compared to the latest larger review, published by Small and Waldron in 1955.

The average age of patients with ameloblastoma is 36 years. In developing countries ameloblastomas occur in younger patients. Men and women are equally affected. Women are 4 years younger than men when ameloblastomas first occur, and the tumours appear to be larger in females. Dominant clinical symptoms such as painless swelling and slow growth are non-characteristic. The ratio of ameloblastoma of the mandible to maxilla is 5 to 1. Ameloblastomas of the mandible occur 12 years earlier than those of the maxilla. Ameloblastomas occur most frequently in the molar region of the mandible. In Blacks, ameloblastomas occur more frequently in the anterior region of the jaws. Radiologically, 50% of ameloblastomas appear as multilocular radiolucent lesions with sharp delineation. Histologically, one-third are plexiform, one-third follicular; other variants such as acanthomatous ameloblastoma occur in older patients. Two percent of ameloblastomas are peripheral tumours. Unicystic ameloblastomas occurring in younger patients have been found in 6%.

Detailed data on 345 patients with ameloblastoma were evaluated for clarification of therapeutic approaches. Chemotherapy and radiation seem to be contraindicated. Ameloblastomas of the maxilla should be treated as radically as possible, ameloblastomas of the mandible should also be treated radically. However, ameloblastomas which radiologically appear as unilocular lesions may be treated conservatively (enucleation, curettage), whenever all areas of the cystic lumen are controllable intraoperatively. Unicystic ameloblastomas occurring in patients 15 years younger than those with multisystic ameloblastoma may be treated conservatively except in cases with invasion of epithelium into the cyst wall. Different recurrence rates have been found for histological variants of the ameloblastoma. Follicular ameloblastomas appear to recur more often than the plexiform type. Unicystic ameloblastomas reveal lower recurrence rates than "non-unicystic" ameloblastomas. The peripheral type of ameloblastoma may be excised, since conservative therapy results in low recurrence rates. Postoperative follow-up is most important in the therapy of ameloblastoma, because more than 50% of all recurrences occur within 5 years postoperatively.

Keywords: ameloblastoma, biological data, recurrence, therapy

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INTRODUCTION

THE AMELOBLASTOMA is probably one of the most controversial neoplasm of the facial skeleton. In 1868 Broca first described this tumour [1]. Churchill [2] in 1934 coined the term ameloblastoma.

This relatively rare epithelial odontogenic tumour has been discussed in two larger reviews [3, 4] and has been the object of numerous case reports and smaller reviews. Robinson [3] reviewed 379 cases of the literature, followed by Small and Waldron [4] who evaluated 1036 cases including the material already published by Robinson [3].

It was the purpose of the present review to: (1) produce an updated bioprofile of ameloblastoma using published data from both case reports and minor reviews from 1960 to 1993; (2) compare the present findings with those of the review by Small and Waldron [4]; (3) identify prognostic parameters with relevance to the therapy of ameloblastomas.

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MATERIALS AND METHODS

Case data

The present review includes publications in English, German, French, Italian, Portuguese, Korean and Japanese (1960–1993). A total of 1500 publications were evaluated, in

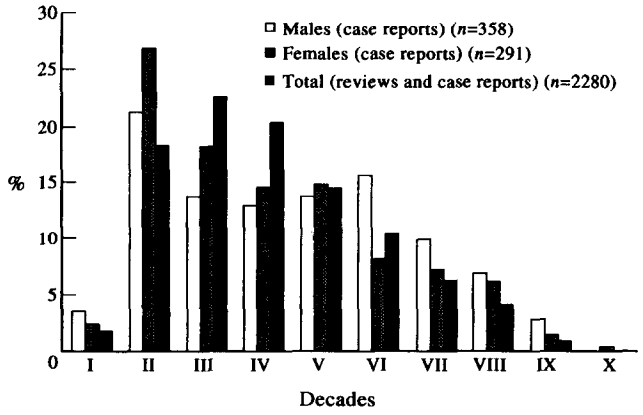

Fig. 1. Age distribution (%).

which data on 4335 ameloblastomas were given in some detail. Of these 3642 cases were reported in minor reviews [5–252], 693 case were published as case reports and the diagnosis was verified in the 397 cases where histological findings were described [5–198]. The histologic evaluation was based on the cytologic criteria for ameloblastomas produced by Vickers and Gorlin [196]. In addition, the criterion for accepting reported cases was that of a histopathological appearance which the authors believed was characteristic of ameloblastoma or cases published by authors of acknowledged capabilities. In 658 cases duplication could not be excluded so that out of 4335 cases of ameloblastoma 3677 could be evaluated. These included 693 case reports [5–198] and 2984 cases in reviews [182–252]. (There is some overlap between references of case reports and reviews, because in some reviews own cases were included.) Data from the 1036 cases published by Small and Waldron [4] and Robinson [3] were used for comparison.

Data for case reports and review cases were computed separately. The following variables were studied: (1) age; (2) sex; (3) race; (4) country of origin; (5) relative frequency (based on reviews); (6) symptoms; (7) localisation; (8) size of tumour; (9) radiography; (10) histology; (11) therapy and (12) recurrence.

Evaluation of data

Data were computed using an IBM compatible PC and the SPSS/PC+ software program. The chi-square test was used for the CROSSTABS procedure and the *t*-test was applied for independent spot checks. A distribution level of 5% was considered significant; a distribution level of 10% was considered to represent a tendency. The average and the mean were also determined. A statistical analysis was only possible on data derived from case reports ($n=693$). Reviews representing averages could only be compared to each other and to the total number of cases represented in this study.

RESULTS

Age distribution

Details for age were retrieved from 2280 cases (review [$n=1630$], case reports [$n=650$]). The median age was 35 years with a range of 4–92 years. The average age of the case reports was 37.4 years and from reviews 35.4 years. The average age including reviews and case reports was 35.9 years. Figure 1 shows the age distribution for males and females. The average age of males of 39.2 years was significantly different ($P<0.05$) from that of females (35.2 years). When taking the case reports alone the age distribution for males and females showed a somewhat higher frequency in the second decade of life (Fig. 1). However, if all cases of ameloblastoma ($n=2280$) were combined the highest frequency fell in the third decade.

Sex distribution

The distribution among males and females were almost identical for both reviews and case reports: 47% females and 53% males (1:1.14) (Table 1).

Racial and geographic distribution

Table 2 shows the distribution of ameloblastomas among Caucasians, Blacks and people of Asian descent (Chinese, Indian Indians, Japanese, Malays and Thai). Relative frequency ranged between 24.8% (Caucasians) and 38.4% (Asians). The average age of Blacks was 28.7 years compared to 39.9 years in Caucasians and 41.2 years in Asians. These differences were highly significant ($P<0.001$).

Ameloblastomas have been reported from almost all parts of the world (Fig. 2) with a higher number of cases being reported from Japan ($n=539$), Nigeria ($n=441$) and U.S.A. ($n=845$). Few cases were reported from Australia ($n=2$) and South America ($n=15$). A total of 1609 cases were reported from developing and 2062 cases from industrialised countries (reviews and case reports combined). The average age of patients with ameloblastoma from developing countries was 27.7 years ($n=1102$) compared to patients from industrialised countries, where the average age was 39.1 years ($n=542$). The difference between these was highly significant ($P<0.001$). When comparing the average age of patients with ameloblastoma in the different continents the following figures were found: United States 39.0 years ($n=744$); South America 13.2 years ($n=11$); Europe 42.3 years ($n=309$); Africa 30.4 years ($n=601$); Asia 35.2 years ($n=890$), and Australia (including New Zealand and Papua New Guinea) 29.5 years ($n=28$). Some of these figures (South America, Australia) are probably not reliable due to the small number of reported cases.

Relative frequency of ameloblastoma

The relative frequency of ameloblastomas when compared to other odontogenic tumours varied between 11 and 92% [185, 198, 209, 220, 228, 230, 237, 238, 252, 253]; 13–43% of all tumours of the mandible were ameloblastomas [22, 220, 230]. If jaw tumours (excluding cysts) were considered, 13–54% consisted of ameloblastomas [187, 202, 208, 209, 231, 237]. Some authors have stated that 6–25% of oral tumours constitute ameloblastomas [203, 210, 228, 247, 252]. The percentage of ameloblastomas in oral biopsies lies between 0.04% in Caucasian Americans [240], 0.33% in black Americans [240] and 5.28% in Nigerians [240] or 6.7% in Thai [245]. Only 0.02–0.7% of entries in general pathology biopsies were ameloblastomas [137, 203, 225, 238, 239, 246, 252].

Symptoms

Of 276 case reports 222 reported a bone hard swelling as the most common clinical symptom of ameloblastoma. When case reports and reviews were combined the most frequent clinical findings were swelling ($n=701$), pain ($n=187$), delayed tooth

Table 1. Sex distribution

	Case reports	%	Reviews	%	Total	%
Males	371	54.5	1266	53.0	1637	53.3
Females	310	45.5	1124	47.0	1434	46.7
Not specified	12		594		606	
Total	693		2984		3677	

Table 2. Occurrence of ameloblastomas in Caucasians, Blacks and Asians

	Case reports	%	Reviews	%	Total	%
Caucasians	281	45.3	393	18.9	674	24.8
Blacks	137	22.1	787	37.7	924	34.4
Asians	191	30.8	849	40.7	1040	38.4
Others	11	1.8	56	2.7	67	2.4
Not specified	73		899		972	
Total	693		2984		3677	

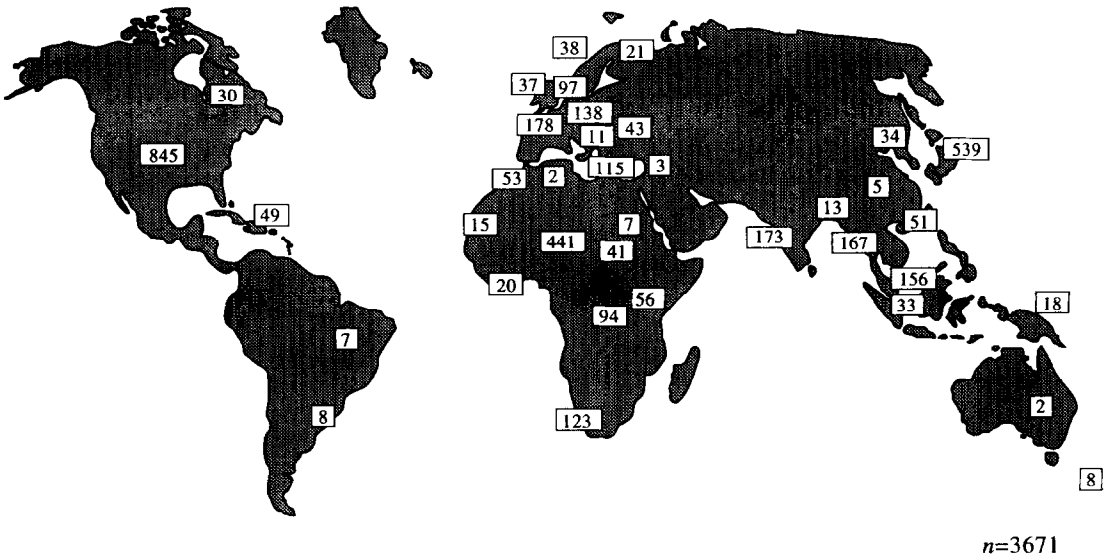

Fig. 2. Geographic distribution of published cases of ameloblastomas.

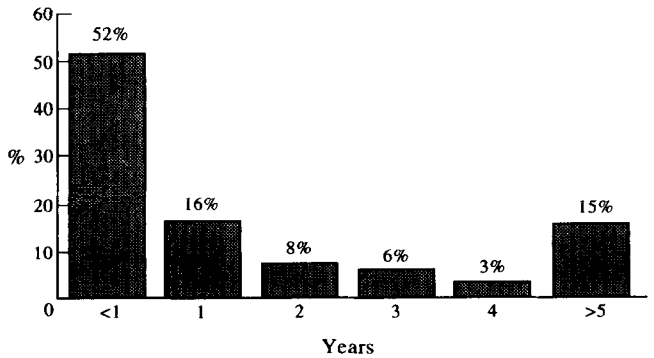

Fig. 3. Duration of symptoms until first diagnosis ($n=918$).

eruption ($n=119$), ulceration ($n=90$), mobility of teeth ($n=68$) and displaced teeth ($n=57$).

The duration of symptoms until initial diagnosis is shown in Fig. 3. Duration of symptoms was detailed for 918 cases. For case reports ($n=198$) the average duration was 27 months. Median duration was 6.5 months and the maximum was 40 years. Duration of symptoms for maxillary ameloblastomas ($n=51$) was 22 months, for mandibular ameloblastomas ($n=142$) 13 months. Patients from developing countries ($n=67$) had an average duration of symptoms of 32.6 months, while those from industrialised countries ($n=130$) reported after 24.5 months. In women ($n=94$) the diagnosis was made after 32 months, in men ($n=104$) after 23 months. In Caucasians ($n=84$) the tumour was diagnosed after 22 months, in Blacks ($n=52$) after 29 months, and in Asians ($n=50$) after 38 months. No statistically significant differences were found.

Localisation

The mandible was affected in 2444, the maxilla in 454 cases. The ratio between maxilla and mandible was 1:5.4. When case reports were evaluated the ratio between maxillary ($n=185$) and mandibular ($n=404$) tumours was 1:2.2. This difference

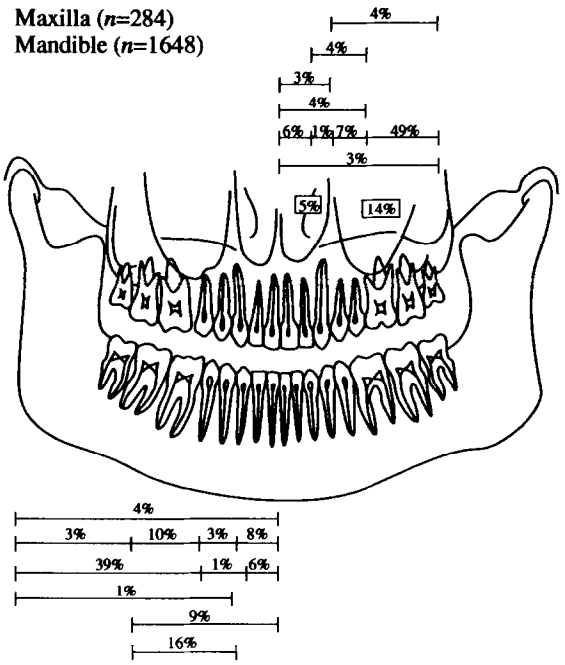

Fig. 4. Localisation of ameloblastoma ($n=1932$) (bars represent size of lesions).

is due to the fact that in case reports maxillary tumours were more often reported. Figure 4 shows the localisation of ameloblastomas. The ratio of ameloblastomas occurring on the right compared to the left side was 1:1.07. In the maxilla the molar region was affected in 49%. The maxillary sinus was involved in 14% and the nasal cavity in 5%. In the mandible 74% of the tumours were not limited to a single group of teeth; 39% of ameloblastomas of the mandible occurred in the molar and ascending ramus area.

Figure 5 shows the localisation according to race. In 21.7% of Black patients the incisor region of the mandible was significantly more frequently affected than in Caucasians (11.7%) and Asians (10.4%) ($P<0.05$). For the mandibular molar area this relation was reversed (Caucasians 40.6%, Asians 44.8%, Blacks 29.0%). In Asians the ramus region was less often affected (16.4%) compared to Caucasians (28.9%) and Blacks (29.0%). It was interesting to note that in Blacks the number of ameloblastomas involving both sides of the jaw was 18.2% compared to 5.2% in Caucasians and 5.8% in Asians ($P<0.01$). Ameloblastomas of the mandible ($n=121$) found in Blacks were more frequent compared to those seen in Caucasians ($n=252$) (84% as against 72% [$P<0.001$]).

There appears to be a statistical significance ($P<0.05$) when localisation and sex were cross-tabulated. In female patients the incisor region (16.2%) and ramus of the mandible (22.1%) was more often affected than in men (incisor 10.8%, ramus 14.8%). In men the premolar region (16.1%) as well as the maxillary sinus (10.6%) were more frequently affected than in female patients (premolar 8.8%, maxillary sinus 5.9%), whereas the molar region was affected equally in men (34.9%) and women (36.8%). Ameloblastomas of the maxilla compared to the mandible were found to occur with equal frequency in women (1:2.4) and men (1:2.0). The average age of patients with tumours of the maxilla was 47.0 years ($n=171$) compared to tumours of the mandible with an average age of 35.2 years ($n=393$) ($P<0.001$).

Size of tumour

The size of tumour was stated in 129 cases and measured to be on average 4.3 cm. Median size was 3.0 cm, and maximum 24 cm. In women ($n=60$) the average tumour size was 5.2 cm compared to 3.6 cm in men ($n=68$) ($P<0.05$). Ameloblastomas in patients from developing countries ($n=15$) had an average size of 6.3 cm compared to those of industrialised countries ($n=110$) with 4.2 cm ($P<0.01$). In Black patients the average tumour size was 6.6 cm ($n=16$), in Caucasians 3.7 cm ($n=56$) ($P<0.05$). In Asians the average tumour size was 4.8 cm ($n=46$).

Radiography

One thousand two hundred and thirty-four radiographic descriptions were evaluated (case reports $n=377$, reviews $n=857$). Unilocular appearance was observed in 51.1%, multilocular or multicystic appearance was seen in 48.9%. Histologically verified unicystic ameloblastomas were included ($n=102$). Frequent radiographic findings were: embedded tooth ($n=107$), root resorption ($n=47$) and undefined borderline ($n=45$). Other radiographic diagnoses were: cupping ($n=5$) and opacity ($n=7$), the former representing peripheral ameloblastomas, the latter desmoplastic ameloblastoma. Of 52 detailed descriptions of the embedded tooth, 42 represented third molars. Ameloblastomas with embedded teeth were more frequently seen in younger patients with an average age of 20.8 years ($n=67$). The oldest patient was 62 years old, however, only 13 patients were older than 30 years. In 72% of ameloblastomas with embedded teeth a unilocular appearance comparable to the radiological appearance of follicular cysts was found. It was of interest that unilocular ameloblastoma including histologically verified unicystic ameloblastomas occurred in patients with an average age of 26.1 years ($n=167$) compared to a multilocular appearance with patients of an average age of 39.3 years ($n=88$) ($P<0.001$). Excluding unicystic ameloblastomas the average age of unilocular ameloblastoma was 29.0 years ($n=90$) and of multilocular ameloblastoma 40.8 years ($n=81$) ($P<0.001$). Histologically verified unicystic ameloblastoma represented either multilocular or unilocular radiological appearance, but there was no difference in average age of patients with unilocular (22.8 years, $n=77$) and multilocular unicystic ameloblastomas (22.6 years, $n=7$).

Histological classification

The follicular (33.9%), plexiform (30.2%) and acanthomatous (11.3%) variants were the most frequently encountered apart from a mixed histological type where more than one histological subtype was seen in the same lesion (15.5%). The histological types of single case reports and reviews excluding unicystic ameloblastoma are shown in Table 3. There were no differences between histological types related to maxilla and mandible. When compared to localisation the plexiform and follicular ameloblastoma showed a tendency to occur more frequently in the molar–ramus region of the jaw (plexiform 61.2%, follicular 58.5%) than in the incisor-canine region (plexiform 10.6%, follicular 20.8%), whereas ameloblastomas of the acanthomatous variant were more frequently located in the incisor–canine region (42.8%) than in the molar–ramus region (31.5%). It was noteworthy that desmoplastic ameloblastomas were often seen in the maxillary sinus (25.0%) and

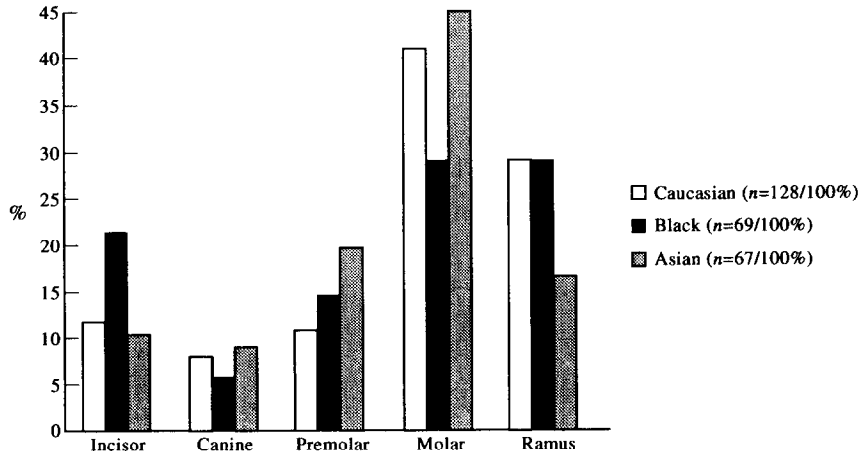

Fig. 5. Localisation (lower jaw) according to race.

Table 3. Histologic variants of ameloblastoma (excluding unicystic ameloblastoma)

	Case reports $n=397$	%	Reviews $n=1210$	%	Total $n=1593$	%
Plexiform (p)	129	32.5	356	29.4	485	30.2
Follicular (f)	112	28.2	433	35.8	545	33.9
Granular cell (g)	17	4.28	39	3.2	56	3.5
Basal cell (b)	8	2.02	14	1.2	22	1.4
Acanthomatous (a)	48	12.1	134	11.1	182	11.3
Desmoplastic (d)	9	2.27	14	1.2	23	1.4
Keratoameloblastoma (k)	2	0.5	0	0	2	0.1
Ameloblastoma of mixed histologic type	72	18.1	177	14.6	249	15.5
Others	0	0	43	3.5	43	2.7
Not specified	296		1774		2070	
Total	693		2984		3677	

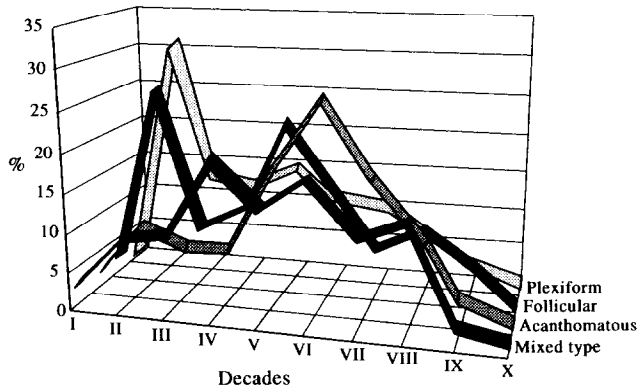

Fig. 6. Age distribution of some histological variants of ameloblastoma.

incisor segments (62.5%). Figure 6 shows the age distribution in relation to the most common histological subtypes. Excluding unicystic ameloblastomas the plexiform ameloblastoma (average age 39.1 years) was seen in significantly younger patients compared to the acanthomatous variant (51.0 years), the basal cell ameloblastoma (53.7 years) and ameloblastomas of mixed histological type (37.0 years) ($P<0.05$ and $P<0.01$). There was also a significant difference between the follicular type (41.0 years) and the acanthomatous ameloblastoma ($P<0.05$). The average age of patients with desmoplastic ameloblastoma was 45.4 years, of granular cell ameloblastoma 45.4 years and of keratoameloblastoma 52.0 years. It was obvious that the plexiform and follicular types occurred more frequently in the second decade of life (Fig. 6). There were no significant differences between either sex or race and histological subtypes.

Table 4. Treatment modalities for ameloblastomas

Therapy	Case reports $n=441$	Reviews $n=1189$	Total $n=1630$	%
Conservative	260	503	763	46.8
Conservative surgery	240	480	720	
Radiation	20	22	42	
Chemotherapy	0	1	1	
Radical surgery	177	667	844	51.8
No therapy	4	19	23	1.4
Not specified	252	1795	2047	
Total	693	2984	3677	

Therapy

Table 4 shows the different therapeutic approaches for treatment of ameloblastomas irrespective of histologic types discussed in the literature. Conservative surgical therapy

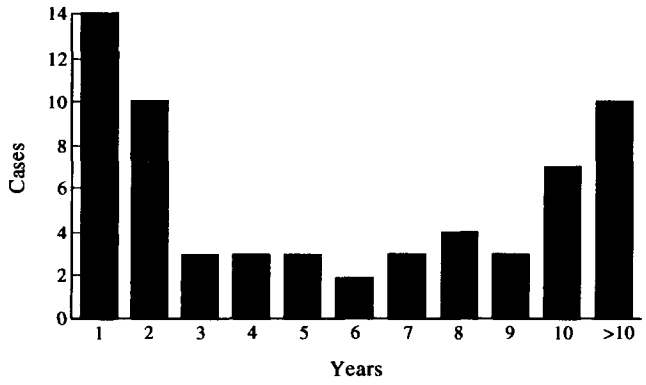

Fig. 7. Period until manifestation of recurrence ($n=62$).

Table 5. Frequency of recurrences in relation to treatment modalities (case reports)

Recurrence	Radical ($n=141$)	Conservative ($n=186$)	Total ($n=327$)
Yes	17.7%	22.6%	20.5%
No	82.3%	77.4%	79.5%

included enucleation, curettage, electrocautery, excision and marsupialisation. Radical surgery included approaches such as marginal resection, segmental resection and total resection of the jaw (maxilla/mandible) with wide margins.

Recurrence rates

Follow-up was described in only 345 case reports and in 71 patients the tumour recurred (20.6%). In 289 cases the period of follow-up was stated and was an average of 4.6 years with a median of 3 years and a maximum of 33 years. 227 patients did not develop recurrence and the average period of follow-up was 4 years with a median of 3 years and a maximum of 29 years. Considering a median of 3 years it appears that the necessary minimal duration of follow-up of 5 years was not always the norm. The period until manifestation of recurrence was noted in 62 cases. Recurrences developed at an average time interval of 7.2 years. The median was 5 years, maximum 33 years. The development of recurrences over time is shown in Fig. 7. When comparing recurrence rates for maxillary and mandibular ameloblastomas in relation to localisation, no significant differences were found.

Recurrence rates in relation to therapy

Table 5 shows the recurrence rates in relation to therapy (case reports). There was no marked difference between the recurrence rate after radical therapy (17.7%) and conservative therapy (22.6%). However, when therapy results of case reports and review data were combined a recurrence rate of 34.7% was found for a conservative approach ($n=622$) and 17.3% for radical therapy ($n=484$). Generally, it can be stated that recurrence rates in reviews were very diverse. For curettage or enucleation the recurrence rate varied between 20 and 90% [192, 236]. While there was no significant difference in recurrence rates for mandibular tumours, when conservative and radical therapy were compared there was a difference ($P<0.1$) for ameloblastomas of the maxilla. After conservative therapy, maxillary ameloblastomas recurred twice as often as after radical therapy. Of interest was that after radical therapy recurrences occurred only after 11.1 years ($n=23$) compared to conservative therapy where tumours recurred after 4.8 years ($n=36$) ($P<0.01$).

Table 6. Frequency of recurrences in relation to histology

Histology	n	Recurrence rate (%)
Plexiform (p)	36	16.7
Follicular (f)	44	29.5
Granular cell (g)	6	33.3
Basal cell (b)	2	50.0
Acanthomatous (a)	22	4.5
Desmoplastic (d)	7	0
Ameloblastoma of mixed histologic type (mix)	28	14.3
Unicystic	73	13.7

Recurrence rates in relation to histological diagnosis

A histological diagnosis was available for 166 patients who developed recurrence. There was a difference between the plexiform (recurrence rate 16.7%) and the follicular (29.5%) variant ($P<0.1$) between the follicular and the acanthomatous (4.5%) type ($P<0.01$) as well as between follicular and mixed (14.3%) ameloblastomas ($P<0.1$). The recurrence rates of follicular (29.5%) and unicystic (13.7%) ameloblastomas were significantly different ($P<0.05$) (Table 6).

Peripheral ameloblastomas recurred in 9.1% ($n=33$) compared to central ameloblastomas (25.6%) ($n=68$) ($P<0.5$). Unicystic ameloblastomas recurred in 13.7% ($n=73$) compared to "non-unicystic" ameloblastomas with a recurrence rate of 22.7% ($n=278$) ($P<0.1$).

Peripheral ameloblastoma

In the present review of 3677 ameloblastomas where tumour site was stated, only 73 were classified as peripheral ameloblastomas (2.0%) (63 case reports [137–182] and 10 from reviews [137, 182, 198, 216, 243, 246]). Central ameloblastomas occurred in younger patients of an average age of 35.6 years ($n=324$) while peripheral ameloblastomas occurred in patients with an average age of 51.0 years ($n=61$). This difference was statistically highly significant ($P<0.001$). The mandible:maxilla ratio for peripheral ameloblastomas was 5:1. Peripheral ameloblastomas occur in the incisor–premolar region (64.8%) twice as often as in the molar–ramus region (35.2) whereas in central ameloblastomas the molar–ramus region (66.5%) was affected twice as often as the incisor–premolar region (33.5%) ($P<0.01$). Radiographically no radiological changes were found in 28 instances ($n=36$); however, in five cases "cupping" with peripheral bone erosion was observed. When comparing histological subtypes of central and peripheral ameloblastomas, respectively, significant differences were found ($P<0.05$). Peripheral ameloblastomas ($n=54$) showed more acanthomatous subtypes (16.7%) compared to 8.6% of the central type of ameloblastoma. Mixed histological variants were more frequently seen in peripheral

ameloblastomas (44.4%) compared to 17.3% of the central type. Follicular and plexiform variants were significantly rarer in peripheral ameloblastomas compared to the acanthomatous and the mixed types ($P<0.05$).

Unicystic ameloblastoma

The unicystic type of ameloblastoma was reported in 102 single cases [95–136] and in 125 cases retrieved from reviews [199, 254, 255]. Six percent of all ameloblastomas ($n=3677$) were of the unicystic type. The average age of patients with unicystic ameloblastomas was 22.1 years ($n=102$) compared to 40.2 years for the "conventional" types ($n=548$) ($P<0.001$). Forty-five percent of patients with unicystic ameloblastomas were between the ages of 10 and 19 years. Histological classification according to Ackermann *et al.* [199] was not always possible in this retrospective analysis of published cases. However, a plexiform pattern was described in 15.7%, a follicular in 8.8%, an acanthomatous in 2.0% and a mixed pattern in 5.9%. All other cases were unicystic without further subclassification.

DISCUSSION

Ameloblastomas of the jaws are relatively rare odontogenic tumours, the biological profile of which presently can only be studied retrospectively. Reviews of published material pose the disadvantages that often not all data are available, different classification of tumours have been used (e.g. unicystic ameloblastoma), and there is no standardisation between the published reports. It is also noteworthy that there may be a selection of patient data, particularly from countries where more cases are reported. These drawbacks notwithstanding, the present study revealed a number of interesting findings.

The average age of patients at the time of initial diagnosis was 35.9 years. Only 1.8% of the patients were younger than 10 years. On average patients realised clinical symptoms 2.3 years prior to first diagnosis, which means that the first clinical symptoms appear at an age between 33 and 34 years. Small and Waldron [4] in 1955 reported an average age of 38.9 years at first diagnosis, an average duration of symptoms of 6.0 years and an average age of 32.0 years at the time of first symptoms. Robinson [3] reported an average age of 30.1 years when symptoms first occurred. Presently, it is only 2 years from initial symptoms to primary diagnosis of an ameloblastoma, compared to 6 years in 1955 [4]. The average age of first diagnosis in industrialised countries was 39.1 years compared to those from developing countries of 27.7 years. This difference was statistically significant. According to Dodge [209] aging processes may be accelerated in developing countries due to poor nutrition and health care. In this context it is interesting that in Papua New Guinea life expectancy of 45% of the population is less than 20 years [226]. In Nigeria it is 40 years [201]. The oldest Nigerian patient with an ameloblastoma was 52 years [201]. However, in an industrialised country (U.S.A.) it is 92 years [149]. It is also noteworthy that the average age depends on extreme values and therefore in the present study the median was also determined. In developing countries the median age was 24 years; in industrialised countries 38 years. Results of the present study support the hypothesis that persons from developing countries develop ameloblastomas 10–15 years earlier than those in industrialised countries.

In the present study of 3071 patients with ameloblastoma 47% were women, and 53% men. These results are comparable to those of Small and Waldron [4]. In addition, a significant age difference between women (35.2 years at first diagnosis) and men (39.2 years at first diagnosis) was found ($P<0.05$). This age difference at first diagnosis cannot be explained by the fact that women seek medical advice earlier, since in this study it was shown that women seek medical advice 9 months later than men.

Incidence and prevalence figures cannot be derived from the data collected in the present study. However, it is possible to compare absolute numbers of cases of ameloblastoma in different population groups. In this literature review covering the years 1960–1993, 1040 ameloblastomas in Asians, 924 in Blacks and 674 in Caucasians were reported. There may be a probable disposition to develop ameloblastoma more often in Asians than in Caucasians and more often in Blacks than in Caucasians. However, it must be considered that the over- or under-reporting has a direct influence on this phenomenon. Between 1960 and 1993 only four reviews [187, 201, 242, 247] were published where incidence rates were reported. Incidence rates for Sweden, South Africa and Nigeria varied between 0.6 and 5.6 new cases of ameloblastoma per 1 million inhabitants per year. In other publications frequencies of ameloblastoma were correlated to the number of oral biopsies. The number of biopsies, however, is dependent on the medical service. Mosadomi [228] indicated that for Africa frequencies are by no means reliable, because many patients die from tumours left untreated. Also, the harvesting phenomenon in developing countries must be considered [226].

In the last 30 years many authors have tried to elaborate on the frequency of ameloblastoma compared to other tumours. It is extremely difficult to compare these studies, because the correlation was made to oral tumours, odontogenic tumours, mandibular tumours, jaw tumours, cysts, etc. According to Small and Waldron [4], 1% of all tumours and cysts of the maxilla and mandible constitute ameloblastomas. Other authors found a frequency between 3 and 19% [190, 216, 244, 252]. The relative frequency of ameloblastomas in correlation to odontogenic tumours was between 11 and 92% [185, 198, 209, 220, 228, 230, 237, 238, 252, 253]. Even within one country (U.S.A.) the figures differed considerably (11–79%) [198, 238].

The spectrum of clinical symptoms found in the present study were also recorded in other reviews [3, 4, 18, 186, 212, 249]. In the present study duration of symptoms until first diagnosis was 1.8 years in Caucasians, 2.4 years in Blacks and 3.1 years in Asians. The average duration of symptoms was 2.3 years. In 1937 patients first sought medical advice after 8.5 years, and in 1955 after 5.8 years [3, 4]. However, even today 15% of patients seek medical advice only after 5 years.

Tumour size varies considerably. Patients from developing countries presented with ameloblastomas which extended down to the fourth rib, weighing 1.5 kg [3, 18, 71, 200, 233, 246]. The average size of tumour in developing countries was larger than those from industrialised countries ($P<0.1$). Ameloblastomas in women were statistically significantly larger than in men. This correlated with the longer duration of symptoms in women.

The ameloblastoma is found most frequently in the mandible, in the region of molars and the ramus. In the maxilla the molar region is the main localisation. However, it was also frequently found in the maxillary sinus and nasal cavity. These

results are comparable to those of Small and Waldron and other authors [4, 217]. The maxilla was affected in 16% in the present study compared to 19% in that of Small and Waldron [4] in 1955. The ameloblastoma is seen more frequently in the anterior region in Blacks (21.6%) compared to Caucasians (12.6%) and Asians (11.9%) ($P<0.05$). This predisposition in Blacks has been noted by Adekeye and Lavery [201] and Sawyer *et al.* [240]. When comparing African and American Blacks, Sawyer *et al.* [240] found that the anterior region was more frequently involved in Black Africans. American Blacks showed the same distribution of localisation as Caucasians.

The present review revealed a unilocular appearance of ameloblastomas in 51% and a multilocular appearance in 49%. Fitzgerald *et al.* [212] also found 50% of cases to be associated with multilocular structures radiographically. Radiographically, tumour borders mainly appeared as sharply delineated, a finding which does not correspond to the histological borders. Of particular interest was the desmoplastic ameloblastoma which is characterised as an ill-defined translucency with some irregular opacities [197, 256, 257]. Therefore, in cases of ill-defined borders desmoplastic ameloblastomas may be tentatively diagnosed. In the present review 45% of ameloblastomas with irregular, ill-defined borders were desmoplastic, although this type of ameloblastoma constitutes only 2% of all ameloblastomas.

Root resorptions due to the presence of tumour were a relatively rare finding and if seen were predominantly found in younger patients. Maxillary ameloblastomas rarely show multilocular structures, a fact which makes the radiological diagnosis of maxillary ameloblastoma difficult [21, 47].

In 107 cases embedded teeth were reported. Of these the lower third molar was the most frequently affected (42 cases). Eversole *et al.* [254] reported that more than 50% of unicystic ameloblastomas were associated with retained third molars. Retained teeth were associated with unilocular ameloblastomas in 72%. The average age of patients with retained teeth and ameloblastomas was 20.8 years. Only 19% of patients with retained teeth were older than 30 years. Only 9.5% of patients with retained teeth developed recurrence, regardless of the mode of therapy. Both Leider *et al.* [222] and Eversole *et al.* [254] found that unicystic ameloblastomas when associated with a retained tooth showed a much lower recurrence rate.

According to the present review follicular (33.9%) and plexiform variants (30.2%) of ameloblastomas constituted the more common histological subtypes. Also the acanthomatous type (11.3%) was relatively frequent, while the basal and granular cell types of ameloblastoma were rare. The desmoplastic ameloblastoma was characterised by extensive production of interstitial collagen [23, 257]; according to the present finding it makes up 1.4% of all reported ameloblastomas. Other authors found a much higher percentage between 8.6 and 13% [33, 256]. It was possible for these authors to review the ameloblastoma material which has been misdiagnosed before the first description of desmoplastic ameloblastoma by Eversole *et al.* [23]. This was not possible for the present review, so the calculated percentage of 1.4% could be too low.

According to Kramer [258] and Regezi *et al.* [238] there is no correlation between histological subtypes, clinical symptoms or biological behaviour. The present review revealed some correlations between the histological subtypes, clinical appearance and radiology. Follicular and plexiform ameloblastomas occur in younger patients and more frequently in the posterior part of the jaws. In contrast, the acanthomatous ameloblastoma is found more frequently in the anterior segments of the jaws and in older patients. The desmoplastic type is seen more frequently in the maxillary sinus and the anterior segments of the jaw. In the case of cortical bone expansion or perforation more than 50% of cases were of the acanthomatous type. Radiologically, the desmoplastic ameloblastoma is characterised by poorly-defined borders which Tanimoto *et al.* [81] explained as due to the compact growth characteristic and persistence of intact bone trabeculae.

Among the therapy modalities of ameloblastomas, surgery in contrast to radiation or chemotherapy is still the therapy of choice. Since ameloblastomas seem to have a low radiosensitivity Shaw and Katsikas [193] recommended radiation therapy only in cases of probable post-surgical persistence of tumour tissue or as palliative treatment. However, complete tumour remission cannot be expected. In the present survey a recurrence after radiation therapy was observed in 68.6% ($n=35$). Chemotherapy was only applied in one patient who developed a recurrence [250].

At the beginning of the period reviewed, i.e. in the 1960s, in many cases the conservative treatment approach was chosen because ameloblastoma at that time was considered to be a benign tumour or a simple follicular cyst. Also the possibilities for reconstruction at that time were limited. Since high recurrence rates were observed after a predominantly conservative approach, the tendency for radical surgery prevailed [201]. According to the present findings recurrence rates after conservative or radical therapy were not significantly different. However, the period of recurrence after conservative surgery was significantly shorter (4.8 years) than after radical surgery (11.1 years).

Presently, more differentiated therapy concepts are accepted by most authors. According to Pilz and Nitzschke [191] the decision whether a radical or conservative approach is more appropriate is dependent on the following factors: (1) size and localisation of tumour; (2) clinical appearance, growth rate, neighbouring structures; (3) histology; (4) clinical presentation of the recurrence; (5) general condition and age of patient.

According to localisation different concepts of therapy are recommended for ameloblastomas. Ameloblastomas of the maxilla must undergo radical surgery. This approach is necessary because of the spongy osteoarchitecture of the maxilla which facilitates spread of the tumour. In addition, the close proximity of vital structures calls for radical therapy [21, 259]. In this context data compiled from single-case reports showed that after a radical approach there was a significantly lower recurrence rate than after conservative surgery. After simple curettage of maxillary ameloblastomas recurrence rates of up to 100% and mortality rates of 60% have been published [192]. Local recurrences of maxillary ameloblastomas pose particular problems of diagnosis whenever tumours develop into the cranial region (sinus ethmoidalis, fossa pterygoidea, fossa temporalis and base of skull). However, diagnosis and postoperative follow-up has been considerably improved with the application of computer tomography (CT) and magnetic resonance tomography (MRT). Patients who had undergone surgery for maxillary ameloblastomas must be followed up lifelong.

When dealing with ameloblastomas of the mandible conservative approaches must be considered more readily, because the postoperative follow-up in mandibular osteostructures by radiography, CT or MRT is easier than that of the maxilla.

The high recurrence rates of between 45 and 90% after conservative therapy as reported in some reports [21, 192, 224, 251] was not confirmed by the present review, in which a recurrence rate of 22.6% was found. In principle it seems possible to preserve the inferior alveolar nerve because no tumour invasion of the neural structures has been observed [260].

An important aspect in treatment planning is the histological diagnosis of the unicystic ameloblastoma. While some unicystic ameloblastomas appear to be treatable by conservative approaches, "non-unicystic" ameloblastomas must preferably be treated radically. Particularly unicystic ameloblastomas which grow intraluminally show a low recurrence rate after conservative surgery. Leider *et al.* [222], Eversole *et al.* [254] and Gardner [255, 261, 262] found a recurrence rate of less than 10% of unicystic ameloblastomas after conservative surgery. In the present review the recurrence rates of unicystic ameloblastomas was 13.7% compared to "non-unicystic" ameloblastomas of 22.7%. This difference was not significant statistically. The experience both morphologically and therapeutically with unicystic ameloblastomas is still limited. However, a conservative approach may be recommended whenever there is no invasion of the cyst wall by ameloblastomatous proliferations. Follow-ups of one to two decades are probably necessary to detect recurrences at an early stage.

Radiological appearance of ameloblastomas may further influence the therapeutical approaches. The multilocular variant results in recurrences in 24%, whereas the unilocular ameloblastoma results only in a recurrence rate of 16%. Conservative therapy of multilocular ameloblastomas revealed a recurrence rate of 30% in contrast to 19.2% after radical therapy. Multilocular ameloblastomas warrant a radical approach with a sufficient safety margin, which should be 1 cm according to Bonn and DeBoom [12].

At present it is generally assumed that the histological type according to the WHO classification excluding the unicystic ameloblastoma, has no influence on the biological behaviour of the tumour [70, 236, 252]. The evaluation of single-case reports, however, confirmed the assumption of Ueno *et al.* [251] that follicular ameloblastomas are characterised by a higher recurrence rate (29.5%) compared to plexiform ameloblastomas (16.7%). The acanthomatous type had a statistically significant lower recurrence rate (4.5%). The other histological subtypes could not be evaluated due to the small numbers.

The peripheral ameloblastoma according to most authors needs conservative surgery with minimal but sufficient safety margins. Recurrences are rare; however, this type of ameloblastoma also needs long phases of follow-up [143, 259, 263, 264].

The age of the patient is another influencing factor relating to the choice of therapy. Patients of advanced age who are fit for surgery should not necessarily undergo radical surgery. Life expectancy and the time span for development of recurrence should be correlated [191, 239]. Also, children under the age of 10 years should not undergo radical surgery [93]. The diagnosis of ameloblastoma in patients of this age bracket should be double checked to avoid overtreatment due to faulty diagnosis (ameloblastic fibroma!). In young patients a two-step procedure has also been suggested [58]. After primary marsupialisation or enucleation a second step of "minimal" radical approach is performed. In a similar approach Eyre and Rule [104] have treated follicular cysts with ameloblastic proliferations. Simple cystostomies of ameloblastomas as the sole therapy are unacceptable [70]. While this approach limits the histological examination and specification the recurrence rate after marsupialisation is particularly high (50%).

The average recurrence rate with the above described differentiated therapeutical approach makes up 20.6% ($n=345$). In 1955 Small and Waldron [4] found a recurrence rate of 33% ($n=352$) and in 1937 Robinson [3] found a recurrence rate of 67% ($n=295$). In all studies the average duration of follow-up was approximately 5 years. The decrease in recurrence rates in the last two decades is probably due to early diagnosis and improved therapeutical approaches. Since, according to the present review, only 53% of recurrences are found during the first 5 years, an extended period of follow-up, if not lifelong, is strongly recommended. In the present survey the latest recurrences appeared after 33 years [191].

QUO VADIS—FUTURE AMELOBLASTOMA RESEARCH

Although considerable insight into the biological behaviour of the ameloblastoma has been accumulated during the past few decades, numerous problems remain unsolved. These relate to standardisation of diagnosis, both radiologically and histopathologically, as well as to therapy.

The problem that was particularly evident in the present review was the wide variety and interpretation of terms and nomenclature related to radiological appearance and histology. Radiological terms like unilocular were often confused with histological terms such as unicystic and multicystic. It is difficult to conceive for many that a multilocular lesion may in fact histologically be a unicystic ameloblastoma. On the other hand a unilocular appearance of a tumour may in fact histologically be multicystic. A clear differentiation between these terms is necessary in order to come up with the proper diagnosis. Standardisation of terms as such is warranted.

Application of a uniform classification such as the WHO classification of odontogenic tumours and cysts, published in 1992, should be a basis for histopathological diagnosis [265]. Only then is comparability of material possible, which otherwise cannot be compared. As has been suggested recently [266] it would be necessary in the future to develop multi-institutional research using a tumour registry or data bank for standardisation of radiological, clinical and histopathological features of ameloblastoma. Only then in the context of a prospective study with standardisation can stricter criteria be worked out.

It is suggested that rare subtypes of ameloblastoma such as the peripheral ameloblastoma, the unicystic ameloblastoma, as well as the desmoplastic ameloblastoma and others should be published as case reports or smaller series.

In addition to clinical documentation, basic research aspects are still of importance. Particularly growth pattern and tumour spread of the different types of ameloblastoma are needed, as are studies of the epithelio-mesenchymal interactions of tumour cells and stroma.

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