Odontogenic tumours: a 25-year epidemiological study in the Marche region of Italy

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Compliance with ethical standards

The study was conducted in accordance with the “Ethical Principles for Medical Research Involving Human Subjects” statement of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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The authors declare that they have no conflicts of interest.

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ABSTRACT

Purpose. Epidemiological data of odontogenic tumours (OT) are conflicting, with significant differences among the countries. This study aims to evaluate incidence and prevalence of OTs in the Marche population in a period of 25 years, according to 4th Edition of WHO Classification.

Methods. In this study, only patients of Marche region treated for OTs were considered. Data were retrieved from Institute of Pathology, Marche Polytechnic University, Italy. Because this is the only tertiary referral centre for Head and Neck pathology within Marche region, the patient sample could be considered well representative of this area. From each case, age, sex, site, diagnosis, and relapses were recorded.

Results. Overall, 100 patients were treated for OTs from 1994 to 2018 in Marche region. The annual incidence rate ranged from 0.13 to 0.39 per 100,000, while life prevalence was 6.50 per 100,000. Mean age of onset for primary OTs was 49.7±20.1 years. 27 patients developed recurrences, showing a mean age of 54±19.7 years and a mean recurrence time of 51.2±34 months.

Conclusion. This is the first epidemiological study on OTs in Italian population according to 4th Edition of WHO Classification. Although limited in their retrospective nature, these findings could accurately estimate epidemiology of OTs in Italy.

Keywords.

Odontogenic tumors; Ameloblastoma; Odontome; Epidemiology; Italy

INTRODUCTION

Odontogenic tumours (OT) constitute a group of heterogeneous diseases that ranges from hamartomatous tissue proliferations to benign and malignant tumours with metastatic potential. These tumours derive from epithelial, ectomesenchymal and/or mesenchymal elements that are, or have been, part of the tooth-forming apparatus [1]. The OTs account for less than 1% of all neoplasms and are found exclusively within the maxillofacial bones or in the soft tissue overlying tooth-bearing areas [2,3]. The etiopathogenesis is still unknown: most OTs arise ex novo, while some lesions may originate from pre-existing odontogenic cysts [2].

Ameloblastoma represents the most common benign epithelial OT, originating from remnants of odontogenic epithelium. This tumour originates from remains of the dental lamina, as indicated by the expression of early markers of the oral epithelium such as PTX2, MSX2, DLX2, RUNX1, and ISL1 [3]. Ameloblastoma mainly affects posterior mandibular region (70-90%), with a peak in the IV-V decades of life. Overall, the data from literature do not show a clear sex preference, although the males seem to be more involved. Odontomas are the most common odontogenic lesion, typically diagnosed during the first two decades, in association with unerupted teeth. Odontomas originate due to genetic mutations of tooth germs and are classically divided into two subtypes: compound and complex. The compound odontomas typically originate in the anterior maxilla, while the complex odontomas are frequently found in the posterior mandible [2]. Odontogenic myxoma is the third most frequent OT, with most cases diagnosed in the II-IV decades of life. It is morecommon in female patients, with a M:F ratio of about 2:1, and two thirds of them are found in posterior mandible [3]. Overall, the other benign OTs are far less common, making it difficult to establish reliable epidemiological data. Most of them affect mandibular region of adult males, although there are exceptions. As an example, the adenomatoid odontogenic tumour occurs twice more frequently in the female sex and in the anterior maxilla, associated with included canines

(60%), preferring the II-III decades of life. Similarly, the primordial odontogenic tumour shows a marked preference for younger patients, with a peak in the II decade of life [1,4].

Malignant OTs are rare entities most commonly affecting male sex, with exception of odontogenic clear cell carcinoma. These tumours typically arise in the posterior mandibular region, with exception of the ghost cell odontogenic carcinoma. Odontogenic carcinomas are more common in patients over the V decade, while odontogenic sarcomas affect younger patients, with a mean age of onset of 27 years. Some entities are extremely rare; as an example, only 3 cases of ameloblastic carcinosarcoma and less than 10 cases of sclerosing odontogenic carcinoma have been published to date [3].

There are no specific follow-up recommendations for OTs. For this reason, the follow-up suggestions for OTs are included in the broader context of general guidelines relating to the diagnosis and treatment of Head and Neck tumours. In particular, for benign OTs an annual follow-up is indicated for the first 5 years, and at least once every two years for at least 25 years but lifelong follow-up is recommended [5]. Regarding malignant OTs, the National Comprehensive Cancer Network guidelines for Head and Neck malignant tumours suggest a postoperative follow-up every 1-3 months for the first year, every 2-4 months during the second year, every 4-6 months from the third to the fifth year, and once a year thereafter [6].

Epidemiological data of benign OTs show significant differences among the countries. According to some authors, ameloblastoma is the most common OT in East Asia and sub-Saharan African [7,8]. These results contrast with those obtained from studies conducted in North America, in which the most frequently diagnosed lesion appears to be the odontome, with ameloblastoma accounting for less than 15% of OT [9,4]. One reason for these discrepancies may be found in the type of data used in the studies, resulting in an underestimation of the OT frequency. Although ameloblastoma seems to be more common in African Americans than in Caucasians, a real geographical difference based on ethnic differences is still to be demonstrated [10,11,4].

Another source of uncertainty is related to histological classification of OT. In 2017, the World Health Organization (WHO) published a new classification of odontogenic lesions, characterised by simplification of histological classification and addition of odontogenic cysts [12]. In the last years, the classification of OT has been highly debated, especially regarding odontogenic keratocyst (OKC). Indeed OKC, previously defined as keratocystic odontogenic tumour, has been reintroduced into the cyst group due to the lack of sufficient evidence to justify its classification as a neoplasm [13,2,3,14]. Accurate information regarding disease occurrence are readily available for common cancers, while comprehensive epidemiological studies on rare tumours lack. Epidemiological data regarding OTs have generally been obtained through single-centre investigations, often in tertiary referral centres. However, this approach is biased in not demonstrating the actual population distribution of OTs.

In Marche region, Italy, due to its socio-demographic conditions and healthcare organization, there is only one tertiary referral centre for Head and Neck pathology. Consequently, it is possible to collect data on OTs in this region with a certain degree of accuracy, assuming that the risk of bias could be judged as lower than other epidemiological studies. This, in turn, could result in a more accurate estimation of the OT epidemiology in Italian population. This study aims to retrospectively determine the incidence and prevalence of OTs in the Marche population, using data from the Institute of Pathology of the Marche Polytechnic University, Ancona, Italy, in a period of 25 years (1994-2018), according to 4th Edition of WHO Classification of Head and Neck Tumours.

MATERIALS AND METHODS

The present retrospective study considered patients treated for OT from January 1994 to December 2018. Data were retrieved and catalogued from clinical records and from the archive of the Institute of Pathology, Marche Polytechnic University, Italy, by a single operator (L.T.), to ensure uniformity of the collected data. Because this is the only tertiary referral centre for Head and Neck

pathology within Marche region, with a specialist diagnostic service for odontogenic lesions, the patient sample in the present study could be considered well representative of this geographical area. The following information were obtained from each case: age, sex, pathologic diagnosis, site distribution, size, and relapses. The size of OTs was determined by measuring the maximum tumour diameter on the macroscopic surgical specimen.

Only the patients of Marche region were included in this study. For this reason, both the birthplace and the place of residence were considered as reliable data to select only patients from the local population of the Marche region and to determine the province of origin. The sample size was the Marche population according to the average yearly population for the period 1994-2018, reported by the Italian National Institute of Statistics (ISTAT) (Supplemental Table S1) [15].

Because the 25-year period considered, histopathological slides of OTs were re-evaluated by two pathologists (C.R. and M.M.) to confirm the diagnosis, according to the current WHO criteria [3]. Any disagreement was settled by consensus including a third investigator, in order to ensure that the final diagnosis was correct. The benign OTs were further categorized into three groups for statistical purposes: “Ameloblastomas”; “Odontomas”; and “Other Benign OT”.

Data analysis was performed using GraphPad Prism software version 7.00 for Windows (GraphPad Software, San Diego, CA; www.graphpad.com). Chi-square test and Fisher’s exact test were used for grouped variables. One-way analysis of variance (ANOVA) and the Bonferroni post hoc test were used for continued variables, and the Kruskal-Wallis and Dunn post hoc tests were used for grouped variables. Furthermore, annual incidence rate and life prevalence were calculated. The level of significance was set at $p < 0.05$.

This study was conducted in accordance with the “Ethical Principles for Medical Research Involving Human Subjects” statement of the Helsinki Declaration. This study received exemption from the institutional review board because of its retrospective nature.

RESULTS

Overall, 119 patients were treated for OTs from 1994 to 2018 and recorded at the Institute of Pathology, Marche Polytechnic University, Italy. Of these, 19 patients were excluded because they were not from Marche region. The annual incidence rate and the life prevalence of OTs were calculated both at regional and provincial levels, using data reported by the ISTAT (Supplemental Table S1) [15].

The annual incidence rate of OTs ranged from 0.13 to 0.39 per 100,000 per year, showing a slightly increasing trend over the years, although not reaching the statistical significance (Figure 1A, Supplemental Table S2). Life prevalence of OTs in Marche region was 6.50 per 100,000, ranging from 5.91 to 7.53 per 100,000 at provincial level (Figure 1B).

131 surgical specimens were retrieved, corresponding to 100 primary OT and 31 recurrences. Table 1 summarizes the distribution of primary OTs in relation to age, sex, site distribution, and size. The mean age of occurrence for primary OTs was 49.7 ± 20.1 years (range 5-98 years), with two peaks of frequency in the second-third decades and in the fifth decade (Figure 2A). Furthermore, 16 OTs were found in paediatric population, with a mean age of 10.8 ± 3.5 years. The mean age of onset of Odontomas (14.8 years) was significantly lower respect to other OT ($p < 0.05$; Figure 2B), while no differences were found among other OTs ($p > 0.05$). A more detailed description of the epidemiology of OTs in paediatric and geriatric patients was reported in Supplemental Tables S3 and S4, respectively.

The mandible was more frequently involved than the maxilla (59 vs 28 cases, respectively), while other sites, such as maxillary sinus and soft tissues, were less commonly affected (17 cases). The posterior mandibular and the anterior maxillary regions were the most commonly affected sites (32 and 13 cases, respectively), while no differences were found regarding the affected side (Figure 3A).

Overall, the mean size of primary OTs was 4.1 ± 1.7 cm (range 0.2-8.5 cm), showing a significant difference between Odontomas and other OTs ($p < 0.05$; Figure 3B). Furthermore, data on the size

of primary benign OTs showed that ameloblastomas were significantly larger than other tumours ($p < 0.05$; Figure 3B).

27 patients developed tumour recurrence, and 4 of them, showed a second recurrence over the years (4 cases of ameloblastoma). Table 2 summarizes the distribution of recurrent OTs in relation to age, sex, localization, mean size, and time to recurrence. The mean age at the first recurrence was 54 ± 19.7 years (range 16-91 years), with a peak of frequency in the fifth decade (Figure 2A). Furthermore, the age difference between primary and recurrent OTs was negligible ($p > 0.05$; Figure 2B).

The recurrent OTs were commonly found in posterior mandible and anterior maxilla (8 and 5 cases, respectively), while no differences were found regarding the affected site (Figure 3A). The mean size of recurrent OTs was 4.1 ± 1.8 cm (range 0.5-6.5 cm), showing no differences with primary tumours ($p > 0.05$; Figure 3B). Lastly, the mean recurrence time was 51.2 ± 34 months (range 12-144 months).

DISCUSSION

The first WHO classification of OTs was published in 1971, and to date, three further WHO classifications have been published. The most relevant aspect of the 4th Edition of WHO Classification was the reintroduction of OKC and calcifying odontogenic cyst into the odontogenic cysts group. Furthermore, new entities were introduced, and some old entities were restored [3,16]. It is clear that changes made in each new edition of the WHO classification make difficult to perform a careful comparison between the different studies [17,1]. Furthermore, most published studies were conducted before the publication of the 4th Edition of WHO Classification. This is the first study to look in detail at the epidemiology of OTs in Italian population according to the 4th Edition of WHO Classification of Head and Neck Tumours.

Most of the studies about the epidemiology of odontogenic lesions were conducted retrospectively, resulting biased in demonstrating the actual population perspective. The main issue with the majority of published epidemiological data for OTs regards the process of data collection. Selecting the pathology accessions over an interval of years, then deriving statistics using the total number of accessions as the population, is not an appropriated method. Indeed, this approach does not accurately represent the total population of a specific region, but only a sample of the population that accessed a specific healthcare service. The patients might have been treated in other regions or countries, the odontogenic lesions might not have been sent for histological analysis, or an asymptomatic lesion might remain undiagnosed. For these reasons, some odontogenic lesions might not have been recorded by the histopathology laboratories, therefore the values of incidence may not be entirely accurate [18]. However, the present study conducted in Marche region could partially overcome these limits. Indeed, in Italy the diagnosis and treatment of OTs, and more generally head and neck tumours, are part of public health responsibility. Furthermore, due to its socio-demographic conditions and healthcare organization, there is only one tertiary referral centre for Head and Neck pathology in Marche region. Therefore, it can be inferred that all cases of OT that appeared in this region were collected with a certain degree of accuracy.

The population of Marche consists of about 1.5 million inhabitants and it is homogeneously distributed throughout the region and its territorial and administrative divisions (i.e. the provinces). Marche region is currently divided in 5 provinces (PU, AN, MC, FM, AP), although the two most southern provinces are considered as one for demographic purposes (AP-FM). Because Institute of Pathology of Marche Polytechnic University is the only referral diagnostic service for OTs in the region, the number of patients could be considered well representative of this geographical area. The present study included only Marche population affected by odontogenic lesions, excluding non-resident patients. The cases were separated in “local cases”, served by the diagnostic service and in “referred cases”, accessioned as referrals. Generally, referred cases were more rare and challenging to diagnose, requiring specialist pathologist advice.

In the present study, the mean age of onset was 49.7 years, in agreement with several authors [19-23,4,24-26], but significantly higher than that found by other studies ($p < 0.05$) [27-35]. In paediatric patients the mean age of onset was 11.8, largely influenced by the odontomas, since these tumours are typically diagnosed in young patients. Indeed, the mean age of odontomas resulted significantly lower than the other OTs (Table 1, Figure 2B, Supplemental Table S3).

In Marche population the OTs showed a male predominance, with an M:F ratio of 1.78:1 (Table 1). These results are in agreement with those reported by several studies [20,22,24,26-29]; however, other authors reported a significant female predilection ($p < 0.05$) [19,21,23,30,31]. Only two studies showed a more balanced M:F ratio, without sex predilection [36,32]. Posterior mandible and anterior maxilla were the most affected sites (32% and 13%, respectively), with a mandible: maxilla ratio of 2.1:1. These data were consistent with those reported by several authors ($p < 0.05$) [21,22,24-26,36,30,31], although some studies demonstrated an even greater mandibular predilection [20,27-29,32]. In the present study, ameloblastoma accounted for 61.1% of all OTs, representing the most common tumour, in accordance with several authors (Table 1) [20,24,36,30,32]. Other studies demonstrated an even greater relative frequency of ameloblastomas, often due to the small number of odontomas reported ($p < 0.05$) [25,27-29,31,37]. These data are in contrast with those reported by other studies, in which relative frequency of ameloblastomas was significantly lower ($p < 0.05$) [19,21,23,4,26]. The second most frequent lesion was odontome, accounting for 13% of all OTs, in accordance with several reports [24,25,36,28,31,32]. However, some authors reported a greater relative frequency of odontomas [19,21,23,30,4], while in other reports the number of odontomas was significantly lower ($p < 0.05$) [20,26,27,29].

Overall, epidemiological data in literature showed significant differences among countries. Ameloblastoma seems to be more common in Asian and African countries, while in North America the most frequently diagnosed OT was odontome (Figure 4) [7,8]. One of the reasons for this discrepancy is the source of data. In Asian and African countries, odontogenic lesions are diagnosed and treated in Maxillofacial Units, while patients from Europe and North America can be treated

both in Hospitals and Dental schools [18,20,4]. In particular, odontomas are commonly diagnosed on the basis of clinical and radiographic exams, without histological assessment, resulting in an underestimation of their frequency [28,38].

Epidemiological heterogeneity may be due to the supposed difference based on ethnic differences, since ameloblastomas appear to be more common in African American than Caucasian patients. Shear et al. reported that the incidence rates of ameloblastoma in African American males and females (1.96 and 1.2, respectively) were significantly higher than those for Caucasian males and females (0.18 and 0.44, respectively) [39]. Gardner confirmed these data, showing an annual incidence rate of 2.29 and 0.31 for African American and Caucasian patients, respectively [40]. These results suggest a higher prevalence of ameloblastomas in Africa, although Simon et al. reported that incidence of ameloblastoma in Tanzania did not differ from European countries [41]. The estimate annual incidence rate accounted in our study is equal to 0.13-0.39 per 100,000 per year, with a range of 3-8 cases per year (Figure 1A, Supplemental Table S2). Data obtained from ISTAT provide only an estimate, although accurate, of the Marche population used for evaluation of the annual incidence rate. For example, these data also include the "net migration rate" (the difference between the number of immigrants and the number of emigrants throughout the year). Nevertheless, due to the rarity of OTs, the effects of these approximations on population size could be considered negligible. Regarding primary OT, all cases reported were surgically treated and were included in a follow-up program. Primary OTs can be asymptomatic and therefore they can be incidentally diagnosed by imaging. For this reason, we cannot exclude that some cases of small and asymptomatic OTs could not have been diagnosed. Nevertheless, the long period considered in this study and the growth rate of OTs, due to their neoplastic nature, suggest that these lesions will sooner or later become clinically evident. Therefore, also the number of undiagnosed cases of OTs in Marche region could be considered negligible.

Our results are consistent with those reported in Swedish population by Larsson and Almeren [42]. According to these authors, the real incidence of OTs is about 0.6 per 100,000 per year, in accordance with other studies conducted in Caucasian populations [3,39,40].

Life prevalence of OTs in Marche region ranges from 5.91 (north) to 7.53 (south) per 100,000. Although the difference reported is not statistically significant, a slightly higher life prevalence is reported in southern provinces. A possible explanation could be attributed to higher values of "ageing index" (the ratio of the number of elderly persons to the number of young persons) [15]. Indeed, greater number of elderly people implies a higher time-related risk to develop OTs in the course of life.

Information about the size of OTs is scarce in the literature, but our findings corroborated those reported by other authors [29]. Regarding OTs growth rate, there is a paucity of literature on this problem and only referred to ameloblastoma. Furthermore, due to its rarity, most reports have been limited to small-scale case studies. The main issue of these data is that many authors simply divided the maximum tumour diameter by the symptom duration to arrive at an estimated monthly growth rate, which falsely assumes a linear growth pattern. In fact, evidences show that ameloblastoma initially exhibits slow growth, but later its growth accelerates [43]. Furthermore, the symptom duration, especially in retrospective studies, could be unreliable and/or unavailable.

31 recurrent OTs were reported in Marche region, showing a mean recurrence time of 51.2 ± 34 months. The optimal surgical treatment for benign OTs has been debated for years, and there is still no consensus about the best treatment options, ranging from enucleation and curettage to block resection. Attempts to remove the tumour with curettage often leave microscopic tumour nests within the bone. Indeed, a conservative approach is associated with high recurrence rate, ranging between 60-80% [44]. Marginal resection is the most used treatment; however, recurrence rates after marginal or block resection reach up to 15% [32]. During the last decades the management protocols for OTs changed and this could have impacted the rate of OTs recurrence reported. Furthermore, the site affected is associated with the risk of recurrence. For example, posterior

maxillary lesions have a worse prognosis, due to the difficulty in obtaining an adequate surgical margin [44]. On the contrary, the histological type of benign OTs seems to be poorly related to risk of recurrence. As expected, no case of recurrent odontome was reported. Indeed, odontomas are tumour-like but nonneoplastic developmental anomalies, composed of developed malformed teeth or tooth-like masses. For this reason, conservative enucleation is adequate treatment and the prognosis is excellent. Radical resection with wide margins, with or without neck dissection, is the treatment of choice for malignant OTs. Adjuvant radiotherapy could be appropriate for cases showing eroded cortical bone, soft tissue extension, aggressive growth, or incomplete surgical margins. Combination of chemo-radiotherapy could be considered when surgical treatment is impossible. Local enucleation and curettage are associated with multiple recurrences and metastasis; however, recurrences and/or metastases may occur even despite aggressive surgery. The prognosis is poor, although it is difficult to determine due to the paucity of cases reported in the literature.

Regarding ameloblastomas, the mean age of onset was 54.9 years, similar to those reported in other Western countries [18,21,4,26]. Interestingly, this value was the highest reported in the literature, probably due to, at least in part, the fact that life expectancy in Marche region is the highest in Italy and one of the highest in the world [45]. Males were more commonly affected than females, in accordance with other studies [18,21,4,25,26,29], although some authors reported a female predilection [20,23,36,30,31]. Regarding the site of onset, ameloblastomas occurred mainly in posterior mandible, confirming what is reported in literature. Ameloblastomas typically recurred after several years, with an average disease-free survival time of 46.1 months. Indeed, more than half of ameloblastomas recur within 5 years of the surgical treatment, although recurrences can occur more than 25 years after surgical resection [3,44].

In the present study, odontomas were typically diagnosed during the first two decades of life, as confirmed by literature [19,20,4,24-26,30,32,38], although some authors reported a slightly higher mean age [18,21,22]. Males were significantly more affected than females (M:F ratio of 2.4:1), as

reported by Taghavi et al. and Naz et al. [22,29]. On the other hand, many other studies found a more balanced M:F ratio or even a female predominance. Regarding the site of onset, odontomas occurred mainly in the maxilla, in agreement with other authors [18,20,23,24,30,31,38]. Several studies considered complex and compound odontomas separately [22,36,32]. Siriwardena et al. reported that complex and compound odontomas were more common in posterior mandible and anterior maxilla, respectively [26].

Malignant OTs are extremely rare neoplasms, representing only 4% of all OTs reported, in accordance with several studies [22,4,25-29,32,38]. In other reports, the relative frequency of malignant OTs was significantly lower, ranging from 0.1% to 0.8% ($p < 0.05$) [19,21,36,30]. Interestingly, Kebede et al. reported a significantly higher frequency of malignant OTs (19.6%) [20]. These authors hypothesized that the use of traditional medicines by some of these patients could have significantly delayed surgical treatments at late stages of disease. This diagnostic and therapeutic delay might have increased the risk of transforming benign OTs into malignant OTs [20]. Malignant OTs typically occur in elderly patients, showing a male predominance, in accordance with several authors [26,29,31,38]. As previously reported, there are no accepted follow-up guidelines or recommendations for malignant OTs. The National Comprehensive Cancer Network guidelines for Head and Neck malignant tumours suggest a postoperative follow-up every 1-3 months for the first year, every 2-4 months during the second year, every 4-6 months from the third to the fifth year, and once a year thereafter [6]. Furthermore, these guidelines agree on the execution of a radiological examination, especially if radiation and chemotherapy are given, to be used also for comparison with subsequent examinations, within 2 months from the end of the treatment. A possible simplified approach for the management of malignant OTs could be a postoperative follow-up every 3 months for the first 2 years, every 6 months from the third to the fifth year, and once a year thereafter.

CONCLUSION

In conclusion, the present study assessed for the first time the prevalence and the incidence of OTs in Italy according to the 4th Edition of WHO Classification of Head and Neck Tumours. The main limitation is the retrospective nature of this study, that increases the potential risk for bias. However, due to the socio-demographic conditions and the healthcare organization of Marche region, the risk of error was minimized.

The direct comparison between this and previous studies is problematic. One reason is that several studies have evaluated the data from pathology services, without a clear definition of the reference population. Another aspect to be considered is the redefinition of OKC as a cyst, with marked effects on the relative frequency of OTs. Nevertheless, these data contribute to assess the epidemiology of OTs in specific geographic regions, although the possible role of genetic and environmental factors requires further investigations.

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FIGURE LEGENDS

Figure 1A. Annual incidence rate of primary OTs (yellow line) and recurrent OTs (red line) in Marche region, showing a slightly increasing trend over the years, although not statistically significant (light grey dashed line).

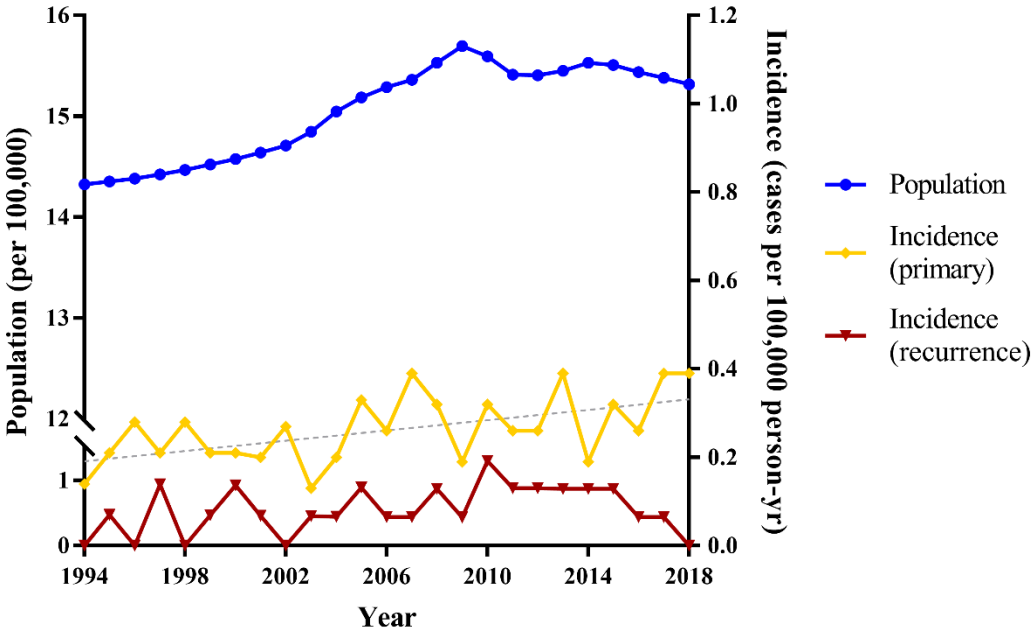


Figure 1B. Life prevalence of OTs in Marche region by provinces.

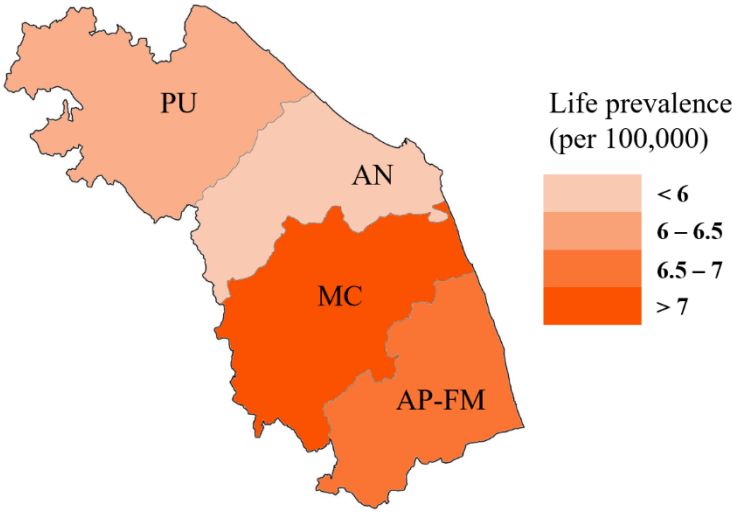


Figure 2A. Age distribution of primary and recurrent OTs.

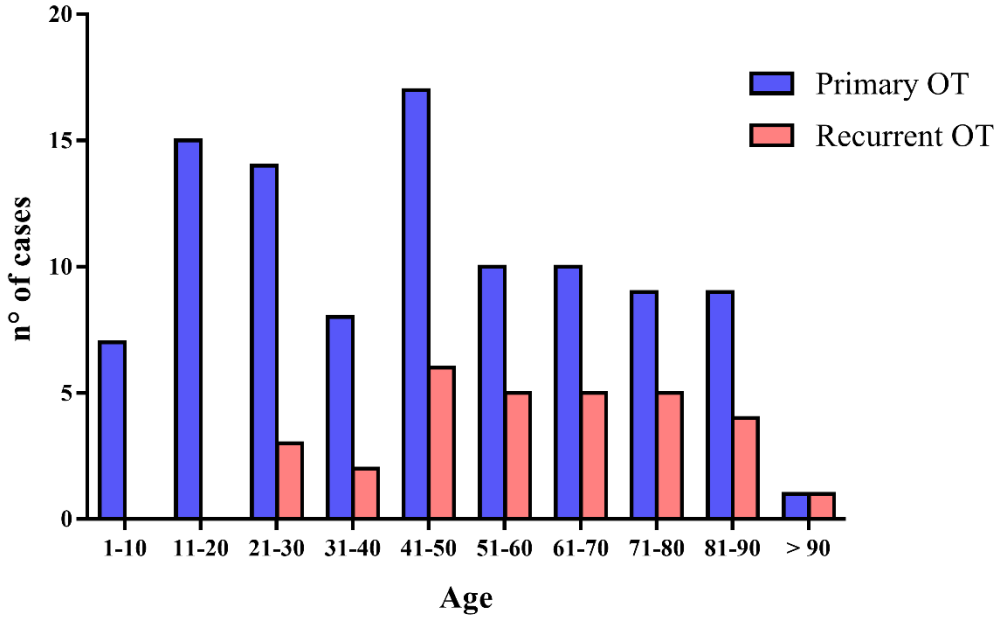


Figure 2B. Age of primary and recurrent OTs, expressed as mean ± SD. Odontomas occur in younger age groups than other OTs. * = $p < 0.05$.

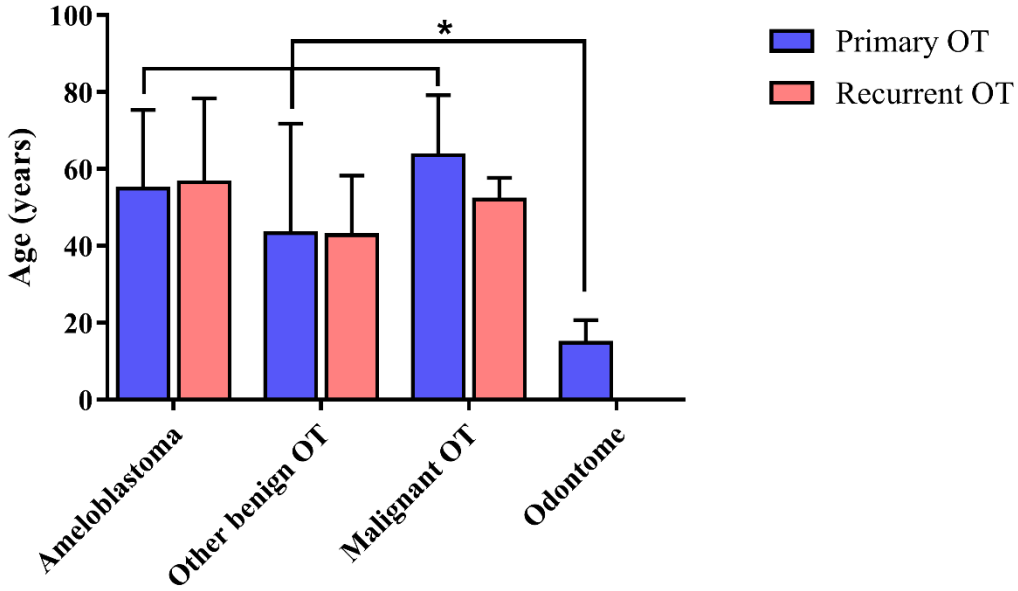


Figure 3A. Site distribution of primary OTs (right side, blue areas) and recurrent OTs (left side, orange areas) by percentile, including those including those confined to a single site and those that extend over a region. Mandible and maxilla have been separated into anterior and posterior regions. A = maxillary sinus; B = nasal cavity; C = maxilla; D = peripheral OTs; E = mandible.

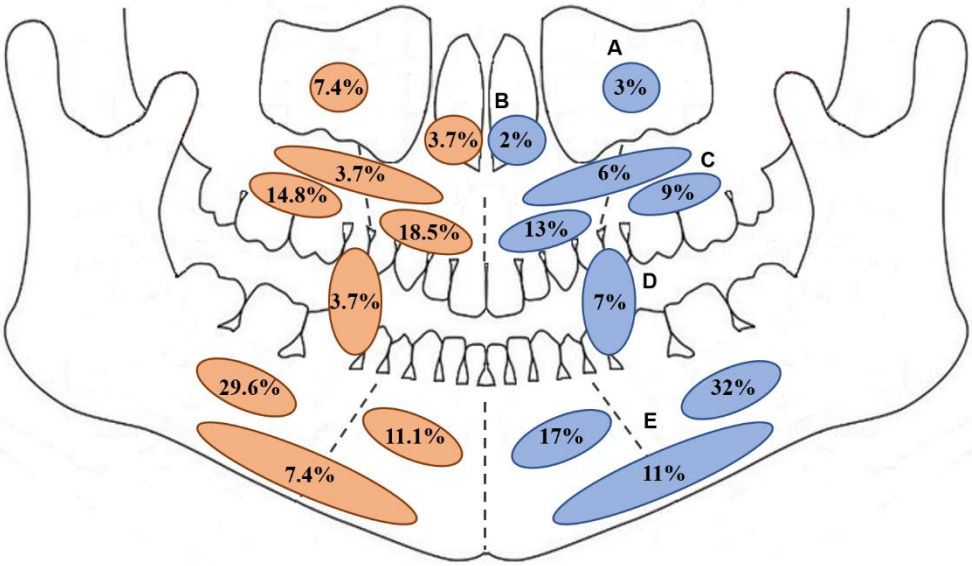


Figure 3B. Size of primary and recurrent OTs, expressed as mean ± SD. Odontomas are significantly smaller than other OTs, while ameloblastomas were larger than other benign OTs. * = $p < 0.05$.

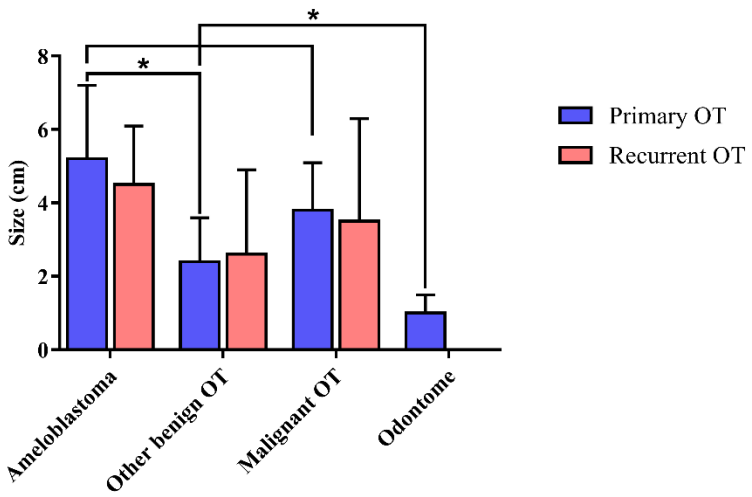
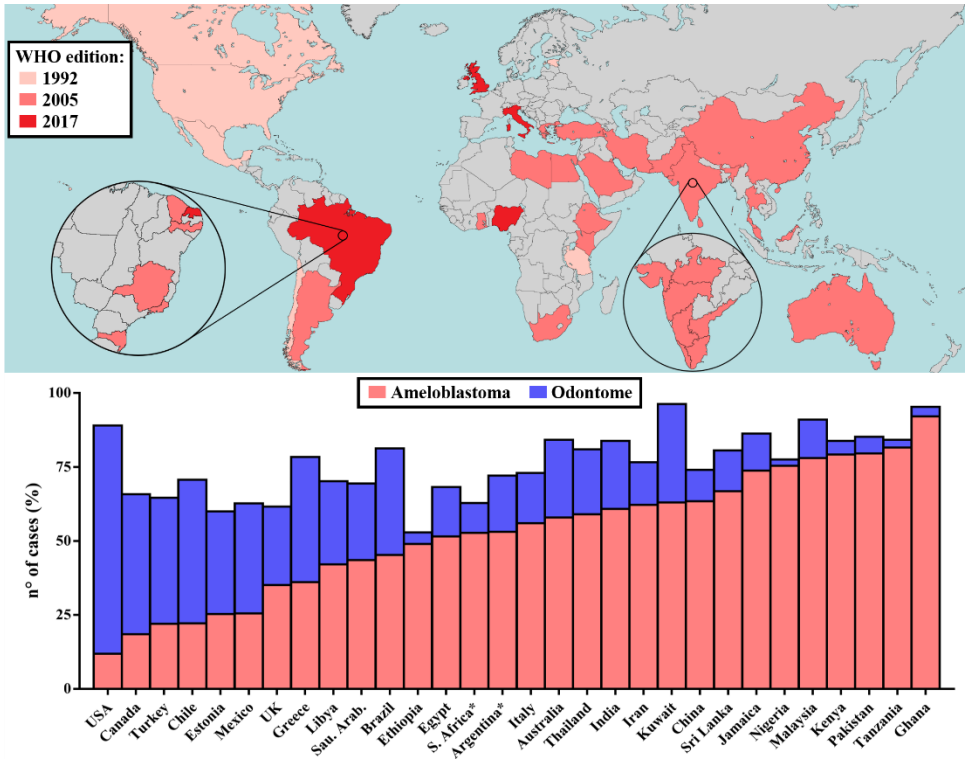


Figure 4. Worldwide distribution of OTs in English-based literature. The picture above shows distribution of epidemiological studies on OTs for each country according to the latest WHO classification, when available. The picture below shows the relative frequency of the two most common OTs, namely ameloblastoma and odontome, in several countries. Ameloblastoma seems to be more common in Asia and Africa, while in North America the most frequently diagnosed OT is odontome.



Supplemental Material

Supplementary Table 1: Average yearly population in Marche region for the period 1994-2018, reported by the Italian National Institute of Statistics (ISTAT).

Supplementary Table 2: Annual incidence rate of odontogenic tumours in Marche population (1994-2018).

Supplementary Table 3: Clinical and pathological data of OTs in paediatric patients of Marche population (1994-2018).

Supplementary Table 4: Clinical and pathological data of OTs in geriatric patients of Marche population (1994-2018).