UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE ODONTOLOGIA

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TUMORES ODONTOGÊNICOS SÍNCRONOS: UMA REVISÃO SISTEMÁTICA

Porto Alegre
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Trabalho de Conclusão de Curso apresentado ao Curso de Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul, como requisito parcial para a obtenção do título de Cirurgiã-Dentista.

Orientadora: Profª. Drª. Manoela Domingues Martins

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Porto Alegre, 26 de janeiro de 2024

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RESUMO

Esta revisão sistemática teve como objetivo incorporar informações publicadas sobre tumores odontogênicos sincrônicos (TOS) com uma análise das características demográficas e clínicas dos casos publicados na literatura. Relatos de casos e séries de casos de TOs foram pesquisados no PubMed, Web of Science, Scopus e EMBASE. Foi realizada análise estatística descritiva. Vinte e oito estudos compreendendo 30 casos de TOSs foram incluídos. Considerando todos os casos publicados, os TOSs ocorreram em 63,3% simultaneamente na maxila e mandíbula (n = 19). As lesões eram bifocais em 43,3% (13 dos 30 casos) e multifocais em 56,7% (17 dos 30 casos). Todos os TOSs disponíveis na literatura apresentavam o mesmo tipo de lesão, sendo que dois deles também envolviam outro TOS diferente (n = 2/6,7% de todos os 30 casos). De todos os casos publicados, os TOSs mais frequentes na literatura foram odontomas (n = 10/33,3% de todos os 30 casos), tumores odontogênicos escamosos (n = 8/26,7% de todos os 30 casos), TOs epiteliais (n = 8/26,7% de todos os 30 casos) e TOs adenomatóides (n = 2/6,7% de todos os 30 casos). Considerando todos os casos de TOS incluídos, a recorrência geral foi de 13,3%. Dentro de seu subgrupo, o TO epitelial calcificante apresentou a maior recorrência (25%). Cinco casos (16,7% do total de 30 casos) apresentavam síndrome previamente associada, sendo relatados dois casos de síndrome de Schimmelpenning. Entre os TOSs publicados, os odontomas foram os mais comuns. Todos os TOs disponíveis na literatura científica apresentaram o mesmo tipo de TO e afetaram principalmente os dois maxilares simultaneamente. Apenas alguns desses casos foram associados a uma síndrome.

Palavras-chave: mandíbula, tumores odontogênicos, patologia oral, sincrônicos.

ABSTRACT

This systematic review aimed to incorporate published information about synchronous odontogenic tumors (SOTs) with an analysis of the demographic and clinical characteristics from the cases published in the literature. Case reports and case series of SOT were searched in PubMed, Web of Science, Scopus, and EMBASE. A descriptive statistical analysis was performed. Twenty-eight studies comprising 30 cases of SOTs were included. Considering all cases published, SOTs mostly occurred simultaneously in the maxilla and mandible (n = 19/63.3%). Lesions were bifocal in 13 (43.3% of all the 30 cases) and multifocal in 17 cases (56.7% of all the 30 cases). All SOTs available in the literature presented the same type of lesion, and two of them also involved another different SOT (n = 2/6.7% of all the 30 cases). Out of all published cases, the most frequent SOTs in the literature were odontomas (n = 10/33.3% of all the 30 cases), squamous odontogenic tumors (OTs) (n = 8/26.7% of all the 30 cases), calcifying epithelial OTs (n = 8/26.7% of all the 30 cases), and adenomatoid OTs (n = 2/6.7% of all the 30 cases). Considering all SOTs cases included, the overall recurrence was 13.3%. Inside a subgroup of the lesion, synchronous calcifying epithelial OT presented the highest (25%). Five cases (16.7% of all the 30 cases) had a previously associated syndrome, with two cases of Schimmelpenning syndrome being reported. Among published SOTs, odontomas were the most common. All SOTs available in the scientific literature showed the same type of OT and mainly affected both jaws simultaneously. Only a few of these cases were associated with a syndrome.

Keywords: jaws, odontogenic tumors, oral pathology, synchronous

LISTA DE ILUSTRAÇÕES

LISTA DE TABELAS

LISTA DE ABREVIATURAS

AOT	Adenomatoid Odontogenic Tumor
CEOT	Calcifying epithelial odontogenic tumor
COF	Cemento-ossifying fibroma
OD	Odontoma
OT	Odontogenic tumor
SOTs	Synchronous odontogenic tumors
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PROSPERO	Prospective Register of Systematic Reviews
SOTs	Synchronous Odontogenic Tumors
SqOT	Squamous Odontogenic Tumor

SUMÁRIO

1 ANTECEDENTES E JUSTIFICATIVA

Os tumores odontogênicos (TOs) compreendem um grupo complexo de lesões heterogêneas originárias dos tecidos epiteliais e/ou mesenquimais remanescentes do desenvolvimento dentário (Kokubun et al., 2022). A etiologia dos TOs consiste em interações indutoras variadas entre o epitélio e/ou ectomesênquima odontogênico (Slootweg & El-Naggar, 2018). São lesões relativamente raras, compreendendo cerca de 1% de todos os tumores dos ossos gnáticos (Bianco et al., 2019). De acordo com a classificação mais recente da Organização Mundial da Saúde (OMS), os TOs são categorizados como epiteliais, mistos e/ou mesenquimais (El-Naggar et al., 2017).

A atual classificação geral dos TOs tem enfoque na natureza biológica benigna ou maligna das lesões, simplificando a estrutura da versão anterior. Na classificação anterior, os tumores de caráter benigno eram fragmentados em segmentos como “epitélio odontogênico com estroma fibroso maduro sem ectomesênquima odontogênico, epitélio odontogênico com ectomesênquima odontogênico, com ou sem formação de tecidos duros e tumores mesenquimais e/ou ectomesenquimais com ou sem epitélio odontogênico”. Todavia, a partir da classificação de 2017, passaram a ser classificados como tumores odontogênicos epiteliais, mesenquimais (ectomesenquimais) e/ou mistos (Wright, J. M.; Vered, M., 2017; Tolentino, E., 2018).

Clinicamente, os TOs podem apresentar-se como lesões assintomáticas de crescimento lento, ou como lesões sintomáticas com comportamento agressivo e infiltrativo (Osterne et al., 2011). Dados epidemiológicos de TO têm sido bem descritos na literatura (Da-Costa et al., 2012; Kokubun et al., 2022; Silveira et al., 2021). As ocorrências síncronas podem ser definidas como a presença de duas ou mais lesões ocorrendo simultaneamente, com intervalo inferior a 6 meses entre os dois diagnósticos, e quando se descarta a possibilidade de serem casos recorrentes ou metastáticos (Zhai et al., 2018). Em contrapartida, é fundamental diferenciar esses casos daqueles conhecidos como tumores híbridos, uma vez que estes combinam as características diagnósticas de dois ou mais cistos e/ou tumores odontogênicos na mesma lesão (Pontes et al., 2022). A literatura científica atual sobre TOs síncronos (TOS) é escassa e compreende apenas relatos de casos isolados e pequenas séries de casos. Esta é a primeira revisão sistemática abordando as características dos TOSs.

A literatura científica carece de uma análise geral e abrangente que demonstre o perfil de ocorrência dos TOS publicados. Nesse sentido, o objetivo do presente estudo foi integrar os dados disponíveis sobre casos publicados de TOSs em uma revisão sistemática de suas características demográficas, clínico-patológicas, de tratamento, acompanhamento e recorrência.

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Synchronous odontogenic tumors: A systematic review

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ABSTRACT

This systematic review aimed to incorporate published information about synchronous odontogenic tumors (SOTs) with an analysis of the demographic and clinical characteristics from the cases published in the literature. Case reports and case series of SOT were searched in PubMed, Web of Science, Scopus, and EMBASE. A descriptive statistical analysis was performed. Twenty-eight studies comprising 30 cases of SOTs were included. Considering all cases published, SOTs mostly occurred simultaneously in the maxilla and mandible (n = 19/63.3%). Lesions were bifocal in 13 (43.3% of all the 30 cases) and multifocal in 17 cases (56.7% of all the 30 cases). All SOTs available in the literature presented the same type of lesion, and two of them also involved another different SOT (n = 2/6.7% of all the 30 cases). Out of all published cases, the most frequent SOTs in the literature were odontomas (n = 10/33.3% of all the 30 cases), squamous odontogenic tumors (OTs) (n = 8/26.7% of all the 30 cases), calcifying epithelial OTs (n = 8/26.7% of all the 30 cases), and adenomatoid OTs (n = 2/6.7% of all the 30 cases). Considering all SOTs cases included, the overall recurrence was 13.3%. Inside a subgroup of the lesion, synchronous calcifying epithelial OT presented the highest (25%). Five cases (16.7% of all the 30 cases) had a previously associated syndrome, with two cases of Schimmelpenning syndrome being reported. Among published SOTs, odontomas were the most common. All SOTs available in the scientific literature showed the same type of OT and mainly affected both jaws simultaneously. Only a few of these cases were associated with a syndrome.

Keywords: jaws, odontogenic tumors, oral pathology, synchronous

1 INTRODUCTION

Odontogenic tumors (OTs) comprise a complex group of heterogeneous lesions originating from the epithelial and/or mesenchymal tissue remnants of tooth development (Kokubun et al., 2022). The etiology of OT consists of varied inducing interactions between the epithelium and odontogenic ectomesenchyme (Slootweg & El Naggar, 2018). According to the most recent classification of the World Health Organization, OT are categorized as epithelial, mixed, and/or mesenchymal (EI-Naggar et al., 2017).

Clinically, OT can present as asymptomatic lesions of slow growth or even as aggressive forms with symptomatic and infiltrative behavior (Osterne et al., 2011). Epidemiological OT data have been well described in the literature (da-Costa et al., 2012; Kokubun et al., 2022; Silveira et al., 2021). Synchronous occurrences may be defined as the presence of two or more lesions occurring simultaneously, with an interval of less than 6 months between the two diagnoses and when the possibility of being recurrent or metastatic cases is ruled out (Zhai et al., 2018). In contrast, it is crucial to differentiate these cases from those known as hybrid tumors, since the latter combines the diagnostic features of two or more odontogenic cysts and/or tumors in the same lesion (Pontes et al., 2022). The current scientific literature on synchronous OTs (SOTs) is scarce and comprises only isolated case reports and small case series. This is the first systematic review addressing the characteristics of SOTs.

As far as we know, the scientific literature lacks a general and comprehensive analysis that demonstrates the profile of occurrence of the published SOTs. In this sense, the objective of the present study was to integrate the available data on published cases of SOTs into a systematic review of their demographic, clinicopathological, treatment, follow-up, and recurrence characteristics.

2 MATERIAL AND METHODS

2.1 Protocol

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations (Page et al., 2020, 2021) and was registered in the Prospective Register of Systematic Reviews (PROSPERO; Center for Reviews and Dissemination, University of York) under the registration number CRD42021238295.

2.2 Search strategy and quality assessment

These sections are described in detail in **Supplementary Methodology Material**.

2.3 Eligibility criteria

All the case reports and case series diagnosed as SOT according to the World Health Organization (EI-Naggar et al., 2017) and that followed the PECOS principle (Moher et al., 2015; Page et al., 2020) were included. The PECOS principle was adapted to the present review of case reports.

(P) Population: patients;

(E) Exposure: synchronous odontogenic tumors; and

(S) Study design: case reports and case series.

Exclusion criteria were articles and conference abstracts, animal studies, systematic reviews, and studies that were neither case reports nor case series. In addition, articles that met the following criteria were excluded (1) synchronous non-odontogenic lesions/ tumors; (2) non-tumoral synchronous odontogenic lesions; (3) non-synchronous OTs; (4) not case report/series; (5) language other than English, (6) article not found, and (7) article that did not provide a histopathological photomicrograph and/or clear description of the morphological findings.

2.4 Study selection

The process of study selection was performed by two independent authors (B.L.N. and B.B.S.). First, the reviewers searched the electronic databases and imported them to the reference manager. Then, duplicates were removed, and titles and abstracts were examined. Next, the full texts of the selected studies were

accessed according to the eligibility criteria. In case of any disagreement regarding study inclusion, a third reviewer was consulted (L.F.S.). Finally, all cases were revised critically. If the case did not provide high-quality radiographic and histopathological images, if they did not look like or did not fully agree with the proposed diagnosis, or if the images of each synchronous lesion were not provided, the article was excluded from the analysis. Furthermore, the authors thoroughly discussed and decided not to include cases of cement-ossifying fibromas. When there were doubts about the diagnoses, the authors of the articles were contacted by e-mail.

2.5 Data extraction

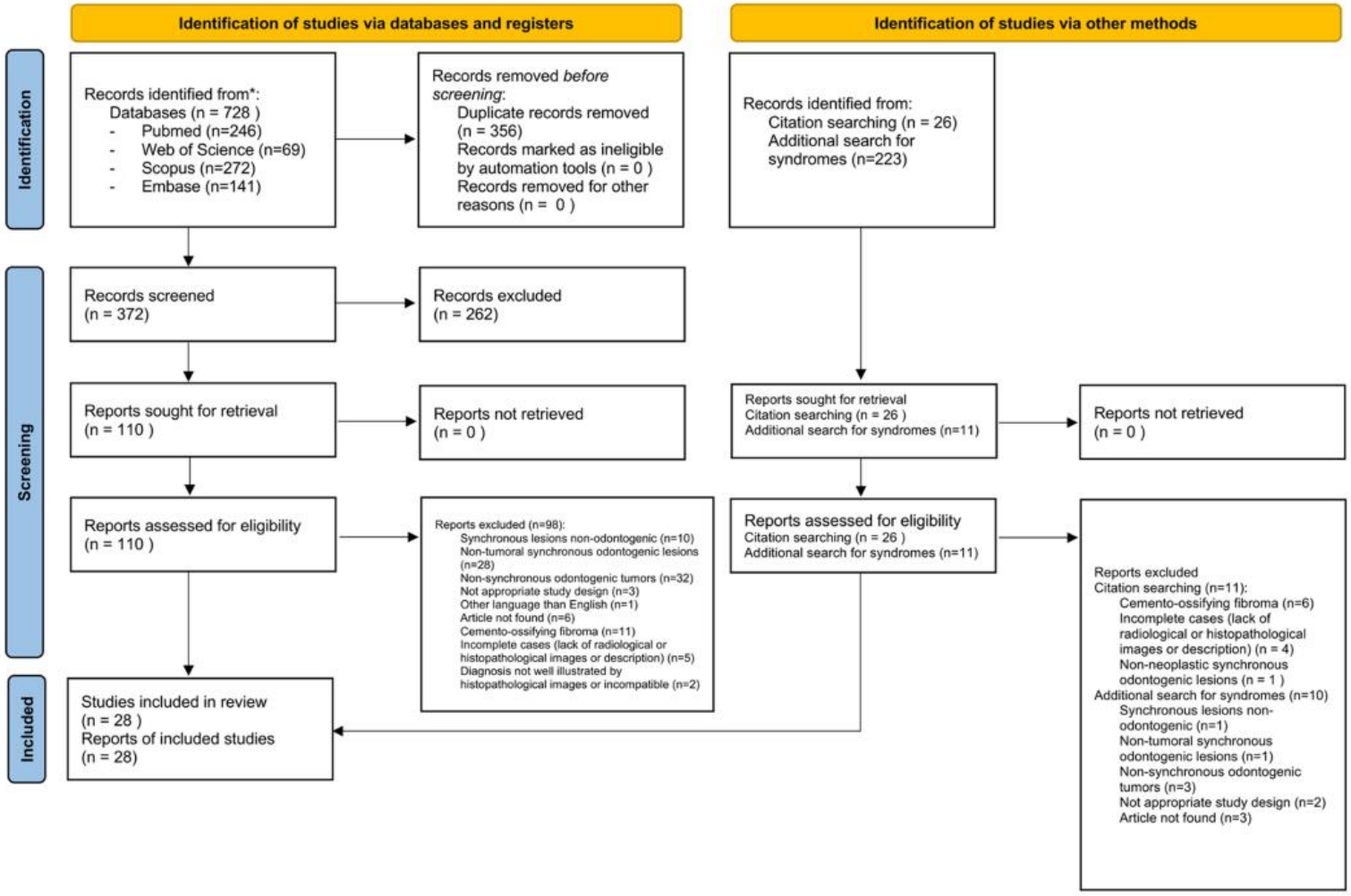
Data extraction was also performed independently by two authors (F.M.S and L.F.S.). The following information was collected from the included articles: author's name, publication date, country, sex, age, syndromes, anatomical location of the lesions, bi or multifocal occurrence, confirmation of the histopathological diagnosis, treatment, follow-up, and recurrence.

3 RESULTS

3.1 Study selection

The flowchart illustrating the search process and selection of the studies included in this systematic review is outlined in **Figure 1.** A total of 728 potentially relevant records were gathered from the electronic databases. After duplicate removal, 372 records were examined based on their titles and abstracts. Of these, 262 studies were excluded as they did not meet eligibility criteria. Then, 110 full-text articles were evaluated, and 98 were excluded according to the pre-established eligibility criteria. Some cases (n = 17 from the database search and n = 11 from the manual search) were initially included but then removed after a critical analysis of the literature. All articles that were excluded at this stage are presented in **Supplementary Material 2** with their respective reasons. Fifteen studies were included after a manual search of the bibliographies of the included studies. In the step regarding the search for syndromes, only one study was included (Hauber et al., 2003). Finally, a total of 28 studies reporting a total of 30 cases of SOTs were included in this systematic review (**Supplementary Material 3**).

Figure 1. Flowchart - PRISMA flow diagram for systematic search and study selection strategy according to Page et al. (2020)



Font: Neumann et al., 2022

3.2 General characteristics of included studies

The cases were reported in 18 countries: The United States of America was the country with more cases 40% out of the total published cases (n=12), followed by Brazil with eight publications (26.7%) and India with 3 (10.0%). The studies were published between 1963 and 2021. General descriptions of the included studies are summarized in **Supplementary Material 3** and **Table 1**. Furthermore, some characteristics of the main groups of SOTs are illustrated in **Figure 2**.

In general, SOT published cases mainly occurred in both jaws with 19 cases out of 30 (63.3%) and in only one jaw in 11 cases (36.7%), occurring primarily in the mandible with a maxilla-mandible ratio of 1:1.75. Follow-up was reported in 16 cases (53.3% of all published cases) with a mean of 27.7 (±26.75) months. Overall, the lesions were reported to be bifocal in 13 cases (43.3% of all published cases) and multifocal (more than two synchronous lesions) in 17 cases (56.7% of all published cases). All cases exhibited SOT composed of the same odontogenic tumors (n = 30/100%); however, two of them also showed another concomitant SOT that was different, as in a case with 13 calcified epithelial OT (CEOT) and one central odontogenic fibroma (McCloy et al., 2021) and another case with multiple odontomas and one adenomatous OT (AOT) (Ernst et al., 2007). A synchronous peripheral ameloblastoma (Hernandez et al., 1992) was described only once. The most frequent lesions encountered in this review were grouped and described in detail in the following sections.

Regarding patients' medical condition, five patients had a syndrome (16.7% of all published cases): two had Schimmelpenning syndrome (Chaves et al., 2020; Ernst et al., 2007), representing 40% of all published cases with syndromes and 6.7% of all the 30 cases. These cases of Schimmelpenning Syndrome were present in the cases of multiple odontomas and an AOT (Ernst et al., 2007), and one case of synchronous squamous OT (SqOT) (Chaves et al., 2020). Furthermore, there was one case each of otodental syndrome (Liu et al., 2017), Pierre-Robin sequence (Hammoudeh et al., 2009), and encephalocranio cutaneous lipomatosis (Hauber et al., 2003) (each of them representing 3.3% of all published cases).

In addition, there were two cases (6.7% of all cases) with a family history of first-degree relatives (parents or siblings) that had been affected by the same OT in the past. Both cases occurred in patients with SqOTs.

The overall recurrence proportion was 13.3% (n = 4 of all the 30 cases, not excluding the studies that did not report this variable). All recurrences occurred in cases treated conservatively (n = 4/100% of all cases). Within a subgroup of the lesion, CEOT had the highest recurrence with 25% represented by only two cases.

Table 1. Summary of the characteristics of the main groups of synchronous odontogenic tumor cases in the literature

SOT	Number of cases *n* (%)	Male-to-female ratio	Mean age (±*SD*)	Anatomical location		Pattern[a]	
				Both jaws	Single jaw	Bifocal	Multifocal
OD	10 (33.3%)[b]	1:1	11.30 (±5.3)	4 (40.0%)[a]	6 (60.0%)[a]	5 (50.0%)[a]	5 (50.0%)[a]
SqOT	8 (26.7%)[b]	3:1	26.37 (±8.0)	6 (75.0%)[a]	2 (25.0%)[a]	1 (12.5%)[a]	7 (87.5%)[a]
CEOT	8 (26.7%)[b]	1:1	39.75 (±9.9)	7 (87.5%)[a]	1 (12.5%)[a]	5 (62.5%)[a]	3 (37.5%)[a]
AOT	2 (6.7%)[b]	0:2	10.00 (±5.65)	1 (50.0%)[a]	1 (50.0%)[a]	1 (50.0%)[a]	1 (50.0%)[a]
Total	30 (100.0%)[b]	1:0.87	24.20 (±15.05)	19 (63.3%)[b]	11 (36.7%)[b]	13 (43.3%)[b]	17 (56.7%)[b]

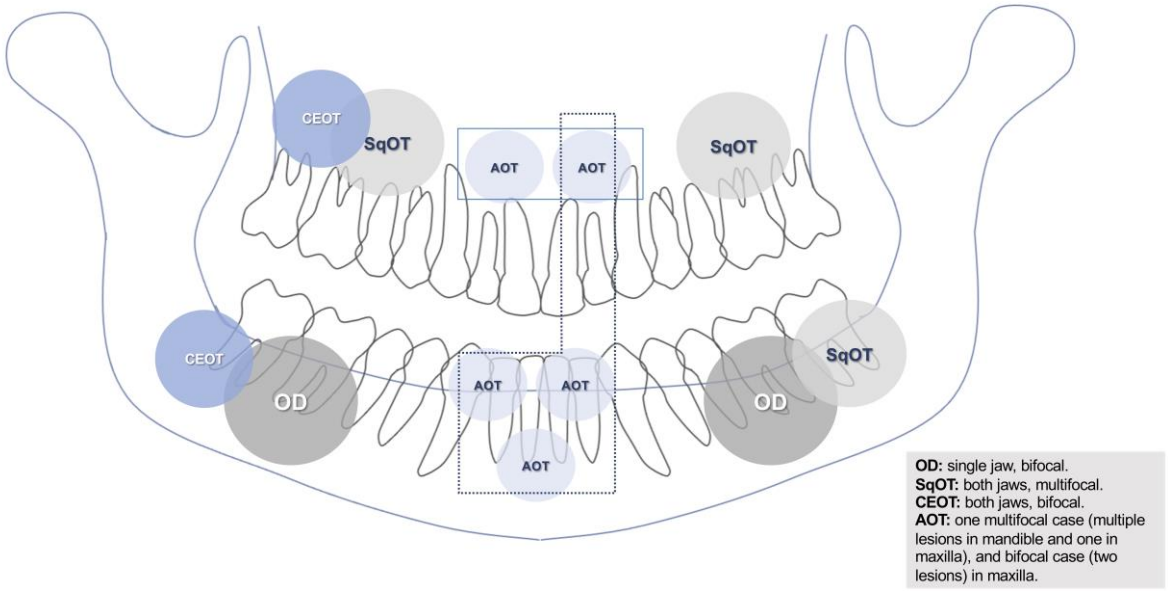
Abbreviations: AOT, adenomatoid odontogenic tumor; OD, odontoma; SqOT, squamous odontogenic tumor; SOT, synchronous odontogenic tumors.

[a]Proportion numbers in relation to each subgroup of lesions.

[b]Proportion numbers in relation to all cases included in this review.

Font: Neumann et al., 2022

Figure 2. Graphic representation of the most frequent appearances found in the literature synchronous odontogenic tumors. The higher the frequency of the group among published synchronous lesions, the larger the circle they are represented into.



Font: Neumann et al., 2022

3.3 Outcomes of the main SOTs

The following subsections will approach the most frequent groups of SOTs found in the literature. Each passage will describe lesions' characteristics in proportion numbers (%) with reference to the total cases of that specific subgroup.

3.3.1 Synchronous odontomas

Odontomas (OD) were the most frequent SOT found in the literature, with 10 cases (33.3% of all published SOTs). Out of these 10 cases of synchronous OD, five were females (n = 5/50.0%), and the mean age was 11.3 (±5.35) years. In four cases (40.0% out of the synchronous OD cases), lesions occurred in both jaws and in five cases (50.0% out of the synchronous OD cases) it occurred exclusively in the mandible. Five cases occurred bifocally (50.0% out of the OD cases) and five (50.0% out of the OD cases) occurred multifocally. Of these 10 cases, five were treated conservatively with surgical excision (n = 5/50.0%). The mean follow-up was 12.50 (±8.66) months, and there was no case of recurrence reported.

3.3.2 Synchronous SqOTs

In the second place, the present review's search yielded eight cases (26.7% of all published SOTs) of SqOT. Out of these eight published cases, 75.0% occurred in males (n = 6), and the mean age was 26.4 (±8.08) years. Six cases occurred in both jaws simultaneously (75.0% of SqOT cases) and two cases occurred only in the maxilla (25.0% of SqOT cases). In total, seven out of the eight cases were multifocal (87.5%) and one case (12.5%) was bifocal. Four cases were treated conservatively representing half of the cases of synchronous SqOTs, three adopted surgical resections as the treatment of choice (37.5% of SqOT cases), and one adopted radiotherapy and chemotherapy (12.5% of SqOT cases). The mean follow-up was 11.0 (±11.36) months and there was one case of recurrence reported (n = 1/12.5% of SqOT cases).

3.3.3 Synchronous CEOT

Synchronous CEOT represented 26.7% of all published SOTs, with eight cases reported in the literature. Out of the eight published cases, half occurred in female patients (n = 4), and the mean age was 39.75 (±9.9) years. Almost all cases of

synchronous CEOTs occurred in both jaws simultaneously with 7 cases representing 87.5% of the published cases, and only one case in the mandible bilaterally (de Oliveira et al., 2009). Three out of eight cases were multifocal lesions (37.5%), and all the others were bifocal (n = 5/62.5%). In Tarsitano et al. (2012), one of the synchronous CEOT lesions was a hybrid with SOT. In McCloy et al. (2021), besides the 13 synchronous CEOT lesions in the same patient, there was also one synchronous central odontogenic fibroma. All published cases of synchronous CEOTs adopted conservative enucleation/surgical excision of at least one of the lesions (100% of CEOT cases). Two out of eight cases also adopted surgical resection of one of the lesions (25%). The mean follow-up was 38.4 (±34.1) months, and the recurrence was 25% out of the published cases of synchronous CEOTs (n = 2).

3.3.4 Synchronous AOT

Two cases of synchronous AOT were included in this systematic review representing 6.7% of all published SOTs. Both cases affected female patients (n = 2/100%), and the mean age between them was 10 (±5.65) years. One case (50.0% of AOT cases) occurred simultaneously in both jaws, and the other occurred only in the maxilla (50.0% of AOT cases); one was multifocal (50.0% of AOT cases) and one was bifocal (50.0% of AOT cases). One case was treated by conservative surgical excision (50.0% of AOT cases) and one did not report the treatment approach (50.0% of AOT cases). Only one case had information regarding follow-up (60 months) and no recurrence was reported.

3.4 Qualitative assessment

The checklist of bias following the critical appraisal of the case reports revealed that all articles provided a clear description of patient's demographic features and most of them described the current clinical presentation of the patient and the diagnostic tests or assessment methods used. In contrast, the patients' history was poorly described and did not provide takeaway lessons in most of the articles included. Details of the risk of bias assessment are described in **Supplementary Material 4**.

4 DISCUSSION

OTs comprise a group of lesions of variable clinical behavior which can clinically manifest as benign or even as malignant neoplasms with metastatic potential (AlSheddi et al., 2015; da-Costa et al., 2012). SOT occurrences are rare and are defined as two or more OTs occurring simultaneously in different locations with a maximum time interval of 6 months. This is the first systematic review to address this subject. In total, 30 cases of SOTs were found in the literature, all of them showing the synchronous occurrence of the same OT (100%). Among these published cases, the most frequent were OD (33.3%), SqOT (26.7%), and CEOT (26.7%). The overall recurrence proportion was 13.3%. CEOT presented the highest within a subgroup (25% from synchronous CEOTs published cases). Five cases (16.7% out of all SOTs cases) were associated with a syndrome. Among the published cases associated with a syndrome, the Schimmelpenning was the only syndrome that appeared twice (6.7% out of all SOTs cases). In addition, this systematic review highlighted several clinical characteristics regarding the behavior of SOT available in the literature.

Since synchronous lesions in oral tissues are not common, unfortunately, a robust knowledge of their etiopathogenesis and possible genetic mutations is scarce in the literature. In some cases of odontogenic lesions, syndromes might be involved in their etiology, for example, in the case of multiple odontogenic keratocysts that are associated with the nevoid basal cell carcinoma syndrome (Sedghizadeh et al., 2007; El-Naggar et al., 2017). However, as some authors have already suggested, future genetic and molecular studies are necessary to elucidate the etiopathogenesis of SOTs (McCloy et al., 2021; Sedghizadeh et al., 2007). Furthermore, none of the cases included in this review reported the presence of Gorlin syndrome.

In this systematic review, two (6.7% out of all SOTs cases) studies reported that the patients had Schimmelpenning syndrome, with diagnoses of multiple odontomas with AOT and SqOT. Several oral manifestations in patients with this syndrome have been reported in the literature, such as hypoplastic and malformed teeth, giant cell granuloma, ankyloglossia, intraoral nevus odontodysplasia, ameloblastoma, bone cysts, and follicular cyst odontodysplasia (Murakami et al., 1999). In the present review, multiple odontomas were also described in cases of Pierre-Robin and Otodental syndromes. It is important to emphasize that Gardner's syndrome is known for its association with multiple odontomas and other oral manifestations such as

osteomas, supernumerary teeth, and dental impaction (Gamba et al., 2013). However, in the present systematic review, there were no cases of synchronous odontomas associated with Gardner syndrome that was complete or that met our eligibility criteria and our critical analysis.

The SOT most frequently detected in the literature were ODs and SqOTs, with ten (33.3% of all published cases) and eight (26.7% of all published cases) lesions, respectively. Men and women were equally affected (1:1) in the synchronous ODs reported in the literature and affected patients with a mean age of 11.3 years among these cases. ODs are frequent among young patients, usually in the second decade of life (EI-Naggar et al., 2017). On the other hand, this review detected a lower mean age (11.3 years) of synchronous ODs. Regarding the predominance of synchronous ODs in this review, it is difficult to assure whether this high frequency is related to an actual higher chance of a synchronous occurrence or is related to its inherent high prevalence in the overall population since ODs are the most common OTs (Ahire et al., 2018; da-Costa et al., 2012; Deepthi et al., 2016). Therefore, a publication bias may be related to this matter in the present review. Similarly, synchronous SqOTs case reports affected patients with a mean age of 26 years, which is lower than the mean age of about 38 years of patients with overall SqOTs (EI-Naggar et al., 2017). SqOTs showed gender predilection, with a male predominance (3:1). Previous studies have also shown that SqOTs show a predilection for male patients but with a smaller male–female ratio (1.8:1) (EI-Naggar et al., 2017).

In terms of recurrence, the present review demonstrated an overall proportion of 13.3% among all published cases. Usually, OT recurrence rates vary considerably depending on tumor type, treatment approach, and other variables (Bi et al., 2021; Mascitti et al., 2020). Usually, aggressive strategies (surgical resection) tend to produce fewer recurrences than conservative approaches (Bi et al., 2021; Hendra et al., 2019). Accordingly, in the present study, all recurrences occurred in cases treated conservatively (e.g., enucleation and surgical excision). In this review, CEOTs had the highest recurrence within a subgroup, that is, with 2 cases (representing 25% of published synchronous CEOTs). Even though CEOTs usually have a recurrence of approximately 12.6% according to the last systematic review (Chrcanovic & Gomez, 2017), this number is lower than the one obtained in the present review (25%). As these findings are only from the published cases, these recurrence numbers are likely misrepresented. However, it is difficult to explain to what extent this higher recurrence

in the present review could be related to an actual potential of the synchronous versions of CEOTs to recur more or if it is a mere bias due to the small sample and conservative approaches employed. Reviews of case series and reports are conditioned to limitations such as lack of generalizability. For this reason, the recurrence numbers in this review do not have external validity and cannot be translated as recurrence rates, such interpretation could only be possible with study cohorts. Finally, these results should also be interpreted with caution since surgical resection causes more patient morbidity. Therefore, the treatment approach should be chosen considering the characteristics of each case.

The present review has some crucial drawbacks, the most important one regarding publication bias. For this reason, the results of the current review should be interpreted with caution since these numbers do not represent the real epidemiological scenario. Due to the rarity of these conditions, all numbers may be overestimated, and demographic information may be misrepresented. Another limitation regards the small sample since these lesions are rare. Further retrospective multicenter studies with a large sample of OTs should be conducted to increase the understanding of the clinicopathologic features of SOTs. Despite all these limitations, systematic reviews of case reports and series still play an important role in summarizing the scientific evidence regarding rare conditions such as the SOTs.

CONCLUSION

In conclusion, the present review detected 30 cases of SOTs that mainly affected women in the 4th decade of life. They were mostly composed of the same OTs; ODs SqOTs and CEOTs were the most frequently found in the literature; a small number of cases was related to a syndrome, with Schimmelpenning being found twice; the overall recurrence among the published cases was 13.3%, and the recurrence of published CEOTs was 25% within its subgroup. Even though this review elucidated some of the main characteristics of SOTs, their etiopathogenesis is still unknown, supporting the necessity of further investigations. The characteristics of SOTs described in this review might guide dental surgeons when facing similar challenging cases in their clinical routine.

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Supplementary Material 1. Methodology detail

Search strategy

Two examiners (B.L.N. and B.B.S.) independently performed electronic searches in the following databases: PubMed, Scopus, Web of Science, and Embase, up to January 2022 and without year or language restriction. The search strategy was developed according to the Population, Exposure, Comparison Outcomes and Study design (PECOS) principle (Page et al., 2020; Moher et al., 2015) using the most cited descriptors in previous articles combining Medical Subject Heading (MeSH) terms and text words with Boolean operators “AND” and “OR” adapting to the syntax rules of each database. Additional manual searches from the reference lists of the included studies were performed. In addition, since most of the studies regarding syndromes do not refer to the tumors as “synchronous”, the authors decided to perform an additional search strategy to confirm that no study was missing. The software reference manager of choice to remove duplicates and organize all the articles was *EndNote X9, Thomson Reuters, Philadelphia, PA*. The search strategy applied to each database is detailed above:

PubMed	(Synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous) AND ("Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms")
Scopus	(Synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous) AND ("Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms")
Web of Science	(Synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous) AND ("Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms")
Embase	(Synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous) AND ("Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms")

Additional search strategy for syndromes:

PubMed	((synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous) AND (Syndrome OR Syndromes OR "Symptom Cluster" OR "Cluster, Symptom" OR "Clusters, Symptom" OR "Symptom Clusters" OR "Gardner Syndromes" OR "Syndrome, Gardner" OR "Syndromes, Gardner" OR "Gardner's Syndrome" OR "Gardner's Syndromes" OR "Gardners Syndrome" OR "Syndrome, Gardner's" OR "Syndromes, Gardner's" OR "Schimmelpenning Syndrome" OR "Syndrome, Schimmelpenning" OR "Schimmelpenning-Feuerstein-Mims Syndrome" OR "Schimmelpenning Feuerstein Mims Syndrome" OR "Syndrome, Schimmelpenning-Feuerstein-Mims" OR "Otodental Dysplasia" OR "Chromosome 11q13 Deletion Syndrome" OR "Otodental Syndrome" OR "Oculootodental Syndrome" OR "Otodental Syndrome With Coloboma" OR "Pierre Robin Syndrome" OR "Robin Syndrome, Pierre" OR "Syndrome, Pierre Robin" OR "Robin Sequence" OR "Sequence, Robin" OR "Pierre Robin's Sequence" OR "Pierre Robins Sequence" OR "Sequence, Pierre Robin's" OR "Pierre-Robin Syndrome" OR "Syndrome, Pierre-Robin" OR "Glossoptosis, Micrognathia, and Cleft Palate" OR "Pierre Robin Sequence" OR "Sequence, Pierre Robin")) AND ("Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms")
Scopus	(TITLE-ABS-KEY ("Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms") AND TITLE-ABS-KEY (syndrome OR syndromes) AND TITLE-ABS-KEY (synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous))
Web of Science	"Odontogenic Tumors" OR "Odontogenic Tumours" OR "Odontogenic Tumor" OR "Odontogenic Tumour" OR "Tumor, Odontogenic" OR "Neoplasms, Dental Tissue" OR "Dental Tissue Neoplasms" (All Fields) and Syndrome OR Syndromes OR “Symptom Cluster” OR “Cluster, Symptom” OR “Clusters, Symptom” OR “Symptom Clusters” OR “Gardner Syndromes” OR “Syndrome, Gardner” OR “Syndromes, Gardner” OR “Gardner's Syndrome” OR “Gardner's Syndromes” OR “Gardners Syndrome” OR “Syndrome, Gardner's” OR “Syndromes, Gardner's” OR “Schimmelpenning Syndrome” OR “Syndrome, Schimmelpenning” OR “Schimmelpenning-Feuerstein-Mims Syndrome” OR “Schimmelpenning Feuerstein Mims Syndrome” OR “Syndrome, Schimmelpenning-Feuerstein-Mims” OR “Otodental Dysplasia” OR “Chromosome 11q13 Deletion Syndrome” OR “Otodental Syndrome” OR “Oculootodental Syndrome” OR “Otodental Syndrome With Coloboma” OR “Pierre Robin Syndrome” OR “Robin Syndrome, Pierre” OR “Syndrome, Pierre Robin” OR “Robin Sequence” OR “Sequence, Robin” OR “Pierre Robin's Sequence” OR “Pierre Robins Sequence” OR “Sequence, Pierre Robin's” OR “Pierre-Robin Syndrome” OR “Syndrome, Pierre-Robin” OR “Glossoptosis, Micrognathia, and Cleft Palate” OR “Pierre Robin Sequence” OR “Sequence, Pierre Robin” (All Fields) and synchronous OR "multiple primary" OR bilateral OR multifocal OR "two-sided" OR simultaneous (All Fields)

Embase	('odontogenic tumors' OR 'odontogenic tumours' OR 'odontogenic tumor' OR 'odontogenic tumour' OR 'tumor, odontogenic' OR 'neoplasms, dental tissue' OR 'dental tissue neoplasms') AND (syndrome OR syndromes) AND (synchronous OR 'multiple primary' OR bilateral OR multifocal OR 'two-sided' OR simultaneous)

Quality assessment

The quality assessment was performed by two independent authors (B.L.N. and L.G.S.) to determine the risk of bias of each study. Whenever differences occurred, a third author was consulted (B.B.S). The critical appraisal of included case reports and case series was conducted using the Joanna Briggs Institute – University of Adelaide tool for case reports or case series (Moola et al., 2020). Articles were evaluated according to the following parameters: a clear description of patient's demographic characteristics, medical history and current clinical condition, clear description of the propaedeutic data, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report.

Supplementary Table 2. Reasons for exclusion of the studies.

Code	Legend	Total
1	Synchronous lesions non-odontogenic	11
2	Non-tumoral synchronous odontogenic lesions	30
3	Non-synchronous odontogenic tumors	35
4	Not appropriate study design	5
5	Other language than English	1
6	Article not found	9
7	Cemento-ossifying fibroma	17
8	Incomplete cases (lack of radiological or histopathological images or description)	9
9	Diagnosis not well illustrated by histopathological images or incompatible	2
	Total	**119**

Author/year	Code
Acharya, S., 2011	3
Adebayo, E. T., 2002	3
Aldred, M. J., 2006	3
Bingham, R. A., 1986	3
Bomfin, L. E., 2013	2
Borghesi, A., 2017	8
Bradley, J. F., 1977	6
Brooks, J. K., 2020	2
Buch, R. S., 2003	5
Chindasombatjaroen, J., 2012	2
Chong Huat, Siar, 1987	3
Cudney, N., 2008	3
Damm, D. D., 1983	3
DeLair et al., 2007	3
Dudani, I. C., 1974	6
Ealla, K. K. R., 2015	3
Feun, L. G., 1991	1
Fletcher, S. M., 2015	1
Fujita, Y., 2019	1
Gamoh, S., 2015	2
Gamoh, S., 2017	2
Gerlach, R. C., 2013	1
Gupta, R. K., 2016	2
Hajalioghli, P., 2015	2
Hammoudeh, J. A., 2009	4
Han, P. P., 2007	2
Happle, R., 1973	6

Hijioka, H., 2015	3
Hirshberg, A., 1994	2
Hogge et al., 2012	3
Hong, S. P., 1991	2
Hunter, H. A., 1951	3
Ide, F., 1999	1
Iida, S., 2006	1
Ikemura, K., 1985	3
Kelly, D. E., 1977	6
Keszler, A., 1987	2
Khandelwal, P., 2015	2
Kim, S. H., 2017	2
Kumar, K. V. A., 2016	3
Lamberg, M. A., 1984	6
Lin, C. C., 2004	2
Liu, Y., 2014	3
Martin, L., 2017	1
Martínez, A., 2009	3
Matsuzaka, K., 2001	2
Mosca, R. C., 2009	3
Moubayed, S. P., 2016	2
Nagao, T., 1982	2
Newaskar, V., 2016	2
Nilius, M., 2019	2
Nithya, S. 2021	8
Oliveira, J. A., 1995	2
Oliveira, J. F., 2012	1
Ozkan, L., 2014	1
Pistóia, G. D., 2001	2
Poleti, M. L.., 2013	2
Pullon, P. A., 1975	3
Reddy, P. S., 2016	2
Reti, R., 2011	2
Rodrigues, D. B., 2015	4
Ryu, D. M., 2000	1
Salehani, A. 2021	8
Sarkar, R. R., 2013	2
Sarmento, D. J. d S., 2013	3
Savage, M. G., 1985	3
Schiff, T., 1995	6
Schulz, M., 2009	3
Seim, P. 2005	3
Shao, Z., 2013	3
Shephard, M., 2014	4
Shimamoto, H., 2011	3

Sigal, M. J., 1988	3
Srivatsan, K. S., 2014	2
Sugiyama, M., 1999	3
Sweet, J. B., 1983	3
Takeda, Y., 1986	3
Vasconcelos, A. C., 2017	2
Willians D., 2018	3
Wilson, C., 2008	2
Zhao, Y., 2012	3

Excluded after critical analysis of the literature	**Code**
Akcam, T., 2012	7
Anbinder, A. L., 2013	7
Barberi, 2003	7
Canger et al., 2004	7
Hauser, 1989	7
Hwang, E. H., 2001	7
Prakash, A. R., 2012	7
Sakuma T. et al., 1998	7
Takeda, Y. and Fujioka Y., 1987	7
Tayfur et al., 2015	7
Yih, 1989	7
Wu, Y. H., 2019	9
Verhelst, P. J. et al., 2018	8
Thomas, 2021	3
Mehkri, S., 2012	9
Botelho, 2019	3
Bader G, 1967	8

Excluded after hand search	**Code**
Schimidseder R, 1975	8
Kumar SK, 2006	2
Baghaei-Rad et al., 1982	8
Malik AS, 1974	8
Mani NJ, 1974	8
Agarwal N, 2012	7
Bertolini F, 2002	7
Bradley ES Jr, 1968	7
Chindia ML, 2008	7
Khanna JN, 1992	7
Ribeiro AC, 2011	7

Update on syndromes	Code
Adebayo et al., 2002	4
Bradley and Orlowski, 1977	6
Habibi et al., 2010	2
Keshgegian et al., 1978	3
Ooya et al., 1976	1
Park et al., 1978	6
Ponti et al., 2012	3
Varghese, M. P., 2019	4
Weber et al., 1992	3
Welborn and Molnar, 1970	6

Supplementary Table 3. Detailed data collected by the included articles

Author(s) (year of publication)	Country	Age (years)	Sex	Patient clinical condition	Anatomical location	Histopathological features (description)	Diagnosis	Treatment	Recurrence /period of recurrence	Follow-up period (months)
Abrahão, A. C., 2009	Brazil	40	Female	NI	L1: Right mandible L2: Left mandible	Normal stratified squamous oral mucosa, and fibrous stroma with few blood vessels and signs of mild chronic inflammation; strands and solid masses composed of polygonal cells with eosinophilic cytoplasm, eosinophilic amorphous substance, and discrete calcification; no cell pleomorphism and mitosis. Amorphous eosinophilic material stained positively for Congo red under polarized light indicating amyloid component.	L1: peripheral CEOT L2: peripheral CEOT	1st: Surgical excision After recurrence: Bone curettage	Yes / 12 months	30 months after recurrence
Ajike SO, 2000	Nigeria	15	Female	Unremarkable	L1: maxilla (bilateral) L2: mandible (bilateral)	Areas with immature enamel and dentin	L1 e L2: compound odontomas	Surgical excision	NI	NI
Arif Dar M, et al., 2015	India	20	Female	Unremarkable	L1: Left mandible L2: Right mandible	Disorganised mass of dentin with pulpal tissue. The dentin was transverse with a longitudinal section of dentinal tubules with focal areas of fused dentinal tubules having a lack of structural architecture. The pulpal tissue showed diffuse bundles of collagen fibres interspersed with numerous endothelial lined blood vessels	L1: Odontoma L2: Odontoma	Surgical excision	No	12 months
Bartake, A. R., 2009	India	14	Female	NI	L1: Anterior maxilla L2: Anterior maxilla	Both lesions contained sheets of variously-sized solid nodules of cuboidal and columnar epithelial cells, nests, and rosette-like structures containing eosinophilic droplets; tubular duct-like spaces lined by	L1: AOT L2: AOT	NI	NI	NI

						single layer of columnar cells with nuclei spread away from the lumen; focal areas of calcification.				
Bordini Jr, J., 2008	Brazil	17	Male	Unremarkable	Both jaws in every quadrant	Structure consisting of dentine and connective tissue resembling a pulp tissue; inner soft and reticular connective tissue covered by stratified epithelium resembling odontoblasts.	Compound odontoma	Surgical excision	No	12 months
Chaves, 2020	Brazil	6	Female	Schimmelpenning syndrome	AMD (right, multiple); AMX (left);	NI	Multiple AOTs	Enucleation	No	60 months
Chomette G, 1984	France	40	Female	NI	L1: Left posterior maxilla L2: left posterior mandible	Epithelial sheets surrounding central amorphous substance and calcification. Tumour cords and clusters are composed of polyedral epithelial cells with eosinophilic cytoplasm. Some cells are degenerating (clear vacuolated cytoplasm, retracted nucleus). Squamous epithelium: tonofilament bundles, numerous intercellular desmosomes. Numerous mitochondria and glycogen bodies; intracytoplasmic cisternae filled with a granular or filamentous substance; frequent autophagic lysosomes.	L1: CEOT L2: CEOT	Surgical enucleation	NI	NI
Croonenborghs, 2020	BEL	14	Male	Family history of tumors; Trauma in 2013	L1: AMX (right) L2: AMX (bilateral) L3: AMX (left)	NI	SqOT	Enucleation with peripheral ostectomy	No	24 months
Elmuradi, 2016	USA	43	Male	Depression and type I diabetes	PMD (left and right) AMX (left) AMD (left) AMD (right)	NI	SqOT	Extensive curettage and peripheral ostectomy	NI	No
Ernst, L. M., 2007	USA	5	Female	Schimmelpenning Syndrome	L1: Maxilla L2: Anterior mandible	L1: irregular accumulations of enamel, dentin, cementum, and pulp tissue. L2: nodular foci of spindle and stellate-shaped cells surrounding numerous duct-like, odontogenic epithelial-lined structures, irregular calcifications scattered throughout.	L1: Multiple complex odontomas L2: AOT	Enucleation	NI	11 months

Gaiger de Oliveira, 2009	Brazil	43	Female	Poor oral condition	L1: posterior maxilla (left); L2:anterior mandible (left)	Irregular cords and nests of polyhedral epithelial eosinophilic cells and amyloid-like material. Sections from both lesions showed portions of oral mucosa that had been widened by the proliferation of tumor cells. These were surrounded by capsules where an amorphous, homogeneous, eosinophilic amyloidlike or dentinoid material could be observed, in addition to dystrophic calcifications in some areas.	L1: CEOT; L2: CEOT	Enucleation	No	Yes / 1 year
Hammoud eh et al., 2009	USA	4	Female	Pierre-Robin syndrome	Bifocal / Posterior mandible bilateral		Complex odontoma (OD)	Enucleation	NI	NI
Hernandez, G., 1992	USA	54	Male	Unremarkable	L1: mandible L2: mandible	Acanthomatous and spongiosis in the surface epithelium with distinct areas of tumor proiiferation in the underlying lamina propria of the gingiva, neoplastic epithelial cells seemed to arise from the basal layer, extending down in the form of finger-like papiilary projections, buds, nests, islands and sheets. Some tumor cells were lying free in the connective tissue stroma, the tumor mass appeared as a direct extension of the basal cell layer of the surface epithelium, neopiastic elements were confined to the upper portion of the gingival corium and did not approach the cortex of the alveolar bone, the parenchyma of the tumor resembled elements of the developing enamel organ, tumor cells had a trabecular and plexiform growth pattern with formation of folicle-like epithelial extensions. Most epithelial cells presented a palisading columnar pattern with numerous micro-vesicles. Nuclei were large and oval shaped. Acanthomatous and cystic changes within the tumoral nests. In the lumen of	Peripheral ameloblastoma	Surgical enucleation with free margins	Yes / 2 months	2 years after recurrence

						some of the cystic areas, parakeratin-like structures. No cell atypia or mitosis. The connective tissue stroma surrounding the tumor was infiltrated by small and medium sized lymphocytes with some plasma ceils. Areas of hyalin degeneration of the connective tissue.				
Hopper, T. L., 1982	USA	22	Female	Facial trauma 12 years before in the anterior maxilla Unremarkable	L1: Right maxilla L2: left mandible	Collagenous connective tissue stroma with multiple islands of well-differentiated, stratified, squamous epithelium varied in shape and size. This connective tissue was composed of mature collagen fibers associated with ovoid to spindle-shaped young fibroblasts. Around each epithelial island, there was a layer of flattened basal cells, and prickle cells. Keratinization in some epithelial nests and others with exfoliation of keratinized cells in the central area, resulting in microcystic formation. Some of the epithelial islands showed intraepithelial calcification. Laminar, calcified bodies within the epithelial nests (von Kossa stain). No mitotic figures or pleomorphism within the epithelial islands.	L1 and L2: SqOT	Surgical resection Surgical enucleation of the tumor (L2)	NI	3 months
Ibituruna, A. C. H., 2019	Brazil	26	Male	NI	L1: Anterior Maxilla L2: Anterior Maxilla L3: Anterior and Posterior mandible	Polyhedral epithelioid neoplastic cells of variable size, with clear and lightly eosinophilic cytoplasm. Some cells showed mild atypia and multinucleated cells were occasionally seen.Tumor stroma was composed of dense irregular connective tissue, with the foci of amorphous Congo red-positive amyloid-like deposits showing apple-green birefringence under polarized microscopy. Some basophilic calcified deposits (Liesegang rings) were also seen.	L1: CEOT L2: CEOT	L1 e L2: curettage L3: enucleation and mandibular resection	No	24 + 72 months

Iwamoto O., 1999	Japan	15	Female	NI	L1: Left posterior mandible L2: right posterior mandible	Pattern A: was a shell-like structure consisting of dentine and enamel, which was lined by reticular odontogenic epithelium on the inner side and covered by a thin cementum layer on the outer side. Pattern B: was a similar shell-like structure without a lining of odontogenic epithelium, in which trabecular-arranged osseocemetum proliferated in contact with the outer surface. There was a background of loose, immature fibrous tissue that included tiny islets of odontogenic epithelium and “woven bone”-like material. The thick surrounding membrane consisted of loose fibrous tissue covered by stratified squamous epithelium and contained cords of odontogenic epithelium, which was rather dense in some areas.	L1: Odontoma L2: Odontoma	Enucleation	No	Yes / 2 years
Larsson, A., 2003	CHE	10	Female	Unremarkable	Multiple tumors (+ 10): anterior maxilla, posterior maxilla, anterior mandible, posterior mandible	The general pattern was AOT-like. The lesional epithelial cells showed no atypia but a few mitoses were readily recorded.The main part of the lesions was made up of sheets of cuboidal or cylindrical cells arranged like convoluted tubules, with duct-like structures, associated with dysplastic dentin However, there were no well-defined roundish ductal or small cystic elements lined by cubical or cylindrical cells, no clearly cribriform, and only insignificant whirled structures and no evidence of dystrophic calcifications, features typical of classical AOT. There was a fibrous capsule at the periphery.	AOT or "AOT-like"	Enucleation	Yes / 9 months later and over the next 5 years	6 years
Leider, 1989 (Case 1)	USA	29	Male	Family history revealed that two siblings,an	AMX; PMX(bilateral); PMD (left)	NI	SqOT	Curettage	NI	NI

				older brother and sister,were treated previously for similar maxillary and mandibular jaw lesions						
Leider, 1989 (Case 2)	USA	25	Male	Family history (sibling of case 1)	AMX (left); PMX (right); PMD (right)	NI	SqOT	Curettage	NI	4 years and 1 month
Leider, 1989 (Case 3)	USA	26	Female	Family history (sibling of case 1 and 2)	AMX; PMX; AMD; PMD (bilateral)	NI	SqOT	Resection	No (multiple sequestrectomies)	NI
Liu, 2017	China	9 years	female	Otodental syndrome	Chin	dentin was fused with 3 tooth-like structures and several pulp stones were existed. Moreover, we found that the necrotic tissue existed in a pulp cavity which was independent of the major root canal system. In addition, the morphology of odontoblast was in a high columnar shape with massive vacuolated changes	Multiple complex odontoma	Surgical treatment	NI	NI
McCloy, 2021	USA	30	Male	Allergy to penicillin and multiple kidney cysts	AMX, PMX, AMD, PMD - bilateral	NI	13 lesions: CEOT 2 lesions: OF	Enucleation and curettage	NI	NI
Mills, W. P., 1986	USA	26	Male	Unremarkable	L1: Posterior mandible L2: Posterior maxilla L3: Posterior maxilla	A dense fibrovascular connective tissue stroma with randomly dispersed and irregularly shaped islands of squamous epithelium. The islands were composed of uniform squamous epithelial cells with bland histologic features and little evidence of cellular pleomorphism. Microcytic vacuolizations and individual cell keratinizations within the epithelial islands were commonly observed. Irregular	L1:SqOT L2: SqOT L3: SqOT	Surgical excision; Resection.	No / in 1985	Until Sep. 1985

						dystrophic calcification of degenerating epithelial cells in some of the islands was less frequently noted.				
Nammalwar, R. B., 2018	India	12	Male	NI	L1: Posterior mandible L2: Posterior mandible	Poorly formed dentin matrix and cementoid areas with lacunae containing cementocytes.The excised surrounding soft tissue with the odontoma showed a poorly differentiated benign lesion composed of irregularly arranged fibrocollagenous tissue, with the cellular fibrous matrix that was containing fibroblasts and portions of the odontogenic epithelium.	L1: Complex Odontoma L2: Complex Odontoma	Enucleation	NI	3 months.
Norris, L. H., 1984	USA	26	Male	Unremarkable	L1: Left posterior Maxilla L2: Right posterior Maxilla	Maxilla: Masses of dense collagenous connective tissue containing numerous small strands and islands of proliferating squamous epithelium, some of which had central areas of keratin. The cells were benign, uniform and regular, with no mitotic activity. Occasionally, there were epithelial nests resembling odontogenic epithelium. Mandible: low-grade epidermoid carcinoma	L1: SqOT L2: SqOT	Radio and chemotherapy	NI	NI
Schreiber, L. K. 1963	Puerto Rico	9	Male	NI	L1: Maxilla L2: maxilla	Mass of dentine with a relatively large central cavity filled with enamel and soft tissues. Around the margins of the dentine is a layer of perpendicularly oriented odontoblasts. The central cavity contains many typical enamel rods, and near the neck of the cavity and extending into the soft mass in the concavity noted grossly is an area of plexiform cords of ameloblasts.	L1: Odontoma L2: Odontoma	Enucleation	NI	NI
Sedghizadeh, P. P. et al., 2007	United States	51	Male	Unremarkable	4 Lesions in maxilla and 1 in mandible	Cords of ovoid to polyhedral neoplastic epithelial cells separated by eosinophilic, fibrous stroma. Lesional cells had abundant eosinophilic cytoplasm, sometimes granular in appearance, and were fairly uniform basophilic nuclei. The nuclei of the neoplastic cells did not	All lesions: CEOT	Enucleation	Yes	NI

						demonstrate significant pleomorphism, atypia, or mitotic figures.				
Só, B. B. et al., 2020	Brazil	33	Female	NI	L1: Mandibula L2: Maxilla	sheets and islands of odontogenic epithelial cells with polygonal shape, homogenous eosinophilic cytoplasm, and large ovoid nuclei. Discrete intercellular bridges between the epithelial cells and minimal nuclear pleomorphism were detected. The tumor islands were surrounded by a fIbrocolagenous stroma containing variable amounts of an eosinophilic to a basophilic amorphous, amyloid-like material.	L1: CEOT L2: CEOT	Enucleation	No	2 years
Tarsitano, A. et al., 2012	Italy	55	Male	Normal and healthy	1 lesion in the maxila and 1 lesion in the mandible	Typical histologic features of asquamous odontogenic tumor were present only in the mandibular specimen. The surgical specimens taken from the 2 sites were evaluated by 2 different pathologists, both of whom supported our original histopathological diagnosis	Multifocal calcifiyng epithelial odontogenic tumor and associated with a squamous odontogenic tumor	Enucleation of maxillary lesion Resection of the mandible	No	42 months
Hauber, K. et al., 2003	Germany	7	Male	The patient was born with a yellowish tumour of the left eye, ipsilateral facial papules, and a hairless lesion on the left parietal scalp.	Multiple lesions in maxilla (left) and mandible (left)	A mixture of enamel, dentin, cementum and pulp	OD	Surgical excision	NI	NI

Supplementary Table 4. Critical appraisal of case reports.

Author/Year	*Were patient's demographic characteristics clearly described?*	*Was the patient's history clearly described and presented as a timeline?*	*Was the current clinical condition of the patient on presentation clearly described?*	*Were diagnostic tests or assessment methods and the results clearly described?*	*Was the intervention(s) or treatment procedure(s) clearly described?*	*Was the post-intervention clinical condition clearly described?*	*Were adverse events (harms) or unanticipated events identified and described?*	*Does the case report provide takeaway lessons?*
Abrahão, A. C., 2009	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Ajike S.O., 2000	Yes	No	Yes	Yes	Yes	No	No	Yes
Arif Dar M, et al., 2015	Yes	No	Yes	Yes	Yes	No	No	Yes
Bartake, A. R., 2009	Yes	No	No	Yes	No	No	No	No
Bordini Jr, J., 2008	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Chaves et al., 2020	Yes	Yes	Yes	No	No	No	No	Yes
Chomette G, 1984	Yes	No	Yes	Yes	Yes	No	No	Yes
Croonenborghs et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Elmuradi et al., 2016	Yes	Yes	Yes	Yes	Yes	No	No	No
Ernst, L. M., 2007	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Gaiger de Oliveira, 2009	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Hammoudeh et al., 2009	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Hauber et al., 2003	Yes	No	Yes	No	No	No	No	No
Hernandez, G., 1992	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hopper, T. L., 1982	Yes	Yes	Yes	No	Yes	No	No	No

Ibituruna, A. C. H., 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Iwamoto O., 1999	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Larsson, A., 2003	Yes	Yes	No	Yes	No	No	Yes	No
Leider, 1989	Yes	No	No	Yes	No	No	No	No
Liu et al., 2017	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
McCloy et al., 2021	Yes	Yes	Yes	No	No	No	No	No
Mills W. P., 1986	Yes	No	No	Yes	No	Yes	No	No
Nammalwar, R. B., 2018	Yes	No	No	Yes	Yes	Yes	No	No
Norris, L. H., 1984	Yes	No	No	Yes	No	Yes	No	No
Schreiber, L.., 1963	Yes	No	Yes	Yes	No	No	No	No
Sedghizadeh, P. P. et al., 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Só, B. B. et al., 2020	Yes	No	No	Yes	Yes	Yes	No	Yes
Tarsitano, A. et al., 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

3 CONSIDERAÇÕES FINAIS

A presente revisão sistemática detectou 30 casos de TOSs que afetaram principalmente mulheres na 4ª década de vida. Os casos eram compostos principalmente pelos mesmos TOs; Os ODs SqOTs e CEOTs foram os mais encontrados na literatura; um pequeno número de casos estava relacionado a uma síndrome, sendo Schimmelpenning encontrada duas vezes; a recorrência global entre os casos publicados foi de 13,3%, e a recorrência de CEOTs publicados foi de 25% dentro do seu subgrupo.

O presente artigo científico fornece evidências de como os tumores odontogênicos síncronos se manifestam, definindo qual a predileção de sexo, idade, sintomatologia, localização e diagnóstico das lesões, bem como quais foram os principais meios de tratamento e *follow-up*. Baseado nos resultados encontrados nesta revisão sistemática, verificamos um panorama abrangente das características demográficas e clínicas dos TOSs, que pode orientar os cirurgiões-dentistas diante de casos desafiadores semelhantes em sua rotina clínica. Contudo, destaca-se a necessidade contínua de estudos e de vigilância clínica para melhor compreensão e manejo dessas condições. Além disso, cabe aos profissionais a capacidade de identificar essas lesões, realizar o correto diagnóstico e possibilitar, então, o melhor prognóstico ao paciente.

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ANEXO – REGISTRO PROTOCOLO PROSPERO - *International prospective register of systematic reviews*

Citation

Manoela Martins, Bruna Neumann, Bruna Só, Felipe Silveira, Lauren Schuch, Lucas Gonçalves. Synchronous odontogenic tumors: a systematic review. PROSPERO 2021 CRD42021238295. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021238295

Review question

The objective of the present study was to integrate the available data published in the literature regarding on synchronous odontogenic tumors into a systematic review of the clinical, imaginological and histopathological features, treatment, follow-up and recurrence frequency**.**

Searches

The search strategy will be constructed according to the Populations, Interventions, Comparison, Outcomes, and Study Design (PICOS) principle. Individual search strategies will be designed for the following electronic databases: PubMed (National Library of Medicine), Web of Science (Thomson Reuters), Scopus (Elsevier), MEDLINE Ovid (Wolters Kluwer) and Embase (Elservier). The electronic databases will be searched to identify relevant studies. The searched publications will be only considered in the English language, with no restrictions on publication year. The search strategy will contain a combination of controlled predefined Medical Subject Heading (MeSH) terms and free terms using the Boolean operators (i.e., OR, AND), always adapted to the syntax rules of each bibliographic database. Additionally, it will be also performed a manual search of bibliographies and reference lists of the included studies to locate any potential unidentified study

Types of study to be included

Case reports and case series of synchronous odontogenic tumors.

Condition or domain being studied

Odontogenic tumors are a heterogeneous group of oral and maxillofacial lesions originated from the epithelial or mesenchymal remnants from tooth development.

Odontogenic tumors may vary from hamartomatous proliferation to benign or even malignant neoplasms with metastatic potential. The development of these lesions may occur centrally inside the bone or peripherally in extraosseous regions and its etiopathogenesis is still nuclear. Odontogenic tumors are relatively rare lesions and comprise around 1% of all tumors the develop in gnathic bones. These tumors may present different clinical and histopathological features, clinically varying from an asymptomatic, slow and expansile growth to rapid, infiltrative and symptomatic lesions. The most recent classification of World Health Organization categorized the benign odontogenic tumors in 3 types: epithelial, mesenchymal, or mist. Synchronous tumors are defined as the second primary tumor being diagnosed in a different site from the first one and within an interval of 6 months or less. Synchronous odontogenic tumors are rare, and no systematic review in this field has been published previously. A systematic review of synchronous odontogenic tumors can provide information regarding which types of odontogenic tumors present a higher chance of a synchronous presentation as well as their main clinical, imaginological, histopathological and management aspects.

Participants/population

Individuals diagnosed with synchronous odontogenic tumors.

Intervention(s), exposure(s)

Synchronous odontogenic tumors.

Comparator(s)/control

Not applicable.

Main outcome(s)

Demographic, clinical, histopathological and management of synchronous odontogenic tumors.

Measures of effect

Based on descriptive analysis.

Additional outcome(s)

None.

Measures of effect

Not applicable.

Data extraction (selection and coding)

The information from the eligible studies will be collected by two reviewers. Cases of disagreements will be discussed with a third reviewer. For each study, the following data will be extracted, using a standardized data collection form: (1) authors; (2) year of publication; (3) country; (4) patient age (years); (5) patient gender; (6) cortical expansion; (7) anatomical location of the synchronous lesions; (8) clinical presentation; (9) reported symptoms; (10) duration; (11) radiological features; (12) lesion size (cm); (13) another associated lesion; (14) treatment; (15) recurrence; (16) follow-up period (months).All the data extracted will be inserted in a database on the EndNote software (Thompson Reuters, New York, NY, USA).

Risk of bias (quality) assessment

Critical appraisal of the included articles was carried out by means of the Joanna Briggs Institute – University of Adelaide tool for case reports or case series (Gagnier JJ et al., 2013). The included articles were evaluated according to the following parameters: clear description of patient's demographic characteristics, medical history and current clinical condition, clear description of the propaedeutic data, treatment, post-intervention clinical condition, adverse events, and lessons provided by the case report.

Strategy for data synthesis

A narrative synthesis of the findings of the included studies will be provided regarding the general characteristics of the synchronic odontogenic tumors analyzed in the studies. The findings will be reported according to the data provided by the included studies.

Analysis of subgroups or subsets

Not applicable.

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Type and method of review Diagnostic, Systematic review

Anticipated or actual start date 01 January 2021

Anticipated completion date 01 June 2021

Funding sources/sponsors

None.

Grant number(s)

State the funder, grant or award number and the date of award

Not applicable.

Conflicts of interest

No

Language

English

Country

Brazil

Stage of review

Stage	*Started*	*Completed*
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct. The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.