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ORIGINAL ARTICLE

Odontogenic tumors: a retrospective study in a Brazilian population according to the 5th WHO classification and historic context of previous classifications

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Abstract:

The World Health Organization (WHO) periodically updates the classification of head and neck lesions, including odontogenic tumors (OT). This study aimed to report the frequency of OT diagnosed in an oral pathology unit according to the latest WHO edition and describe the classifications' historical context. All clinicopathological records and microscopic slides of OT specimens diagnosed between 2000 and 2024 were retrieved from the files of an oral pathology unit in Brazil. Diagnoses were re-assessed, and the tumors were classified following the 5th WHO Classification of head and neck tumors. A total of 153 cases were evaluated. OT were predominant in women (80 cases; 52.3%), and the patients were mostly diagnosed in the fourth decade of life. Most of OT belonged to the epithelial group. Conventional ameloblastoma (CA) was the most prevalent tumor (68 cases; 44.4%), followed by odontoma (48 cases; 31.4%). Two cases of CA were re-classified as adenoid ameloblastoma. Systems' classifications of OT have been based on tooth growth phase, tumor histogenesis, biological behavior, and immunohistochemical and molecular analyses. The current edition did not describe any significant changes. We verified that OT are uncommon and that further classifications will rely on specific genetic and molecular profiles.

Keywords: Odontogenic tumor; World Health Organization; Classification; Oral pathology.

INTRODUCTION

Odontogenic Tumors (OT) comprise a group of lesions related to the development of teeth and their supporting tissues - odontogenic epithelium and/or mesenchymal cells[1]. These neoplasms are uncommon, accounting for <2–3% of all oral and maxillofacial diseases. Considering all neoplasms in the human body, the prevalence of OT is approximately 0.002–0.003%[2]. The lesions range from harmatomatous to benign and malignant lesions with variable microscopic features and biologic behavior[3]. The incidence and prevalence of OT, as well as their clinicopathological characteristics vary worldwide, which demands a better comprehension of risky groups and the potential factors involved with their pathogenesis[3,4].

To designate the terminology of OT internationally, the World Health Organization (WHO) has published a book series of classification of head and neck tumors, including odontogenic cysts, indicating several diagnostic criteria, such as clinicopathological features, surgical specimen aspects, microscopic description, and treatment modalities. More recently, molecular findings and genetic profiles were also incorporated[5-7].

Currently, benign OT are divided into three groups. Tumors of epithelial origin comprise adenomatoid

Statement of Clinical Significance
The 5th WHO classification of odontogenic tumors demonstrates the importance of using molecular and genetic studies to comprehend the biological behavior of these tumors, to enhance decision-making and to provide effective prognostic monitoring. Still, odontogenic tumors are uncommon and conventional ameloblastoma remains de most prevalent lesion in this group.

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odontogenic tumor (AOT), squamous odontogenic tumor (SOT), calcifying epithelial odontogenic tumor (CEOT), unicystic ameloblastoma (UA), extraosseous ameloblastoma (EA), conventional ameloblastoma (CA), adenoid ameloblastoma (AA), and metastasizing ameloblastoma (MA). Mixed OT encompass odontoma (OD), primordial odontogenic tumor (POT), ameloblastic fibroma (AF), and dentinogenic ghost cell tumor (DGCT). Odontogenic fibroma (OF), cementoblastoma (CB), cemento-ossifying fibroma (COF), and odontogenic myxoma (OM) are included as tumors with mesenchymal origin. Sclerosing odontogenic carcinoma (SOC), ameloblastic carcinoma (AC), clear cell odontogenic carcinoma (CCOC), ghost cell odontogenic carcinoma (GCOC), primary intraosseous carcinoma, not otherwise specified (IC, NOS), odontogenic carcinosarcoma (OC), and odontogenic sarcomas (OS) are grouped under malignant OT section[7-9].

The changes provided for OT through the years reflect the current knowledge regarding clinicopathological data of these lesions. The modifications include new nomenclatures, description of new entities, and updates of pre-existing neoplasms considering new scientific evidence[7,10]. In this scenario, international standardization of OT allows clinicians and pathologists to employ and follow the same sort of information to establish an accurate diagnosis and establish different treatment modalities, enhancing interdisciplinary collaboration and training programs[9,11]. Moreover, the revision of diagnostic material from oral pathology files provides additional material to subsequent studies involving epidemiology, biomarkers, new treatment modalities, and prognosis establishment[1,12,13]. Then, the present study aimed to assess the frequency and OT types from an oral pathology service in line with the latest WHO classification for head and neck tumors and review the literature regarding the historical background of such categorizations.

MATERIAL AND METHODS

This study was approved by the Ethics Committee of the Federal University of Pernambuco, Recife, Brazil (Process no. process no. 6.306.297). It is also in accordance with the Helsinki Declaration of 1975, as revised in 2024.

"An electronic search was carried out by one author in February 2005 without time restriction using PubMed database and included the following terms and their synonyms: "Odontogenic tumor*", "Classification*", "History", "Antecedents", "World Health Organization", "WHO", "Classification for head and neck tumors". There was no language restriction."

In sequence, all cases diagnosed as OT between January 2000 and July 2024 were retrospectively retrieved from the oral pathology unit files of the Federal University of Pernambuco (Brazil). Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were obtained, and new histologic sections (5μm thick) were stained with hematoxylin-eosin (H&E) for microscopic description and diagnostic confirmation by at least two oral pathologists, following the current WHO Classification of head and neck tumors (2022). The clinical data were retrieved from the patients' files and comprised patients' sex and age, tumor location, and final diagnosis. Cases with incomplete description or lacking this information, and reports without slides or paraffin embedded blocks were excluded. In addition, specimens whose diagnostic report was not in accordance with the microscopic slide content and did not comprise OT were excluded. Collected data was systematically organized in datasheets, using Microsoft Office Excel software, version 2407 (Microsoft Corporation, Redmond, Washington, USA). Descriptive analyses were carried out using SPSS version 25.0 (IBM, New York, USA) and included absolute numbers, percentages, mean values, and standard deviations.

RESULTS

Demographics and tumors' diagnoses

Two hundred and seventy-one cases of OT were initially retrieved. However, 153 cases remained for analyses due to lack of clinical data, inconsistent diagnosis or absence of paraffin blocks and/or glass slides. Between all groups, the tumors were more common in females (80 cases; 52.3%) and most patients were diagnosed in the fourth decade of life (mean age: 30.7 years; age range: 1-83 years). All lesions were benign. The frequency of OT groups did not present any modification between the 4th and the 5th WHO editions[6,7]; most of our sample consisted of epithelial neoplasms (87 cases; 56.9%), followed by mixed-origin lesions (52 cases; 34%) (Table 1). Tumors of epithelial origin exhibited an equal distribution between males and females while mixed OT were more prevalent in females in both editions (28 cases; 35%) (Table 2). In addition, CA was the most diagnosed tumor (67 cases; 43.8%), followed by OD (48 cases; 31.4%).

Table 1. Demographic features and frequency of odontogenic tumors groups before the 2022 World Health Organization classification of head and neck tumors.

Feature	n=153	%
Sex		
Female	80	52.3
Male	73	47.7
Age (mean age: 30.7 years)		
≤ 30.7	48	31.4
≥ 30.7	75	49.0
NA*	30	19.6
Tumor classification group		
Odontogenic epithelium	87	56.9
Mixed	52	34.0
Odontogenic ectomesenchyme	14	9.2

*Information not available.

Following review of all cases according to the latest WHO Classification of head and neck tumors (2022), we observed that CA remained the most prevalent neoplasm among epithelial lesions (67 cases; 43.8%), despite two cases (2.3%; within group) that were re-classified as AA (Figure 1). Mixed and mesenchymal lesions did not present any changes, and the most common tumors were OD (92.3%; within group) and OM (9%; within group), respectively (Table 3). As demonstrated in Table 4, AA exclusively involved middle-aged males, while female individuals with FA encompassed the lowest mean age (18 years old). The commonest OT between adult males and females was CA (35 and 32 cases, respectively), followed by OD (23 men and 25 women). Amongst OT derived from the ectomesenchyme, CB mostly affected females from the 5th decade of life (4 cases; 66.7%), as observed in OM cases, which comprised patients in their thirties.

Table 2. Sex distribution of odontogenic tumors according to their groups.

Sex/Tumor classification	n=153	% within sex	% of total
Female			
Odontogenic epithelium	43	53.8	28.1
Mixed	28	35.0	18.3
Odontogenic ectomesenchyme	9	11.3	5.9
Male			
Odontogenic epithelium	44	60.3	28.8
Mixed	24	32.9	15.7
Odontogenic ectomesenchyme	5	6.8	3.3

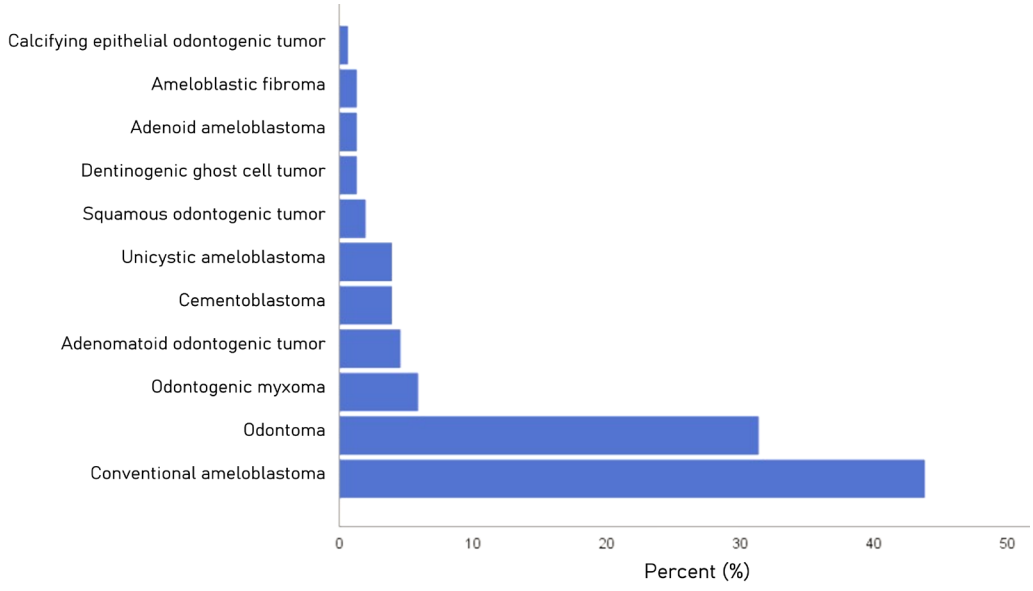

Figure 1. Bar chart exhibiting the frequency of odontogenic tumors according to the 2022 World Health Organization classification of head and neck tumors.

Literature review

An illustrated timeline with the hallmarks of the literature review is presented in Figure 2.

Early reports regarding odontogenic tumors

It seems to be a disagreement regarding the first OT depiction; some authors affirm that a complex OD was detailly described by Pierre Fauchard in 1746[2,14], while Ide et al.[15] assert that the Fauchard's illustrations likely represented a peripheral ossifying fibroma. Either way, the first published report of an OT was on a bony-hard lesion in the maxilla, which was published in the American Journal of Dental Science in 1839. This lesion was later considered as a CB[16,17].

First classification attempts

In the 19th century, the number of reported cases of different OT had increased considerably. Then, a French physician named Pierre Paul Broca[18] published a monograph classifying several neoplasms. His work included the term *odontome* to define all tumors originated from the odontogenic structures and proposed a classification based on the tooth growth phase at the onset of malformation[18]. Few years later, Malassez (1885)

Table 3. Frequency of odontogenic tumors following the current World Health Organization classification of head and neck tumors.

Tumor classification/Tumor name	n=153	% within group	% of total
Odontogenic epithelium			
Conventional Ameloblastoma	67	77	43.8
Unicystic Ameloblastoma	6	6.9	3.9
Adenomatoid Odontogenic Tumor	7	8	4.6
Calcifying Epithelial	1	1.1	0.7
Odontogenic Tumor	3	3.4	2
Squamous Odontogenic Tumor	2	2.3	1.3
Adenoid Ameloblastoma	2	2.3	1.3
Mixed			
Odontoma	48	92.3	31.4
Odontogenic Ghost Cell Tumor	2	3.8	1.3
Ameloblastic Fibroma	2	3.8	1.3
Odontogenic ectomesenchyme			
Odontogenic Myxoma	9	64.3	5.9
Cementoblastoma	5	35.7	3.3

Table 4. Frequency of odontogenic tumors diagnosed in this study according to patients' age and sex.

Tumor name	mean age (years)	Male (n and %)	Female (n and %)
Conventional Ameloblastoma	36	35 (97.2)	32 (2.7)
Unicystic Ameloblastoma	22.5	4 (66.7)	2 (33.3)
Adenomatoid Odontogenic Tumor	27	6 (85.7)	1 (14.3)
Calcifying Epithelial Odontogenic Tumor	NA	1 (100)	0
Squamous Odontogenic Tumor	25	1 (33.3)	2 (66.7)
Adenoid Ameloblastoma	50.5	2 (100)	0
Odontoma	22.7	23 (48)	25 (52)
Odontogenic Ghost Cell Tumor	40.5	1 (50)	1(50)
Ameloblastic Fibroma	18	0	2 (100)
Odontogenic Myxoma	30.3	4 (44.4)	5 (55.6)
Cementoblastoma	45.4	2 (33.3)	4 (66.7)

NA: information not available.

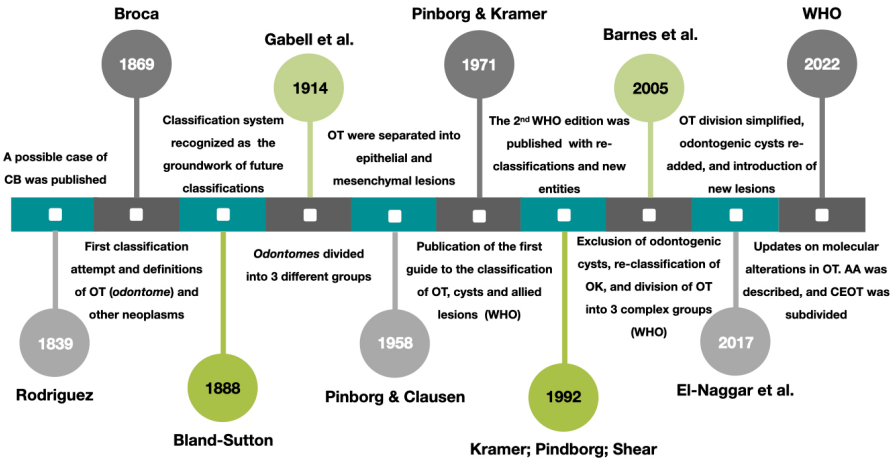

Figure 2. An illustrated timeline with the hallmarks of the literature review.

presented little modifications in Broca's organization[18], although both works did not achieve international recognition[2,17]. In 1888, Bland-Sutton provided a classification system taken on the nature of specific cells of the tooth germ from which the tumor arose[19]. This system was considered the groundwork of modern odontogenic cysts and OT classifications[20].

Subsequently, the British Dental Association asked three clinicians to elaborate a report on OT. The authors modified the Bland-Sutton's classification, maintained the term *odontome* for all lesions, and grouped the tumors in three categories:

1. The epithelial *odontomes* which included "multilocular cysts" and "non-neoplastic cysts";
2. The composite *odontomes* comprising elements from both epithelium and mesenchyme;
3. The connective tissue *odontomes* that contained fibrous and other connective tissue lesions and arose from dental mesenchyme[21].

Terminology modifications through time

More in-depth studies gradually allowed the replacement of the term *odontome* by OT that corresponded with the cell of origin. For instance, the name adamantoblastoma was replaced by ameloblastoma in 1930[22,23]. The connective tissue *odontomes* were named fibromas or cementomas according to their structure, and the composite neoplasms preserved the original nomenclature – *odontomes* or odontomas[2]. In 1946, Thoma and Goldman excluded odontogenic cysts from the previous Bland-Sutton grouping[24]. This new classification was extensively accepted and included in several textbooks. The American Academy of Oral Pathology, which was established in 1952, also adopted this classification, adding minor changes, such as the use of the term odontoma to define lesions with both epithelial and mesenchymal components[2,25].

Insights regarding the pathogenesis of odontogenic tumors and contributions on tumors' classifications

As years passed by, the debate on the pathogenesis of OT became widespread. In this context, suggested that the epithelial-mesenchymal interaction could enlighten the cellular changes observed in tumor formation[26]. Then, the authors separated the tumors into epithelial and mesenchymal units[26,27]. In sequence, the epithelial group were subdivided in the following groups:

1. Tumors without inductive changes in the connective tissue, like CEOT and ameloblastoma, and
2. Tumors that induce modifications in the mesenchyme, such as AF and OD. The third subgroup composed exclusively by mesoderm and included OF and OM[2,26].

The World Health Organization initiative and first publications

Attending the demand for definitions of tumor types and implementation of a universal nomenclature, the WHO Collaborating Centre for the histological classification of OTs and allied lesions was established in 1966 (Royal Dental College, Copenhagen, Denmark). In the same year, professors Ivor Kramer and Jens Pindborg drafted an initial categorization including jaw cysts[2]. After years of case studies and revisions by

experts of oral and general pathologists, a classification system was adopted[28]. In 1971, the first guide to the classification of OT, cysts and allied lesions was finally published by WHO. This textbook was based on lesions' histogenesis, with division between benign and malignant tumors[2,29].

The second edition of the WHO classification, named Histological Typing of Odontogenic Tumors', was published 21 years later. The editors maintained the essentials of the previous edition, although some lesions were re-classified and new variants and neoplasms were included, like desmoplastic ameloblastoma and SOT[30,31]. Tumors and other lesions related to bone were also added[30-32].

World Health Organization classification revisions and so on

Ten years after the launch of the second edition, Philipsen and Reichart recognized the crescent advances regarding the comprehension of OT development with immunohistochemical and molecular biology techniques. They suggested a revision and update of the last OT classification based on tumors' biological behavior and divided the lesions into benign, malignant and non-neoplastic[30].

The Editorial and Consensus Conference of WHO (Lyon, France, 2003) provided sufficient material to the new WHO Blue Book and Genetics of Tumors of Head and Neck, which was released in 2005[5].

This edition divided the tumors in three categories:

1. Odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyme;
2. Odontogenic epithelium with odontogenic ectomesenchyme, with or without hard tissue formation; and
3. Mesenchyme and/or odontogenic ectomesenchyme with or without odontogenic epithelium[2,5].

Controversially, odontogenic cysts were excluded from this classification, which redefined odontogenic keratocyst (OK) as keratocystic odontogenic tumor (KCOT) due to its local aggressiveness and high recurrence rate[8]. Similarly, calcifying odontogenic cyst was replaced into the tumor section, named as calcifying cystic odontogenic tumor[5,8]. Some OT sections were considered confusing and with debatable scientific evidence, compromising the credibility of the Blue Book[8,12].

Based on the principles of summarization, clinical relevance, and scientific validity, the 4th edition of the World Health Organization's Classification of Head and Neck Tumors was designed and published[6,10]. The core changes were the update and reincorporation of odontogenic cysts in the textbook and simplification of subgroups, including only epithelial, mesenchymal, and mixed OT[6]. New entities were introduced, like sclerosing odontogenic carcinoma and desmoplastic ameloblastoma, while others were removed such as ameloblastic fibro-odontoma and ameloblastic fibrodentinoma, considered developing OD[9]. This edition also highlighted the improved understanding of etiopathogenesis of ameloblastoma; collectively, the incidence of *BRAF*, *RAS* and *FGFR-2* mutations in the studied cases was approximately 79%[9,10]. The consensus group of the 4th edition of the WHO classification settled to revert calcifying cystic odontogenic tumor and KCTO into calcifying odontogenic cyst and odontogenic keratocyst, respectively[6,9].

The 5th Edition of the World Health Organization Classification of Head and Neck Tumors

Five years after the previous edition, the latest material presents critical updates in line with the complex studies involving molecular alterations in OT, some of which having targeted-therapy potential. To provide more accurate diagnostic characteristics for each OT, every lesion includes Essential and Desirable Diagnostic Features[4]. Ameloblastic fibro-odontoma and ameloblastic fibrodentinoma remained under the spectrum of developing OD, although there are cases harboring BRAF V600 and exhibiting locally aggressive behavior and recurrences[1]. Adenoid ameloblastoma was introduced as a newly individually entity from the group of ameloblastomas[7,33]. The term CA was reintroduced. Contentiously, metastasizing ameloblastoma remains in the category of benign tumors, despite its mortality rate of 30%[6,7,34]. In addition, CEOT was divided into three microscopic subtypes: clear cell, cystic/microcystic and non-calcified/Langerhans cell rich, which stands as an uncertain diagnosis due to its microscopic and molecular features that resembles the amyloid subtype of OF[4].

DISCUSSION

This study evaluated the changes of OT diagnoses following the 5th WHO classification for head and neck tumors and provided an extensive review about the OT classifications through time, describing enhancements and limitations that have influenced the diagnostic process and tumors' typification. In general, it seems to be a relatively steady context on OT nomenclatures and little conceptually differences between the new and last two WHO publications[5,6]. On the other hand, insights

regarding the importance of immunohistochemical, genetic and molecular studies to understand the etiopathogenesis of OT have been discussed for more than 20 years[28]. To date, different mutations have been identified in CA, UA, AOT, CEOT, and OM, although these still don't contribute to define clinicopathological profiles or treatment applications[9,10].

As we observed, there is a higher prevalence of OT in females, ranging from 55–62% of the cases[12,35,36]. Also, OT were diagnosed in a wide age-group, ranging from 0–90 years[1,3,10]. There was no case of malignant OT in our study. Other authors reported an average of 3.2 cases (range: 1–6 malignant tumors), reflecting its rareness in different cohorts[1,3,12,36,37]. Despite variations in geographic regions and populations, it seems to be a well-established demographic data on OT. In line with our sample, the lesions originated from the odontogenic epithelium exhibit a similar distribution in both sexes, being CA the commonest OT in all groups[36,37].

Firstly introduced in 1930 by Ivy and Churchill[23], the terminology of ameloblastoma has been significantly modified; in 2017, the adjective "solid/multicystic" was removed due to its irrelevant biological weight and to avoid confusion with UA[10,12]. The present edition re-incorporated the descriptive term "conventional" possibly to provide a clearer and more accurate reference for pathologists[4,7]. This neoplasm has a peak incidence in the 4th and 5th decades of life, as found in the present study[1,35]. After sample revision following the 5th WHO classification[7], 2.3% of all OT former diagnosed as CA were re-defined as AA; the same number (2 cases; 0.4%) was described by Rees et al.[1]. A systematic review retrieved 30 cases of AA and showed that this new entity mostly affects men in the 5th decade of life[36]. Nevertheless, the few retrospective studies and the lack of sufficient data to assess the tumor biological behavior may lead to diagnostic mistakes and misguided treatment approaches.

Another lesion with classifying difficulties is the AOT. Its frequency varies among studies, ranging from 7-28 cases including our sample. According to Wright et al.[8], this epithelial neoplasm produces a dentinoid-like material, which is evidently not a product from odontogenic epithelium. Then, the classification of AOT based on its developmental histogenetic origin is difficult to perform. The 5th WHO classification for head and neck tumors did not present any substantial changes to AOT; there was a commentary regarding the Schimmelpenning syndrome, which can be associated with multiple AOT[4,7].

In line with our results, OD demonstrates a similar prevalence between males and females. This lesion usually involves adolescents and young adults[1,12]. Up to-date, OD are identified as the second most common lesion after CA, although its actual predominance may be occult because of unreported cases[4]. The last two WHO editions have stated that OD are hamartomas instead of true neoplasms[6,7]. It is likely that developing OD contains soft tissue resembling dental papilla with prominent epithelial components, while the presence of dental hard tissue induction is doubtable. These characteristics correspond to AF, which can be hard to differentiate them[9,10]. The WHO Blue Book and Genetics of Tumors of Head and Neck (2005) designed ameloblastic fibro-odontoma (AFO) as a neoplasm lesion and ameloblastic fibro-dentinoma (AFD) was included in the spectrum of AF[8]. The 4th (2017)[6] and 5th (2022)[7] WHO editions re-organized these lesions as developing OD, resulting in divergences between professionals, considering the local aggressive behavior with expansive and osteolytic growth of AFO, in contrast to OD[9,12]. In addition, some cases harbor BRAF PV600 mutations, suggesting a close association of AF with AFO and AFD[38].

According to our findings, OM remains the most frequent tumor in the mesenchymal group, which occupies the 3rd position of three OT groups[12,35,36]. In contrast to other studies[1,3,12], we found a slight female predominance, which can be explained by our total sample. The patients affected by OM are usually diagnosed between the 2nd and 3rd decades of life, as we described[1,12]. No major changes were revealed for OM in 2017 and 2022 by WHO[4]. Even though, the current edition reported the identification of activating mutations in the MAPK/ERK signaling pathway in OM, which represent a potential target-agent for treatment through pathway inhibition and tumor reduction[7].

The inclusion of a bigger and multicentric sample with complete clinicopathological description and additional records of the cases like imaging exams would have strengthened our findings. It is important to highlight that we collected cases from an oral pathology unit, which may also have affected our results due to possible heterogeneities in the type of biopsy, therapeutic schemes, and follow-up period implemented by each oral medicine and/or oral surgery service. Elucidation of the activated molecular pathways would enhance opportunities for adjunct and, perhaps, targeted therapy. Furthermore, for future contributions, access to molecular data to investigate its association with the clinicopathological profile of OT would support pathologists' diagnosis routine.

CONCLUSION

In conclusion, odontogenic tumors account for a small number of lesions, being more common in adult women. In line with other studies, CA corresponds to most of the cases. The recent editions of the WHO introduced few new concepts and nomenclatures regarding OT, focusing on their etiopathogenetic findings. We believe that further classifications will mainly consider molecular analyses.

AUTHORS' CONTRIBUTIONS

CIRF: Supervision, Validation, Writing – review & editing. LKTD: Investigation, Methodology, Writing – original draft. CVBLC: Formal analysis, Visualization. MLAP: Data curation, Formal analysis. EJAC: Resources, Writing – review & editing. DECP: Writing – review & editing. JFLC: Conceptualization, Methodology, Supervision, Validation.

CONFLICT OF INTEREST STATEMENT

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Competing interests: The authors have no relevant financial or non-financial interests to disclose.

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