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Conceptual changes in ameloblastoma: suggested re-classification of a "veteran" tumor

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Abstract

Objectives: The merging of ameloblastoma (AM) with mural unicystic ameloblastoma (UAM-M) was suggested by the 2017 WHO based on similar treatment needs. In an international multicenter study, we investigated the characteristics of their merged product (merged-AM), and raised the possibility of unifying AM and UAM (total-AM).

Materials and methods: AM and UAM (luminal/intraluminal/mural), separate and combined, were analyzed for demographic/clinical/radiological features. ANOVA and chi-square tests were followed by univariate and multivariate analyses, and significance was set at $p<0.05$.

Results: The patients' mean age was 39.6+20.3y in merged-AM (147 AM, 76 UAM-M), 45.1+19.4y in AM ($p=0.009$). Merged-AM comprised 51.3% multilocular/48.7% unilocular tumors, AM comprised 72.5%/27.5%, respectively ($p<0.001$). Merged-AM was associated with impacted teeth in 30.8%, AM in 18% ($p=0.023$). The probability of merged-AM for multilocularity increased by 2.4% per year of age (95%CI 0.6-4.2, $p=0.009$). Association with impacted teeth decreased by 7.9% per year of age (95%CI 1.9-14.39, $p=0.009$). Merged-AM did not differ from total-AM ($p>0.05$).

Conclusions: Merged-AM partially differed from AM, but differences appeared to diminish in an age/time-wise manner. Merged-AM and total-AM were nearly indistinguishable. Therefore, AM and UAM may be considered a continuous spectrum of one type of tumor, further necessitating revision of the treatment approaches.

Introduction

The current consensus is that ameloblastomas are comprised of intrabony conventional/multicystic components, now termed ameloblastoma (AM) and unicystic ameloblastoma (UAM), as well as of a peripheral counterpart (El-Naggar, Chan, Grandis, Takata & Slootweg, 2017). UAM was segregated from AM more than 4 decades ago on the basis of involvement of a young age group, a distinctive unilocular radiological appearance and the

macroscopic appearance of a single cystic cavity (Leider, Eversole & Barkin, 1985; Robinson & Martinez, 1977; Vickers & Gorlin, 1970). Furthermore, UAM was divided histomorphologically into luminal (L), intraluminal (IL) and mural (M) subtypes (Ackerman, Altini & Shear, 1988). The accepted therapeutic approach for an intraosseous ameloblastoma is in accordance with its macroscopic and microscopic features and expected biological behavior, and it is comprised of resection with safety margins of about 1.5 cm beyond the radiological margins. A more conservative approach that includes enucleation/curettage is common practice for UAM-L/IL subtypes (Neville, Damm, Allen & Chi 2016). On these clinical grounds, the 2017 WHO Classification of Head and Neck Tumours suggested merging AM and UAM-M into one entity (merged-AM) (El-Naggar et al., 2017), inferring that UAM-L/IL subtypes will become mere components of UAM. The current genetic findings revealed that mandibular AM and UAM (all types) share the *BRAF* V600E mutation (74% and 94%, respectively) (Heikinheimo, Huhtala, Thiel, Kurppa, Heikinheimo, et al., 2019), which highlighted a common aberration in this entire group of intrabony tumors. Therefore, we designed an international multicenter study with a 2-fold aim: (1) to define the demographic and clinico-radiological characteristics of merged-AM in comparison to the current classification, and (2) to challenge the need to further separate the intrabony ameloblastomas into AM and UAM and discuss it in view of the advances in our knowledge on the genetic landscape of ameloblastoma and currently available novel treatment modalities.

Materials and methods

For this retrospective study, cases of AM and UAM ameloblastomas (classified as L, IL, and M) were retrieved from the files of the Department of Oral Pathology, School of Dental Medicine, Tel Aviv University, Tel Aviv, Israel (1991-2018), Department of Tumor Pathology, Institute of Oncology, Istanbul University, Istanbul, Turkey (2011-2019), Department of Oral Pathology, São Leopoldo Mandic Research Center, Campinas, Brazil (2000-2018), and HUSLAB, Helsinki University Hospital, Helsinki, Finland (2014-2018) with the approval of the local IRBs. All selected tumors were diagnosed by specialists in oral pathology in each of the departments that contributed cases. Confirmation of the diagnoses was based on the microscopic findings of the final surgical specimens and serial sections, especially in cases of UAM. The patients were then treated according to the submitted diagnosis and accepted standards of care.

Collected data included the histopathological diagnosis, age and gender of the patients, tumor location, clinical parameters (face asymmetry, cortical expansion, soft tissue swelling, tooth mobility, tooth displacement and presence of fistula), symptoms (pain/discomfort, difficulty in swallowing, limited mouth opening and hypoesthesia/paresthesia) and radiological features [locularity (unilocular/multilocular), definition of margins (well-defined versus partially and ill-defined), association with impacted tooth, impact of tumor on adjacent tooth/teeth (displacement, resorption), cortices (expansion/thinning/perforation) and anatomical structures (inferior alveolar canal, maxillary sinus)]. The radiological findings of the impact of the tumors on the cortices were based on computerized tomography (CT) scans, cone beam CT (CBCT) scans and on information retrieved from the surgical reports.

Statistical tests included ANOVA for analyzing differences in age and the chi-square test for examining differences in all of the categorical parameters. This was followed by comparing AM, AM and UAM-M (merged-AM) and AM and UAM-L/IL/M (total-AM) by mean of univariate and multivariate tests. Statistical significance was set at $p<0.05$. Calculations were performed with SPSS, version 22 (IBM, Chicago, IL, USA).

Results

A. General

The data of the study are summarized in Table 1 and statistical outcomes are tabulated in Table 2.

The mean age of patients with merged-AM was lower than those with AM (39.6+20.3y and 45.1+19.4y, respectively) ($p=0.009$) but greater than those with UAM-L/IL (25.1+12.8y) ($p<0.001$). Distribution of cases per decade of life revealed that the peak of frequency was in the third decade in the merged-AM group (20.4%) and in the fourth decade in the AM group (18.4%). The gender distribution in the merged-AM group was similar to that of the AM group (male-to-female ratio 1.5:1).

There were no differences regarding trends of location, clinical features and symptomatology between merged-AM and AM.

The radiological features in merged-AM had an almost equal distribution of 51.3% multilocular and 48.7% unilocular cases, while 72.5% were multilocular and 27.5% unilocular in AM ($p<0.001$). The frequency of well-defined margins in merged-AM was higher but statistically

insignificant compared to AM (65.3% and 54.5%, respectively) ($p>0.05$). Moreover, 30.8% of merged-AM cases were associated with an impacted tooth, but only 18% of AM cases ($p=0.023$).

Fifty-three of the merged-AM cases with a mean age of 25.1+14.9y were associated with an impacted tooth (dentigerous cyst-looking), while 122 cases with a mean age of mean age 45.7+17.8y were not, representing an older mean age compared to that of patients with tumors associated with an impacted tooth ($p<0.001$).

There were 20 tumors associated with an impacted tooth among the AM cases whose mean age was 28.3+18.3y, and 92 cases whose mean age was 47.6+17y were not, representing an older mean age than that of patients with AM associated with an impacted tooth ($p<0.001$).

Among the UAM cases (N=80, all subtypes), 46 (13 UAM-L/IL, 33 UAM-M) with a mean age of 23.2+12.1y were associated with an impacted tooth, while 34 cases (5 UAM-L/IL, 29 UAM-M) with a mean age of 36.3+18.4y were not, representing an older mean age compared to that of patients with UAM associated with an impacted tooth ($p<0.001$).

B. Comparing AM, merged-AM and total-AM

Univariate analysis

The results of combining all ameloblastoma tumors (AM and UAM) into a single entity, total-AM, are shown in Table 3. Comparisons of demographic, clinical and radiological features between AM, merged-AM and total-AM yielded statistically significant differences between all three with regard to age, locularity and association with an impacted tooth (Fig. 2). No significant differences were found between merged-AM and total-AM ($p>0.05$).

Multivariate analysis model

The model included the variables of tumor group (AM, merged-AM, total-AM), age, locularity and association with an impacted tooth. The probability for multilocularity in AM was 7.87 higher than in merged-AM (95%CI 3.06-20.24, $p<0.001$) and 5.46 higher than in total-AM (95%CI 2.21-13.48, $p<0.001$). The probability of merged-AM for multilocularity increased by 2.4% per year of age (95%CI 0.6-4.2, $p=0.009$) and the probability of total-AM increased by 2.9% per each year of age (95%CI 1.1-4.9, $p=0.002$). There was no significantly increased probability of an association with an impacted tooth in merged-AM or total-AM compared to AM ($p>0.05$), however, the parameter of age lowered the probability of such an association by 7.9% for each year of age (95%CI 1.9-14.39, $p=0.009$).

Discussion

This study was undertaken since the 2017 WHO Classification of Head and Neck Tumours (El-Naggar et al., 2017) suggested reassigning UAM-M to the AM group based on the both types of lesions requiring the same aggressive surgical approach. In contrast, the current recommended standard of care for UAM-L/IL consists of a conservative approach. We believed that proposed merging called for an investigation of the subsequent changes in the demographic and clinical-radiological landscape of merged-AM *versus* AM. Furthermore, we proposed the possibility of changing the current concept of classifying intrabony ameloblastomas into AM and UAM to a concept of a single tumor with a spectrum of clinical, demographic and radiological features.

We found that by merging AM with UAM-M to a single entity, that of merged-AM, there were changes in its characteristics compared to the "original" AM, which included a younger mean and median age, a radiological appearance of the lesions with an almost equal distribution between unilocular and multilocular presentation (*versus* a multilocular predominance in AM) and a higher frequency of tumors with well-defined margins, as well as a higher association with impacted teeth. Notably, the clear-cut male predisposition for AM was in contrast to the almost equal gender distribution reported in the literature (Reichart, Philipsen & Sonner, 1995), a finding that could be sample-related.

One of the weaknesses of comparing merged-AM to UAM-L/IL is the sample size, with merged-AM comprising 223 tumors and UAM-L/IL only 31 tumors. Moreover, defining the histopathological subtypes of UAM, i.e., L/IL/M, depends upon the experience of the examiner in not over-diagnosing a dentigerous cyst with epithelial hyperplasia, on the one hand, and on conducting a meticulous examination of multiple sections in each tumor to search for mural growth, on the other hand. Thus, the actual discrepancy in the frequency of these subtypes could be even larger, with the UAM-L/IL being overestimated and UAM-M being underestimated. In our sample, 29% of the cases were L/IL types, which was slightly lower than the 33% reported by Philipsen & Reichart (Philipsen & Reichart, 1998) and 50% reported by Ackerman et al. (Ackerman et al., 1988).

The accepted position that UAM is a distinct entity with defined clinical, radiological, macroscopic and microscopic features, may actually be the result of different impacts from adjacent structures (e.g., impacted teeth) and microenvironmental factors. Although UAM was the main type of ameloblastoma associated with an impacted tooth in our study (52.8%) as well as in

the literature (52-100%) (Philipsen & Reichart, 1998), AM also showed a substantial association with impaction (18% in our study, 15-40% in the literature) (Philipsen & Reichart, 1998). We found that the probability of an interaction between ameloblastoma and an unerupted tooth decreased significantly with age, which is in accordance with the chronology of the process of tooth eruption. Moreover, irrespective of the type of ameloblastoma (AM/UAM/merged-AM), whenever the tumor was not associated with an impacted tooth, the mean age of patients was over 30 years of age compared to younger patients whose tumors were associated with impaction, a finding which is supported by others (Leider et al., 1977; Mohammed, Mahomed & Ngwenys, 2019; Philipsen & Reichart, 1998; Robinson & Martinez, 1977). According to some authors, the UAM-L/IL histological subtypes were found to be the most frequently associated with an impacted tooth ("dentigerous" type of UAM), unlike UAM-M, which was usually not associated with an impacted tooth (Gardner & Corio, 1984; Philipsen & Reichart, 1998). This follows the current accepted practice, which favors a conservative surgical approach for UAM-L/IL and could imply that the physical interaction between an ameloblastoma and a developing tooth may have an impact on the subsequent emerging tumor. Furthermore, it has been recently found that the histological subtypes of ameloblastoma were defined by the expression of different clusters of genes and molecular pathways (Hu, Parker, Divaris, Padilla, Murrah, et al., 2016). In addition, microenvironmental activation of the immune and inflammatory reactions as well as specific nerve-derived signals could be fundamental for the pathogenesis of ameloblastomas, with a direct modulation of their proliferation and invasiveness (Pagella, Catón, Meisel & Mitsiadis, 2020). These interactions together with factors like age and time, could jointly contribute to the clinical presentation of ameloblastomas, including their radiological features.

A considerable amount of confusion between AM and UAM can be found at a microscopic level. There are cases of AM that morphologically show extensive cystic changes and cases of UAM with extensive intraluminal (plexiform) growth that essentially occupy the majority of the lumen, so much so that they could be diagnosed as AM (Gardner, 1981; Ledesma-Montes, Mosqueda-Taylor, Carlos-Bregni, de León, Palma-Guzmán, et al., 2007). This highlights the existence of cases in which the histomorphological boundaries between AM and UAM are blurred, and may suggest a continuum of a single entity. In addition to histomorphology, there is also evidence for blurred boundaries of biological behavior, where the rate for recurrence in UAM after conservative treatment (i.e., enucleation/curettage) ranged between 40% to 100%, similar to AM treated in the same manner (Janquera, Ascani, Vicente, García-Consuegra & Roig, 2003; Ord,

Blanchaert Jr, Nikitakis, & Sauk, 2002; Rosenstein, Pogrel, Smith & Regezi, 2001; Sampson & Pogrel, 1999); others reported lower rates of recurrence, 7% - 35% (Fregnani, da Cruz Perez, de Almeida, Kowalski, Soares, et al., 2010; Kahn, 1989; Lau & Samman, 2006; Ledesma-Montes, et al., 2007; Li, Wu, Yu, & Yu, 2000), but it seems that as follow-up was longer, the higher rate of recurrence was reported (Ord et al., 2002).

The current consensus for the most adequate treatment approach for ameloblastoma is dependent upon the clinical status and histopathological findings. There is an overall agreement on the provision of radical surgical treatment for AM and UAM-M and a conservative approach for UAM-L/IL (El-Naggar et al., 2017). However, several recent systematic reviews and meta-analyses have found it difficult to reach unequivocal conclusions and treatment recommendations (Almeida, Andrade, Barbalho, Vajgel, & Vasconcelos, 2016; Antonoglou & Sándor, 2015; Hendra, Kalla, Van Cann, de Vet, Helder, et al., 2019; Seintou, Martinelli-Klay & Lombardi, 2014; Troiano, Dioguardi, Cocco, Laino, Cervino, et al., 2017). The main reasons lay in the availability of only retrospective studies and a high risk of bias, small numbers of patients, unclear/absent distinctions between AM and UAM, the use of different treatment techniques and the resultant difficulty in comparing outcomes and short or lack of follow-up periods in many of the sources. These problematic issues further emphasized the dilemma of radical *versus* conservative treatment for ameloblastomas, especially in young patients for whom large ablative defects created by radical surgery entail physiological, functional, esthetic and psychological complications.

In a recent elegant study, the authors showed that the mutational landscape in a large series of ameloblastomas comprising both AM and UAM, was related to different geographic areas, age and gender of patients, histological subtypes and recurrence rate (Gültekin, Aziz, Heydt, Sengüven, Zöller, et al., 2018). They found that a single mutation, usually in the *BRAF* gene, was associated with a lower recurrence rate than tumors harboring multiple mutations. This could be used for stratifying patients with ameloblastomas, irrespective of the current AM/UAM classification, for determining the extent of the surgical procedure and follow-up protocols. Moreover, revealing the mutational status of ameloblastomas can be considered as a "game changer" that offers the possibility of using targeted pharmacologic therapy to minimize or avoid the need for radical surgery for either AM or UAM (Fernandes, Girardi, Bernardes, Fonseca, & Fregnani, 2018; Kaye, Ivey, Drane, Mendenhall, & Allan, 2014; Tan, Pollack, Kaplan, Colevas, & West, 2016). In this way, a tumor that would otherwise necessitate extensive and debilitating

surgical procedures, can be pharmacologically reduced to a point where a conservative surgical approach becomes curative. Thus, these newly accumulated genetic and molecular findings seem to challenge the relevance of the current clinico-histopathological separation of AM and UAM. Moreover, as shown in the present study, the product of mergence between AM and UAM (L/IL/M), i.e., total-AM, had an indistinguishable profile from merged-AM (AM + UAM-M). In light of this, we suggest to unite all subtypes of intrabony AM into one entity that exhibits a spectrum of manifestations influenced by variable biological- and time/age-related parameters. Obviously, this unified entity has to be further explored in greater depth in studies with larger numbers of macroscopically proven UAM and associated histological subtypes.

In conclusion, as long as surgery was the only treatment modality for ameloblastoma, there was a strong rational for the classification of UAM as a distinct clinico-histopathological entity from AM, and for the proposal of merging UAM-M and AM. The lack of significant differences between merged-AM and total-AM, reinforced by recent molecular and genetic findings, may be the basis of a revised concept of re-classification (molecular/genetic stratification instead of the current clinico-histopathological classification), according to which an ameloblastoma is a single entity constituting a continuous spectrum of one type of tumor. Consequently, a change in the present treatment paradigm is expected, so that the pharmacological approach will replace radical surgery.

Conflict of Interest

Authors declare no conflict of interest

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Table 1 Features of ameloblastomas referring to the current and WHO proposed classifications: AM – ameloblastoma, UAM – unicystic ameloblastoma; UAM-T – unicystic ameloblastoma total (luminal + intraluminal + mural), UAM-M – unicystic ameloblastoma mural type; UAM-L/IL – unicystic ameloblastoma luminal/intraluminal; excluding the parameter of age, results are presented as N(%)

		Current classification				WHO Proposed classification
		AM	**UAM-T**	**UAM-M**	**UAM-L/IL**	**merged-AM**
Age, y (mean +SD; median; range)		45.1+19.4; 44; 9-87	27.8+15.7; 22; 10-83	28.9+16.6; 23; 10-83	25.1+12.8; 21; 11-62	39.6+20.3; 36; 9-87
Gender F/M (%)		57(38.8)/90(61.2)	50(46.7)/57(53.2)	32(42.1)/44(57.9)	18(58.1)/13(41.9)	89(39.9)/134(60.1)
Location: only mandible N(%)	Anterior	16(12.7)	6(5.7)	4(5.3)	2(6.7)	20(9.9)
	Premolar	13(10.3)	9(8.6)	7(9.3)	2(6.7)	20(9.9)
	Premolar-molar	41(32.5)	37(35.2)	29(38.7)	17(56.7)	70(34.8)
	Post-ramus	52(41.3)	51(48.6)	34(45.3)	8(26.7)	86(42.8)
	Crosses midline	4(3.2)	2(1.9)	1(1.3)	1(3.3)	5(2.5)
	Total (N)	126	105	75	30	201
Clinical features N(%)	Facial asymmetry	22(21.4)	15(20)	14(24.1)	1(5.9)	36(24.7)
	Soft tissue swelling	64(57.1)	27(35.5)	23(39)	4(23.5)	87(50.8)
	Cortical expansion	91(73.4)	58(74.4)	50(71.4)	18(64.3)	141(72.7)
	Tooth mobility	40(40.4)	27(29)	16(24.2)	11(40.7)	57(34.3)
	Fistula	17(16.2)	2(2.8)	1(1.9)	1(5.9)	18(11.3)
	Tooth displacement	16(17.6)	14(20.3)	12(22.6)	2(12.5)	28(19.4)
Symptoms	Pain/	70(60.9)	42(43.8)	32(45.1)	10(40)	102(54.8)

N(%)	discomfort					
	Difficulty in swallowing	0	0	0	0	0
	Limited mouth opening	3(2.9)	0	0	0	3(1.9)
	Paresthesia	21(20)	6(8)	6(10.3)	0	27(16.6)
Radiological features N(%)	Locularity (unilocular/ multilocular)	30(27.5)/79(72.5)	64(84.2)/13(15.8)	47(79.7)/12(20.3)	17(94.4)/1(5.6)	77(48.7)/91(51.3)
	Margins (well -defined; others partially or ill-defined)	67(54.5)	85(85.9)	59(84.3)	26(89.7)	126(65.3)
	Assoc with impacted tooth	20(18)	46(58.2)	33(54.1)	13(72.2)	53(30.8)
	Impact on near tooth/teeth	55(50.5)	59(58.4)	40(55.6)	19(63.3)	95(53)
	Impact on cortex	101(91)	62(81.6)	48(81.4)	14(82.4)	149(87.6)
	Impact on near structures	38(32.8)	24(68)	20(34.5)	4(22.2)	58(33.3)

Table 2 Statistical differences referring to the current and WHO proposed classification of ameloblastomas (AM – ameloblastoma, UAM – unicystic ameloblastoma; UAM-T – unicystic ameloblastoma total (luminal + intraluminal + mural), UAM-L/IL – unicystic ameloblastoma luminal/intraluminal)

		Current classification				WHO Proposed classification	
		AM *vs* **UAM-T**	**AM** *vs* **UAM-M**	**AM** *vs* **UAM-L**	**UAM-M** *vs* **UAM-L/IL**	**merged-AM** *vs* **UAM-L/IL**	**merged-AM** *vs* **AM**
Age		<0.001	<0.001	<0.001	0.213	<0.001	0.009
Gender		<0.001	<0.001	0.756	0.427	0.297	0.213
Location - mandible	Anterior *vs* posterior (to canines)	0.107	0.137	0.372	0.859	0.822	0.538
Clinical features	Facial asymmetry	0.97	0.83	0.24	0.002	0.201	0.96
	Soft tissue swelling	0.0057	0.035	0.02	0.375	0.057	0.362
	Cortical expansion	0.307	0.899	0.463	0.652	0.485	0.992
	Tooth mobility	0.112	0.039	0.844	0.18	0.183	0.337
	Fistula	0.01	0.014	0.457	0.971	0.782	0.338
	Tooth displacement	0.818	0.602	0.889	0.596	0.735	0.853
Symptoms	Pain/discomfort	0.019	0.05	0.091	0.837	0.237	0.364
	Difficulty in swallowing	-	-	-	-	-	-
	Limited mouth opening	-	-	-	-	-	-
	Paresthesia	0.184	0.171	0.252	0.882	0.377	0.58
Radiological features	Locularity (unilocular *vs* multilocular)	<0.001	<0.0001	<0.0001	0.268	<0.001	<0.001

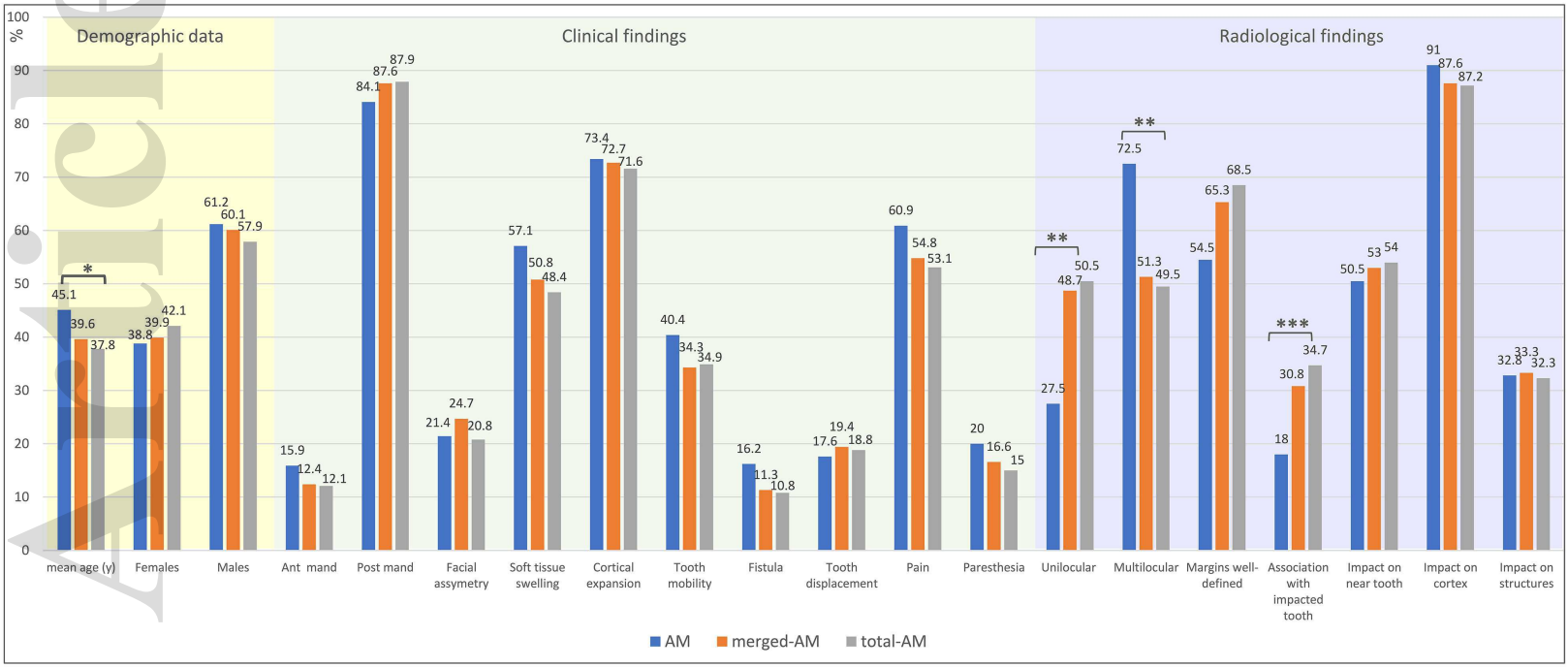
	Margins (well-defined *vs* all others)	<0.001	0.0001	0.001	0.703	0.015	0.071
	Associated with impacted tooth	<0.001	<0.001	<0.001	0.272	0.001	0.023
	Impact on near tooth/teeth	0.380	0.380	0.694	0.486	0.294	0.879
	Impact on cortex	0.095	0.115	0.504	0.793	0.808	0.496
	Impact on near structures	0.961	0.954	0.627	0.578	0.580	0.979

Table 3 Features of all types of intrabony ameloblastomas (AM), total-AM - "solid/multicystic + unicystic [N(%)]

Age, y (mean + SD; median; range)		37.8+19.9; 33; 9-87
Gender (F/M) (N=254)		107(42.1)/147(57.9)
Location – only mandible	Anterior	22 (9.5)
	Premolar	22 (9.5)
	Premolar-molar	87(37.7)
	Post-ramus	94(40.7)
	Crosses midline	6(2.6)
	Total (N)	231
Clinical features	Facial asymmetry (N=178)	37(20.8)
	Soft tissue swelling (N=188)	91(48.4)
	Cortical expansion (N=222)	149(71.6)
	Tooth mobility (N=192)	67(34.9)
	Fistula (N=176)	19(10.8)
	Tooth displacement (N=160)	30(18.8)
Symptoms	Pain/discomfort (N=211)	112(53.1)
	Difficulty in swallowing (N=176)	0
	Limited mouth opening (N=177)	3(1.7)
	Paresthesia (N=180)	27(15)
Radiological features	Locularity (unilocular/ multilocular) (N=186)	94(50.5)/92(49.5)
	Margins (well-defined) (N=222)	152(68.5)
	Assoc with impacted tooth (N=190)	66(34.7)
	Impact on near tooth/teeth (N=211)	114(54)
	Impact on cortex (N=187)	163(87.2)
	Impact on near structures (N=192)	62(32.3)

Legend to figure

Fig. 1 Illustrative profiles of ameloblastoma (AM), merged-AM (ameloblastoma + unicystic ameloblastoma, mural type) and total-AM (ameloblastoma + unicystic ameloblastoma) according to all examined parameters. Mean age in years; all other parameters are given as %; Ant mand – anterior mandible; Post mand – posterior mandible; *AM vs merged-AM, $p=0.027$; AM vs total-AM, $p=0.001$; merged-AM vs total-AM, $p>0.05$; **unilocularity less frequent in AM than in merged-AM and total-AM, $p<0.001$; multilocularity: more frequent in AM than in merged-AM and total-AM, $p<0.001$; ***association with an impacted tooth less frequent in AM than in merged-AM and total-AM, $p=0.006$



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