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REVIEW ARTICLES

Global frequency of benign and malignant odontogenic tumors according to the 2005 WHO classification

Leorik Pereira da Silva [1]
Rômulo Augusto de Paiva Macedo [1]
Marianna Sampaio Serpa [2]
Ana Paula Veras Sobral [3]
Lélia Batista de Souza [1]

Abstract:

Odontogenic tumors are a heterogeneous group of lesions with variable clinical behavior. This manuscript aimed to determine the global frequency and distribution of OT based on the 2005 WHO classification. The manuscript performed a systematic search conducted in only one database (PubMed/Medline). We identified 8,658 articles, of which 495 articles were evaluated. After applying the inclusion and exclusion criteria, 42 papers were selected. Summed up, a total of 13,490 cases of OT were diagnosed. Most cases were found in Asia (n=6,472) and North America (n=2,599). Keratocystic odontogenic tumor (KCOT) (32.1%) was the most frequent neoplasm, followed by ameloblastoma (AMB) (30.6%) and odontoma (ODO) (17.3%). Malignant tumors were uncommon, accounting for 4.7% of all tumors. Of those, malignant ameloblastoma (n=184) and ameloblastic carcinoma (n=115) were the most common tumors. Overall, OT were more prevalent in men (n=4,896), with a male:female ratio of 1.2:1. The age ranged from 1 to 92 years; however most tumors occurred between the second and fourth decades of life. The mandible was the most common anatomical site, with a mandible:maxilla ratio of 2.8:1. The prevalence profile of OT shows a geographical variation; moreover, studies based on prior WHO classifications present a different incidence and frequency. The 2005 WHO classification of OT altered the distribution of these lesions and possibly made KCOT the most common OT observed worldwide.

Keywords: Odontogenic Tumors; Epidemiology; Jaw Neoplasms.

[1] Federal University of Rio Grande do Norte, Natal-RN, Brazil.
[2] A.C. Camargo Cancer Center, São Paulo-SP, Brazil.
[3] University of Pernambuco, Camaragibe-PE, Brazil.

Correspondence to:
Rômulo Augusto de Paiva Macedo.
E-mail: romuloapmacedo@gmail.com

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INTRODUCTION

Odontogenic tumors (OT) consist of several lesions derived from tooth-forming apparatus presenting various histological, cytological, and architectural patterns. They range from hamartomatous lesions to true neoplasms (benign or malignant), exhibiting distinct clinical behaviors[1-3]. In order to better comprehend these lesions, facilitate communication between physicians and improve treatment, the World Health Organization (WHO) developed a classification system for OT in 1971. The edition (2005) highlights their histological types and biological behaviors, by dividing them in groups[4].Some re-organizations made along the WHO classifications result in great divergences between authors. The inclusion of KCOT and CCOT as OT, formerly considered cysts, is one of the most controversial discussions. Several papers published after the 2005 WHO classification maintains considering KCOT and CCOT as cysts, not including them in OT studies[5,6]. This leads to different epidemiological profiles of cysts and OT[3,7,8]. However in the WHO classification 2017 reconsidered his position and classified these lesions as odontogenic cysts[9]. Furthermore, previous studies show the prevalence of OT differs according to the geographical location; nevertheless, the lack of standardization concerning the edition of the WHO classification makes it necessary to better describe the frequency of these tumors. Thus, the objective of this study was to determine the global epidemiology of OT through a systematic search of the literature considering only studies based on the 2005 WHO classification.

MATERIAL AND METHODS

A systematic search was conducted in the PubMed/Medline database for papers published from January 2006 to December 2016. Studies that evaluated the incidence and/or frequency of OT following the 2005 WHO classification were selected[4]. Entry terms included: "odontogenic tumors", "odontogenic tumours", "odontogenic lesions", "epidemiology" and "WHO classification", using the Boolean operators "AND" and "OR". The selected papers must have met the inclusion criteria described below:

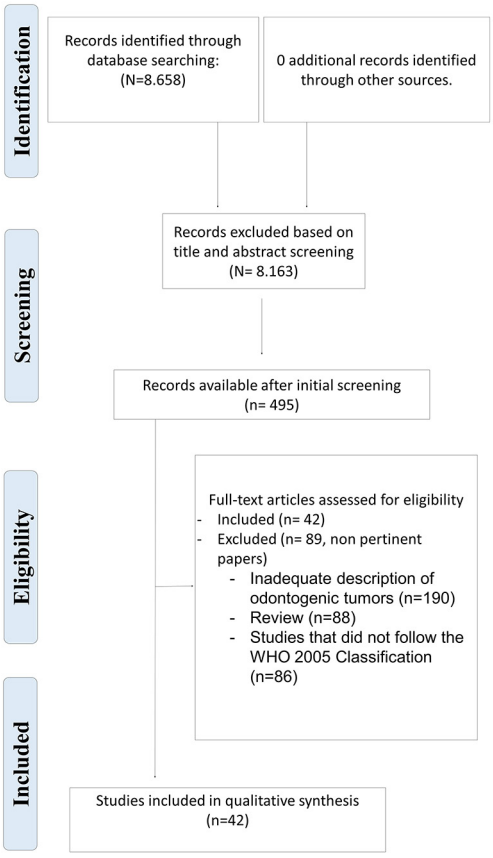
• The paper must be full text and written in English;

• Incidence or frequency of OT must be described;

• 2005 WHO classification of head and neck tumors must be followed;

• Country or city where the study was conducted must be informed.

Case reports, papers that followed the 2005 WHO classification but excluded any type of tumor, and those that described the incidence of only one type of OT were not considered. For the initial selection, two independent evaluators screened titles and abstracts. We initially found 8,658 articles, after a critical analysis of abstracts, 495 articles were selected. Then, the papers judged pertinent were analyzed in their entirety and the 42 studies selected were defined in a consensus meeting and included in the systematization of the data (Figure 1). Information regarding the geographic location, gender, age (categorized in decades of life), anatomical location, and histological type of tumor were recorded.



RESULTS

A total of 42 papers met the established criteria: 15 in Asia, 9 in South America, 9 in Africa, 6 in North America, 2 in Europe and 1 in Oceania (Table 1). They described from 14 to 1,677 cases of OT and summed up, they accounted for 13,490 cases of OT. The majority of the studies was conducted in Asia (n=6,472; 48%) and the minority in Oceania (n=93; 0.7%).

Table 1. General features of studies based on the 2005 WHO classification of odontogenic tumors

Author (year)	Country	n	Most common tumor	% of Malignant tumors	M:F ratio	Man:Max ratio
Buchner *et al*.[8] (2006)	USA	1,133	Odontoma	0.5%	NI	NI
Jing *et al*.[10] (2007)	China	1,642	Ameloblastoma	3.0%	1.4:1	4:1
Avelar *et al*.[11] (2008)	Brazil	238	Keratocystic odontogenic tumor	0.0%	1:1.3	2:1
Lima *et al*.[12] (2008)	Brazil	42	Odontoma	0.0%	NI	NI
Elarbi *et al*.[13] (2009)	Libya	35	Odontoma	0.0%	1:1	1.6:1
El-Gehani *et al*.[14] 2009	Libya	148	Keratocystic odontogenic tumor	0.0%	1.3:1	2:1
Luo and Li[15] (2009)	China	1,309	Keratocystic odontogenic tumor	5.9%	1.3:1	3.5:1
Gaitán-Cepeda *et al*.[16] (2010)	Mexico	134	Keratocystic odontogenic tumor	0.0%	1:1.5	NI
Saghravanian *et al*.[17] (2010)	Iran	165	Ameloblastoma	1.8%	1:1.1	2.4:1
Tawfik *et al*.[18] (2010)	Egypt	82	Ameloblastoma	3.7%	1.2:1	4.8:1
Ali *et al*.[19] (2011)	Kuwait	61	Keratocystic odontogenic tumor	0.0%	1:1.1	2.6:1
Mamabolo *et al*.[20] (2011)	South Africa	743	Ameloblastoma	3.1%	1.5:1	7:1
Osterne *et al*.[21] (2011)	Brazil	185	Ameloblastoma	0.0%	1.2:1	2.1:1
Varkhede *et al*.[22] (2011)	India	120	Ameloblastoma	0.0%	1.4:1	2.7:1
Chaisuparat *et al*.[23] (2012)a	Thailand/USA	14	Ameloblastic carcinoma	100%	2.4:1	1.8:1
Costa *et al*.[24] (2012)	Brazil	201	Keratocystic odontogenic tumor	5.0%	1.3:1	2.3:1
Saxena *et al*.[25] (2012)	India	31	Ameloblastoma	0.0%	1:1	2.2:1
Servato *et al*.[26] (2012)	Brazil	431	Odontoma	0.2%	1:1	1.2:1
Siriwardena *et al*.[27] (2012)	Sri Lanka	1,677	Ameloblastoma	1.4%	1:1	2.8:1
Chrysomali *et al*.[28] (2013)	Greece	652	Keratocystic odontogenic tumor	0.2%	1.2:1	2:1
Iatrou *et al*.[29] (2013)	Greece	40	Odontoma	0.0%	1.5:1	1.3:1
Johnson *et al*. (8) (2013)	Australia	93	Keratocystic odontogenic tumor	0.0%	1.5:1	2.3:1
Koivisto *et al*.[30] (2012)	USA	1,020	Keratocystic odontogenic tumor	0.0%	1.2:1	1.5:1
Servato *et al*.[31] (2013)	Brazil	240	Keratocystic odontogenic tumor	2.1%	1:1.1	2.6:1
Anyanechi *et al*.[32] (2014)	Nigeria	156	Ameloblastoma	3.2%	1.2:1	11:1
Bassey *et al*.[33] (2014)	Nigeria	79	Ameloblastoma	0.0%	5:1	4.6:1
Ebenezer and Ramalingam[34] (2010)	India	107	Odontoma	1.0%	1:1.6	2.4:1
Fang *et al*.[35] (2014)	China	109	Ameloblastoma	0.0%	1.7:1	1.9:1
Martínez Martínez *et al*.[36] (2014)a	Mex/Bra/Gua	25	Ameloblastic carcinoma	100%	1.1:1	6.2:1
Naz *et al*.[37] (2014)	Pakistan	179	Ameloblastoma	1.7%	1.7:1	4.7:1
Ramos *et al*.[38] (2014)	Brazil	78	Keratocystic odontogenic tumor	0.0%	1:1	2.7:1
AlSheddi *et al*.[39] (2015)	Saudi Arabia	188	Keratocystic odontogenic tumor	1.3%	1.4:1	1.8:1
Lawal *et al*.[40] (2015)a	Nigeria	21	Ameloblastic carcinoma	100%	2.1:1	2.5:1
Lee *et al*.[41] (2015)a	USA	295	Malignant ameloblastoma	100%	1.6:1	1.8:1
Sekerci *et al*.[42] (2015)	Turkey	218	Ameloblastoma	5.9%	1:1	3.5:1
Deepthi *et al*.[43] (2016)	India	305	Ameloblastoma	1.0%	1:1.1	3:1
Iyogun *et al*.[44] (2016)	Nigeria	63	Ameloblastoma	0.0%	1:1.2	4.2:1
Jaeger *et al*.[7] (2016)	Brazil	504	Keratocystic odontogenic tumor	0.2%	1:1	2.6:1
Goteti[45] (2016)	Libya	85	Ameloblastoma	1.1%	1.3:1	2:1
Nalabolu *et al*.[46] (2017)	India	161	Ameloblastoma	0.0%	2.2:1	2.8:1
Peker *et al*.[47] (2016)	Turkey	192	Keratocystic odontogenic tumor	0.0%	1.2:1	2:1
da Silva *et al*.[3] (2016)	Brazil	289	Keratocystic odontogenic tumor	0.3%	1:1.3	2.5:1

NI: Not informed; n: number of cases; %: Percentage; M: Male; F: Female; Max: Maxilla; Man: Mandible; USA: United States of America; Mex: Mexico; Bra: Brazil; Gua: Guatemala.

[a]The study only evaluated malignant tumors

The most prevalent tumor worldwide was KCOT (n=4,328; 32.1%) followed by AMB (n=4,132; 30.6%) and ODO (n=2,339; 17.3%); however, in Asia and Africa AMB was more common (Figure 1). Since Turkey and Russia are transcontinental countries (Eurasia), Turkey was included in Asia as studies performed there were located in Southwestern Asia [43,48]. No study was published in Russia.

Table 2. Gender and anatomic site distribution of benign and malignant odontogenic tumors.

Histological Types	GENDER				ANATOMIC SITE				TOTAL	
	Male Cases (%)	Female Cases (%)	NI Cases (%)	M:FRatio	Maxilla Cases (%)	Mandible Cases (%)	NI Cases (%)	Man:Max Ratio	Cases	%
Odontogenic epithelium, without odontogenic ectomesenchyme										
Ameloblastoma	1,764 (42.7)	1,429 (34.6)	939 (22.7)	1.2:1	362 (8.7)	2,903 (70.3)	867 (21.0)	8:1	4,132	30.6
Keratocystic odontogenic tumor	1,635 (37.8)	1,091 (25.2)	1,602 (37.0)	1.5:1	690 (15.9)	2,059 (47.6)	1,579 (36.5)	3:1	4,328	32.1
Adenomatoid odontogenic tumor	131 (33.1)	183 (46.2)	82 (20.7)	1:1.4	194 (49.0)	118 (29.8)	84 (21.2)	1:1.6	396	2.9
Squamous odontogenic tumor	4 (16.7)	12 (50.0)	8 (33.3)	1:3	3 (12.5)	8 (33.3)	13 (54.2)	2.6:1	24	0.2
Calcifying epithelial odontogenic tumor	65 (41.7)	56 (35.9)	35 (22.4)	1.1:1	33 (21.2)	81 (51.9)	42 (26.9)	2.4:1	156	1.2
Odontogenic epithelium with odontogenic ectomesenchyme										
Ameloblastic fibroma/fibrodentinoma	44 (29.9)	52 (35.4)	51 (34.7)	1:1.2	23 (15.6)	78 (53.1)	46 (31.3)	3.4:1	147	1.1
Ameloblastic fibro-odontoma	26 (28.2)	33 (35.9)	33 (35.9)	1:1.2	18 (19.5)	39 (42.4)	35 (38.1)	2.1:1	92	0.7
Odontoameloblastoma	2 (66.7)	1 (33.3)	0 (0.0)	2:1	2 (66.7)	1 (33.3)	0 (0.0)	1:2	3	0.02
Odontoma	553 (23.6)	576 (24.7)	1,210 (51.7)	1:1	605 (25.9)	631 (27.0)	1,103 (47.1)	1:1	2,339	17.3
Dentinogenic ghost cell tumor	16 (69.6)	7 (30.4)	0 (0.0)	2.3:1	7 (30.4)	16 (69.6)	0 (0.0)	2.3:1	23	0.2
Calcifying cystic odontogenic tumor	104 (34.0)	85 (27.6)	118 (38.4)	1.2:1	112 (36.5)	120 (39.1)	75 (24.4)	1:1	307	2.3
Mesenchyme/Odontogenic ectomesenchyme										
Cementoblastoma	34 (24.6)	60 (43.5)	44 (31.9)	1:1.7	26 (18.8)	80 (58.0)	32 (23.2)	3:1	138	1.0
Odontogenic fibroma	34 (21.5)	47 (29.5)	78 (49.0)	1:1.4	39 (24.5)	62 (39.0)	58 (36.5)	1.6:1	159	1.2
Myxoma	145 (29.2)	175 (35.2)	177 (35.6)	1:1.2	157 (31.6)	185 (37.2)	155 (31.2)	1.2:1	497	3.7
Malignant odontogenic	339 (57.9)	211 (36.0)	36 (6.1)	1.6:1	151 (25.7)	381 (65.0)	54 (9.3)	2.5:1	586	4.3
Odontogenic tumors NS	0 (0.0)	0 (0.0)	163 (100)	-	0 (0.0)	0 (0.0)	163 (100)	-	163	1.2
TOTAL	4,896 (36.3)	4,018 (29.8)	4,576 (33.9)	1.2:1	2,422 (17.9)	6,762 (50.2)	4,306 (31.9)	2.8:1	13,490	100

NI: Not informed; NS: Not specified; %: Percentage; M: Male; F: Female; Max: Maxilla; Man: Mandible.

Tumors of odontogenic epithelium, without odontogenic ectomesenchyme

The most frequent tumors in this group were KCOT and AMB. Both occurred more in men, with a male/female ratio of 1.5:1 and 1.2:1, respectively. For the other tumors, women were more affected. Apart from AOT, the mandible was the most common anatomical site (Table 2). The age of the patients ranged from 1 to 87 years and was more prevalent between the 2nd and 4th decades of life (Table 3).

Tumors of odontogenic epithelium with odontogenic ectomesenchyme

ODO was by far the most frequent tumor in this group, occurring more in women, followed by CCOT, which was more common in men. Higher incidence in the mandible was observed, with the exception of ODA (Table 3). The age ranged from 2 to 92 years and was more prevalent between the 1st and 2nd decades of life. CCOT, in particular, was more common between the 2nd and 5th decades (Table 3).

Table 3. Age distribution of benign odontogenic tumors (categorized by decades of life).

Histological Types	Age Range	Decade of life									Total		
		1st	2nd	3rd	4th	5th	6th	7th	>8th	NI	n	% (All)	% (Group)
Odontogenic epithelium, without odontogenic ectomesenchyme													
Ameloblastoma	1-86	85	610	817	673	503	289	200	102	853	4,132	30.6	32.0
Keratocystic odontogenic tumor	5-87	67	580	692	551	366	255	198	76	1,543	4,328	32.1	33.5
Adenomatoid odontogenic tumor	7-70	10	182	64	26	14	5	0	1	94	396	2.9	3.0
Squamous odontogenic tumor	9-69	1	1	3	4	1	5	3	0	6	24	0.2	0.2
Calcifying epithelial odontogenic tumor	6-79	13	16	19	25	22	20	7	5	29	156	1.2	1.2
Odontogenic epithelium with odontogenic ectomesenchyme													
Ameloblastic fibroma/fibrodentinoma	6-69	14	33	25	12	7	2	4	0	50	147	1.1	1.2
Ameloblastic fibro-odontoma	2-50	26	22	3	3	1	1	0	0	36	92	0.7	0.7
Odontoameloblastoma	9-29	1	0	1	0	0	0	0	0	1	3	0.02	0.02
Odontoma	3-84	207	501	188	105	47	50	19	13	1,209	2,339	17.3	18.1
Dentinogenic ghost cell tumor	17-70	0	5	5	4	2	4	1	2	0	23	0.2	0.2
Calcifying cystic odontogenic tumor	9-92	19	67	40	30	20	16	13	13	89	307	2.3	2.4
Mesenchyme/Odontogenic ectomesenchyme													
Cementoblastoma	6-83	7	34	30	16	15	6	1	2	27	138	1.0	1.1
Odontogenic fibroma	4-60	5	18	26	9	15	12	3	0	71	159	1.2	1.2
Myxoma	3-70	31	111	95	67	31	18	4	3	137	497	3.7	3.9
Odontogenic tumors NS	-	-	-	-	-	-	-	-	-	163	163	1.2	1.3
TOTAL	1-92	486	2,180	2,008	1,525	1,044	683	453	217	4,308	12,904	95.7	100

NI: Not informed; NS: Not specified; n: Number of cases; %: Percentage.

Tumors of mesenchyme and/or odontogenic ectomesenchyme, with or without odontogenic epithelium

The most frequent tumor in this group was MYX. Overall, all tumors occurred more in women and the mandible was the most common location (Table 2). The age ranged from 3 to 83 years, being more prevalent between the 2nd and 3rd decades of life (Table 3).

Malignant odontogenic tumors

Malignant OT represented only 4.3% of all tumors. MAMB was the most common tumor, followed by AMC. All malignant OT affected more men, with a male:female ratio of 1.6:1, and the mandible was the most common anatomical site (Table 1). The age ranged from 7 to 82 years. Despite the wide age distribution, these tumors showed an increased incidence from the 4th decade of life on (Table 4).

Table 4. Age distribution of malignant odontogenic tumors (categorized by decades of life).

Histological Types	Age Range	Decade of life									Total		
		1st	2nd	3rd	4th	5th	6th	7th	>8th	NI	n	% (All)	% (Group)
Odontogenic carcinomas													
Ameloblastic carcinoma	16-79	0	1	12	15	14	13	14	5	41	115	0.9	19.6
Clear cell odontogenic carcinoma	9-77	1	0	4	3	5	4	4	1	3	25	0.2	4.3
Primary intraosseous squamous cell carcinoma	19-82	0	2	3	10	22	21	29	10	8	105	0.7	17.9
Malignant ameloblastoma	30-49	0	0	0	1	1	0	0	0	182	184	1.4	31.4
Intraosseous squamous cell carcinoma (arising in KCOT or OC)	44-55	0	0	1	0	2	3	0	0	0	6	0.04	1.0
Ghost cell odontogenic carcinoma	19-59	0	1	2	2	3	1	1	1	0	11	0.09	1.9
Odontogenic sarcomas													
Ameloblastic fibrodentinosarcoma	19	0	1	0	0	0	0	0	0	0	1	0.01	0.2
Ameloblastic fibrosarcoma	7-59	1	4	8	3	1	2	0	0	8	27	0.2	4.6
Ameloblastic fibro-odontosarcoma	NI	0	0	0	0	0	0	0	0	2	2	0.02	0.4
Malignant odontogenic tumors NS	NI	0	0	0	0	0	0	0	1	109	110	0.8	18.7
TOTAL		2	9	30	34	48	44	48	18	353	586	4.3	100

NI: Not informed; NS: Not specified; n: Number of cases; %: Percentage; KCOT: Keratocystic odontogenic tumor; OC: Odontogenic cyst.

DISCUSSION

OT are relatively uncommon lesions. Due to their various clinical and histological presentations, a better knowledge regarding their frequency is required. Data shows the frequency of OT differs according to the geographical location. Retrospective studies conducted in South America, North America and Europe show an incidence between 2.2% and 5% among all diagnosed oral lesions[3,22,29,31]. On the other hand, in Africa[15] and Asia[16,28] studies report a higher frequency, comprising up to 8.9% of all oral lesions.

In the present review, benign OT accounted for the majority of the cases (n=12,904; 95.7%) and malignant OT represented only 4.3% (n=586) of all tumors. Except for studies that only evaluated malignant OT[24,37,41,42], the overall incidence of these tumors range from 0 to 5.9%[8-7-23,25-36,38-40,43-48], corroborating our data.

Regarding the gender, most OT occurred in men. However, some studies in South America[3,12,32], North America[17] and Asia[20] showed a higher incidence of these tumors in females. The age varied widely throughout the decades of life. In general, a higher prevalence between the 2nd and 4th decades of life was observed, according with other review papers[49,50]. ODO and AFO were the exception, occurring more in the first and second decades of life. In contrast, malignant OT occurred more in older patients, with a peak incidence from the 4th decade of life on, as also reported by Avelar *et al.*[49] and Johnson *et al.*[50].

Mandible was the main anatomical location with a mandible:maxilla ratio of approximately 2.8:1, similarly to other papers[49,50]. Nevertheless, the studies performed in Africa[19,21,33,34,45] presented a higher mandible:maxilla ratio when compared to studies conducted in other continents, reaching up to 11:1.

KCOT was the most common neoplasm considering all OT. On the other hand, previous studies based on the 1971 and 1992 WHO classification[32,49,50], aside from showing a smaller incidence of OT, they reported AMB and ODO as the most frequent tumors. Regardless of whether there is an agreement on the classification of this tumor, the fact is the inclusion of KCOT in the 2005 WHO classification, in addition to increase the overall frequency of OT, also led to a change in the epidemiological profile of these tumors worldwide[3,8,17]. Nevertheless, we emphasize that the KCOT was removed from the recent WHO classification of odontogenic tumors, it was once again classified as cyst, this fact certainly will lead to a different profile of global incidence from now on[9].

In the Asian and African continent, despite the introduction of the tumors (KCOT and CCOT), AMB remains the most frequent tumor[11,18,19,21,23,26,28,33,36,38,43-47]. Besides that, globally, AMB currently represents the second most common OT diagnosed based on 2005 WHO classification.

The third most prevalent tumor was ODO. The low incidence of these tumors may happen because of underdiagnosed. The indolent behavior, self-limited growth and pathognomonic radiographic appearance lead many surgeons to perform their removal and discard them, not sending samples for histopathological analysis. Still, ODO was the most frequent tumor in some studies conducted in Europe[30], North America[10], South America[13,27], Asia[35] and Africa[14].

In relation to the malignant OT, MAMB was the most frequent one in our review. This tumor, also named as metastatic AMB, accounted for 31.4% of the malignant OT. Interestedly, North America was the only continent to report MAMB as the most common malignant tumor[42]. In the other continents, AMC followed by PIOSCC were more frequent. In this review, AMC was the second most common malignant neoplasm, representing 19.6% of all malignant OT. Concerning the diagnosis of MAMB, it may be difficult, as it does not present pleomorphism, necrosis, mitosis and other malignancy characteristics. Except for the ability to emit nodal and/or distant metastasis, they are morphologically identical to a conventional AMB[4]. Because of this imprecise clinical and histopathological behavior, the recent WHO classification recategorized MAMB as a benign tumor, naming "Metastasizing (malignant) ameloblastoma"[9]. We consider this classification controversial, since the ability to emit metastasis is characteristic of cancer.

A single case in this review diagnosed as odontogenic carcinosarcoma was classified as unspecified malignant tumor, since the WHO (2005) excluded this tumor from the classification due to the absence of evidence as a separate entity from other odontogenic carcinomas[4,35]. However, sclerosing odontogenic carcinoma and odontogenic carcinosarcoma has been added to the recent WHO classification[9], although rare, the addition of these tumors will also change the incidence of malignant OT from now on.OT present different incidence profiles according to the geographical location, which became evident in this paper. The five main tumors diagnosed worldwide in descending order were: KCOT, AMB, ODO, MYX and AOT. However some odontogenic tumors are unreported. In addition, the incidence and frequency of

these tumors are different when compared to studies based on the WHO classifications prior to 2005. There was a significant change with the addition of KCOT and CCOT in the 2005 WHO classification of head and neck tumors that led to an increase of approximately 35% in the total number of OT diagnosed to date.

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