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CLINICAL REVIEW

Oral metastasis as the first indication of undiscovered malignancy at a distant site: A systematic review of 413 cases

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Abstract

This systematic review is the first to provide evidence regarding demographic, clinical, and imaging characteristics, as well as information related to survival, of patients with oral and maxillofacial metastases of occult primary tumors. Case reports, case series, and cross-sectional studies were included. Ten databases were searched. The risk of bias was assessed using the Joanna Briggs Institute appraisal tools. Overall, 353 articles (413 patients) were included. Statistically significant associations between survival and multiplicity of metastatic foci, and between each of the main primary sites and some features of the oral lesions were observed. Some clinical and imaging characteristics can help dentists in raising diagnostic suspicions and also in relating to plausible primary sites. Early diagnosis of oral and maxillofacial metastases can positively affect the survival rate when they are the only focus of dissemination, conferring an important role on the dentist.

KEYWORDS

diagnosis, mouth neoplasms, neoplasms, neoplasm metastasis, oral, oral manifestations, systematic review, unknown primary

1 | INTRODUCTION

The spread of a malignant tumor to the oral and maxillofacial region is considered a rare cancer event, occurring in 1%–8% of cases, and usually occurs in advanced disease.[1–3] However, in 20%–35% of cases, the oral and maxillofacial region is the only focus of distant dissemination.[1,4] In these cases, rapid and timely systemic measures can be taken to avoid metastases in multiple organs and, therefore, could potentially improve the survival of these patients.[5,6]

Occult primary tumors at the time of metastases diagnosis, or, OPTMD, is a term that has been applied to cases in which the primary tumor has not yet shown clinical signs and symptoms, but it was discovered after investigation. They differ from cancers of unknown primary sites (CUP), a heterogeneous group of cancers for which the site of origin remains occult even after detailed investigation and is often associated with a poor prognosis as patients are treated with a nonselective empirical therapy.[6] Identification of the primary tumor is always important since it could improve the survival rate.[5] As both situations can present cases of unknown primary site at the time of diagnosis of oral metastasis, both are suitable for inclusion in the review.

In patients with known malignancy, past or present, metastatic risks are evident and should be considered[7];

but in cases of OPTMD, the diagnosis of malignancy is made from the metastatic lesion. Early diagnosis may be as challenging as important for a better prognosis, especially if the lesion is a single focus of spread, a situation that is more likely precisely when the primary tumor is still occult.[8,9]

Oral metastases do not always present with clinical and radiographic signs of a malignant tumor. They generally mimic inflammatory, reactive, or hyperplastic benign lesions with nonspecific appearance.[10,11] The most qualified examinations for the investigation of primary tumors are mainly PET-CT, laboratory tests for specific tumor markers, and immunohistochemical studies. Even considering that clinical and imaging characteristics of oral metastases have a secondary role in this process, they are still able to contribute as "pieces in this investigative puzzle," narrowing the range of possibilities, directing to more plausible primary tumors and, consequently, shortening the search time.

In 2020, Kirschnick et al.[11] carried out a systematic review of metastases to the oral and maxillofacial region, describing demographic, clinical, and imaging characteristics, as well as survival rate, using five databases and 217 studies, but with no mention of the primary tumor being known or occult or of the multiplicity of metastatic foci.

Thus, we aimed to conduct the first systematic review of cases of oral and maxillofacial metastases of occult primary tumors. We have compared survival rate, between patients with a metastatic tumor at a single maxillofacial site and patients with metastatic tumors at multiple sites, of which at least one is maxillofacial.

2 | MATERIAL AND METHODS

2.1 | Development of the research question and eligibility criteria

The following questions motivated this research: "In patients with metastases in the oral and maxillofacial region, arising from unknown primary tumors, what are the clinical and imaging characteristics capable of triggering diagnostic suspicions, tracking the primary site, or differentiating between oral metastasis as a single site versus multiple foci of a disseminated disease?" and "Can these two distinct situations impact the prognosis?"

Metastatic tumors of the oral and maxillofacial region, histopathologically diagnosed as the spread of occult primary tumors and published in the form of case reports, case series, and cross-sectional studies, in English, Portuguese, Spanish, and French were included. Considering that oral and maxillofacial metastases are very rare and, when they do appear, they are usually published in the form of reports and case series, it seems that the only and best scientific evidence for this pathology comes even from these descriptive observational studies.

The exclusion criteria were as follows: (1) unavailable full version, (2) insufficient relevant information, and (3) oral and maxillofacial metastases that (a) were discovered during autopsies, (b) originated from hematological malignant tumors, and (c) originated from primary malignant tumors of the head and neck region.

2.2 | Protocol and records

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[12] It was registered in the Prospective Register of Systematic Reviews (PROSPERO), under the number CRD42020189704.

2.3 | Sources of information and search strategy

The following databases were searched: PubMed/Medline, Scopus, Embase (via Elsevier), Virtual Health Library (BVS), Cochrane Library, Web of Science, and gray literature (Google Scholar, OpenGrey, and Brazilian Digital Library of Theses and Dissertations-BDTD). The reference lists of the selected articles were manually tracked to detect any relevant studies that were not retrieved through the electronic search. The search strategy is summarized in Table S1, Supporting Information. The references found in the databases were exported to a reference manager, EndNote Web® (Thomson Reuters, New York, NY).

2.4 | Study selection

The selection process was performed in two phases. In phase 1, two authors (T.C.K. and F.A.N.H.) worked independently and used titles and abstracts to identify eligible articles. In phase 2, the same authors read the full texts and excluded those that did not meet the inclusion criteria. Any disagreements between the two authors were resolved by discussion until a consensus was reached. When there was no consensus, a third author (V.C.V.) was consulted, and the decision was final. The inter-examiner kappa value was greater than 0.8.

2.5 | Data collection process and data extracted

Data collection for the selected studies was performed by the first reviewer. The second reviewer (F.A.N.H.)

confirmed the accuracy of the data collected. Any disagreements were resolved by consulting a third reviewer (V.C.V.). The following information was extracted from each study: author, patient profile (sex, age, and ethnicity), presence of systemic diseases, location of the lesion, evolution time, symptomatology, past or current history of malignancy, clinical appearance, imaging features, histopathological diagnosis, primary site, treatment, and survival rate.

2.6 | Risk of bias within studies

The risk of bias was assessed using the modified Joanna Briggs Institute's critical assessment tools, for case reports, case series, and cross-sectional studies. Each question was answered with "yes," "no," "unclear," or "not applicable."

Two reviewers (T.C.K. and F.A.N.H.) analyzed the risk of bias separately and classified the articles as "high risk" (when the study reached up to 49% "yes" to the considered parameters), "moderate risk" (50%–69% "yes"), and "low risk" (greater than 70% "yes"). A conference was held between the two reviewers, and disagreements were resolved by consensus. The numbers were generated using RevMan 5.4 software (Review Manager 5.4, Cochrane Collaboration).[13]

2.7 | Analysis of evidence and statistics

A database covering the variables and classifications was organized in a Microsoft Office Excel 2016 spreadsheet (Microsoft Corporation, Redmond, WA) to tabulate the statistical data. The data obtained were analyzed using SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY). A descriptive analysis of the results was conducted. Moreover, association analyses between the collected variables were developed, with PRIMARY TUMOR as an independent variable, which was associated with the multiplicity of metastases (only in oral and maxillofacial regions or at multiple sites), metastases, location (soft tissue, jaw bones, or both), signs and symptoms (symptomatology, paresthesia, dysphagia, bleeding, dental mobility, and lymphadenopathy), clinical features (surface, consistency, size, color, clinical appearance, and evolution time), and imaging features (radiolucid, radiopaque, mixed, poorly delimited, cortical bulging, tooth displacement, root resorption, and pathological fracture). Another association analysis was performed between MULTIPLICITY OF METASTASES (only in the oral and maxillofacial region or in multiple sites), as an independent variable, and survival rate. For the nominal qualitative variables, chi-square and Fisher's exact tests were used. In addition, for the analysis of data referring to the survival rate, which presents an ordinal qualitative variable, the Mann–Whitney test was used. Only cases in which the time from diagnosis to death was reported were included in the survival rate analysis. In all tests, statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Selection and characteristics of the studies

A total of 65.984 articles were identified from the databases. However, 22.040 were removed as they were duplicates, and 42.723 were considered irrelevant after reading the titles and abstracts. All 1.214 remaining articles were read in full. Of these, 861 were excluded after applying the inclusion criteria (Table S2). Finally, 353 papers were included in the quality analysis. The PRISMA flowchart summarizes the selection process, including the reasons for exclusion (Figure S1). Of the 353 studies analyzed, 328, 17, and 11 were case reports, case series, and cross-sectional studies, respectively, with the references available in Supporting Information. A total of 413 patients were included in the study. The studies were published between 1927 and 2021. Table S3 shows the individual results of these studies.

3.2 | Bias risk analysis

The assessment of the risk of bias per study is summarized in Figure 1A–C. Details are shown in Tables S4–S6. Among the 353 articles selected for qualitative analysis, 97, 185, and 74 studies had low, moderate, and high risk of bias, respectively.

3.3 | Synthesis of studies

3.3.1 | General characteristics of lesions

Metastases to the oral and maxillofacial regions were observed mainly in patients between the sixth and eighth decades of life (29.3%, 27.4%, and 18.9%, respectively). The absolute values for all age groups are shown in Figure 2. There was a predilection for men (64.4%, 266 out of 413), with a mean age of 59 years (±16.3). The most evident primary sites were the lungs ($n = 87$), kidneys ($n = 75$), liver ($n = 47$), thyroid ($n = 32$), and

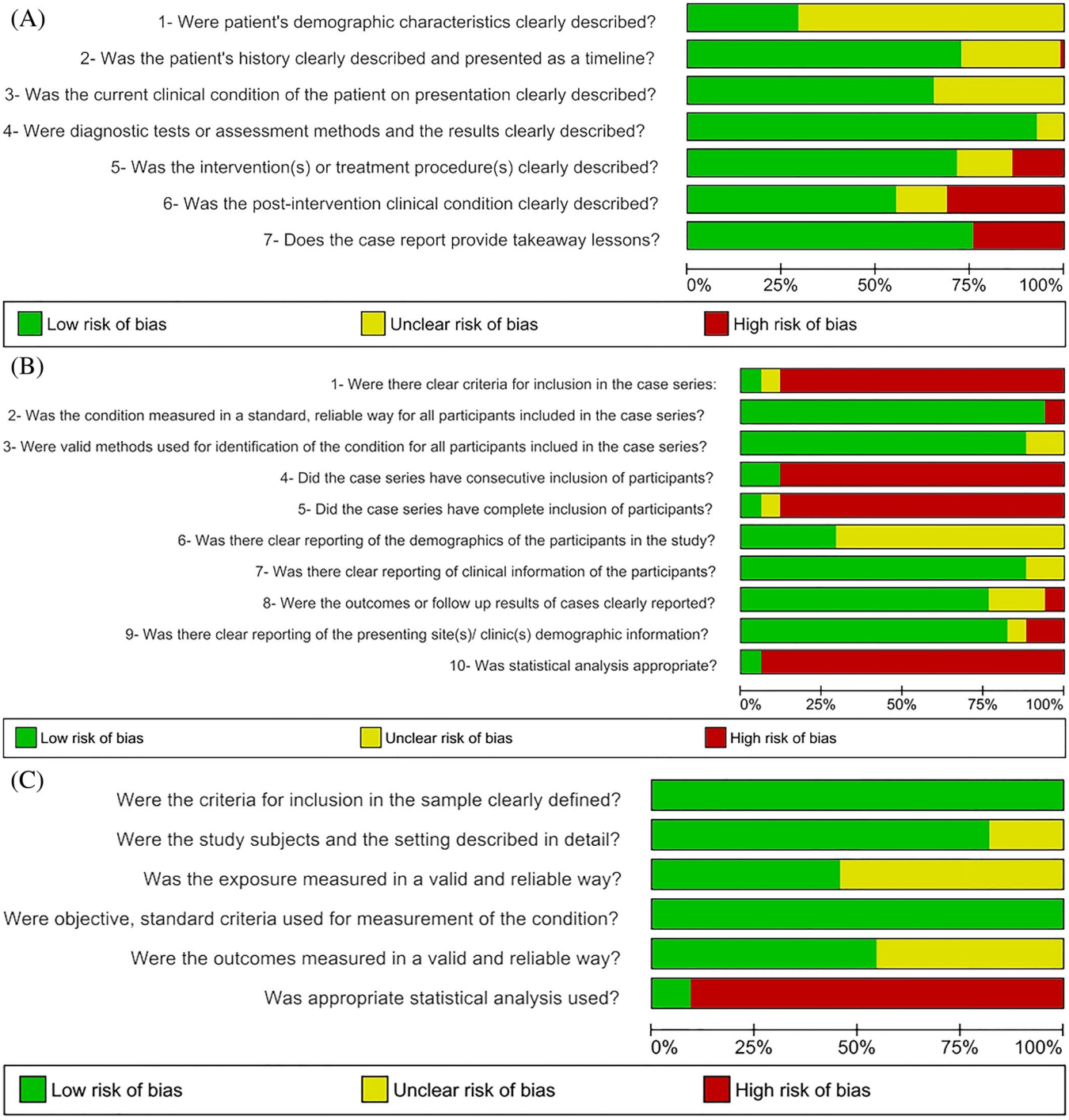

FIGURE 1 Risk of bias for (A) case reports, (B) case series, and (C) cross-sectional studies, showing the percentages of studies, according to the risk, for each guiding question [Color figure can be viewed at wileyonlinelibrary.com]

prostate ($n = 26$). Figure 3 shows the main primary sites found between the sexes.

Adenocarcinoma (28.3%, 117 of 413) was the most prevalent histological type, followed by hepatocellular carcinoma (11.4%, 47 of 413) and renal cell carcinoma (9.7%, 40 of 413). The oral and maxillofacial regions were the only metastatic sites in 52.1% (215 of 413) patients. The jaws were involved more frequently than the soft tissues (235 and 178 respectively), with the mandible (91.1%, 214 of 235) and the attached gingiva (39.3%, 70 of 178) being the most affected sites.

Among the signs and symptoms, the value of the denominator was evaluated, excluding cases with information not provided by the authors. Pain was the most prominent feature ($n = 152$ of 241, 63.1%), followed by paresthesia ($n = 82$ of 94, 87.2%). Of the 235 intraosseous

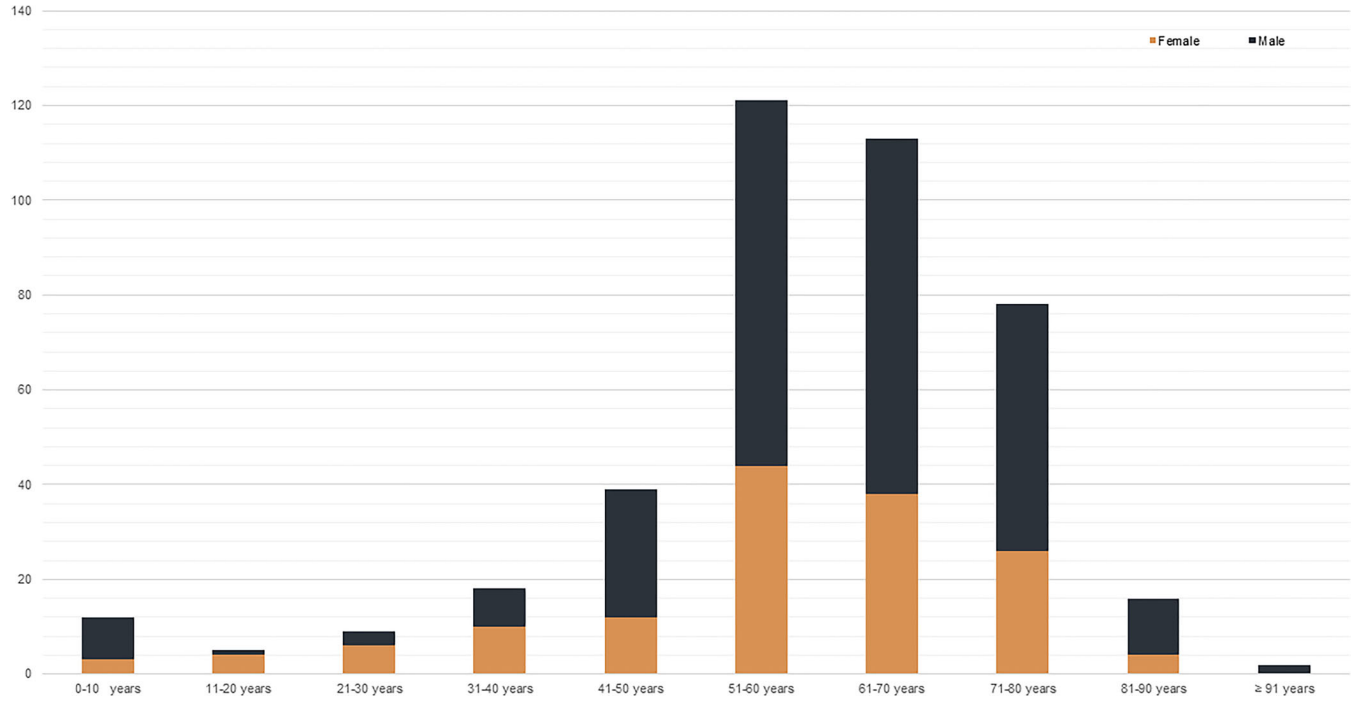

FIGURE 2 Prevalence of oral and maxillofacial metastases of occult primary tumors by age group between sexes [Color figure can be viewed at wileyonlinelibrary.com]

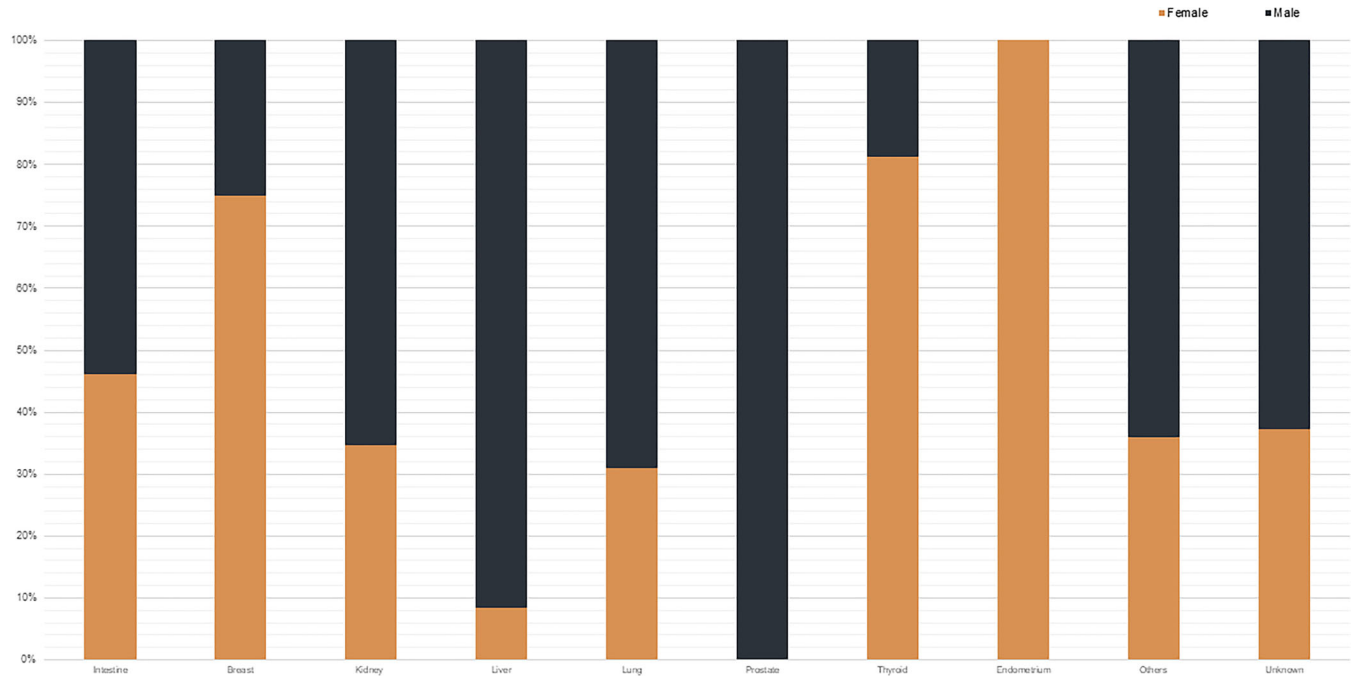

FIGURE 3 Main primary sites of oral and maxillofacial metastases between sexes [Color figure can be viewed at wileyonlinelibrary.com]

cases, pain was present in 109 (75.7%) patients. In contrast, only 44.2% (42 of 178 soft tissue lesions) were associated with pain. Paresthesia was a common finding in intraosseous lesions, especially in carcinomas originating from the prostate, where it was present in 46.1% (12 of 26 cases).

In the soft tissues, the gingiva was the most affected area (39.3%, 70 of 178). The primary sites most likely to

metastasize to the gingiva were the lungs (10.6%, 19 of 178) and the liver (5.6%, 10 of 178). The clinical appearance was variable, but the description most mentioned was swelling (76.8%, 317 of 413). Some features were absent in many reports, which may explain the low percentage values: normal color (38.9%, 44 of 113), firm consistency (48%, 72 of 150), normal surface (46.7%, 64 of 137), and no cervical lymphadenopathy (69.9%, 116 of 166). There was a history of tooth extraction in 64 patients (15.4%, 64 of 413). Previous antibiotic therapy was found in 29 patients (7.0%, 29 of 413). The most frequently considered clinical hypothesis/differential diagnoses were benign lesions, such as pyogenic granuloma, giant cell peripheral granuloma, and fibrous epulis. The most common radiographic description was an osteolytic/radiolucent area (75.6%, 189 of 250), with imprecise limits (40.6%, 101 of 249). Radiopaque or mixed injuries were rarely mentioned (11.6%, 39 of 248). Detailed information about CT and PET-CT is provided in Table S3. Among the treatments implemented, palliative treatment was the most common (25.5%, 80 of 314). In most cases, the disease progression was poor, with 4-year survival in only 2.1% (4 of 189) of patients and death in less than 3 months in 45.5% (86 of 189) of patients.

3.3.2 | Analysis of the association of variables

In the association between primary tumors and multiplicity of metastases, we noticed a statistically significant association ($p = 0.015$). In primary tumors involving the thyroid and liver, we found a higher prevalence of localization only in the oral and maxillofacial regions, while in primary tumors involving the intestine/colon, endometrium, and breast, there was a higher prevalence of multiple metastases. Another significant association was found between the primary tumor and location in the oral and maxillofacial regions ($p < 0.001$). Tumors from the thyroid, prostate glands, and breast most frequently metastasize to the bone tissues, while tumors from the kidney and endometrium to the soft tissues. The complete list of the primary tumors, with their respective percentages, is presented in Table S7).

Considering the associations between primary tumor and signs and symptoms of metastatic oral and maxillofacial lesions, we observed a significant association with pain ($p = 0.003$), paresthesia ($p = 0.018$), bleeding ($p = 0.007$), and cervical lymphadenopathy ($p = 0.005$). The presence of symptoms (mainly pain) was characteristically common in metastatic tumors from the prostate gland, intestine/colon, and lungs, while metastases from the kidney, liver, thyroid, and lungs were generally asymptomatic. Paresthesia, classically associated with malignant intraosseous lesions, has rarely been observed, especially in metastatic lesions from the lungs and kidneys. The same has occurred with bleeding, rare especially in metastatic lesions of the intestine/colon, liver, breast, lung, and prostate glands. Likewise, cervical lymphadenopathy was generally not frequent, but appeared reasonably in association with metastatic lesions from lung tumors (45.8%, 22 of 48). Dysphagia and tooth mobility were not statistically significant ($p > 0.05$). A complete list of the signs and symptoms of oral and maxillofacial metastatic lesions from each primary tumor is reported in Table S8.

Considering the associations between primary tumor and clinical characteristics of metastatic lesions, we noticed a significant association between lesion size ($p = 0.017$), evolution time ($p = 0.042$), and clinical appearance ($p < 0.001$). Oral and maxillofacial metastatic lesions of tumors from the lungs, kidneys, and thyroid presented with the largest dimensions at the time of diagnosis (greater than 2 cm). Most lesions had been noticed less than 3 months before, with no distinction among the primary tumors. Consistency did not vary, and most lesions were firm. For some characteristics, a trend toward uniformity was observed, regardless of the primary tumor. This is the case of volumetric increase as a form of presentation in almost all cases of soft tissue lesions. Among the clinical characteristics, surface, consistency, and color were not present a statistically significantly different ($p > 0.05$). The complete list of the clinical features of metastatic lesions from each primary tumor is shown in Table S9.

In the associations between primary tumors and imaging characteristics of oral and maxillofacial metastatic lesions, we noticed a significant association between radiolucency ($p = 0.027$), radiopacity ($p < 0.001$) poorly delimited ($p = 0.005$), and cortical bulging ($p = 0.019$). The radiographic image appeared to be independent of the primary tumor. The most common radiological feature was radiolucency (75.6%, 189 of 250), with only a few reports of radiopacity in metastatic lesions from the prostate gland and breast. The other imaging characteristics collected did not present a statistically significant difference ($p > 0.05$), as shown in Table S10.

Of the reported 189 cases of death, survival was better in cases of oral and maxillofacial lesions that were single metastatic focus (Figure 4). Multiple lesions and unproven single metastases had worse survival rates ($p = 0.002$), with more than half of the cases having a survival of less than 6 months, in comparison with metastases exclusively in the oral and maxillofacial region, in which almost half of the cases had a survival of >6 months.

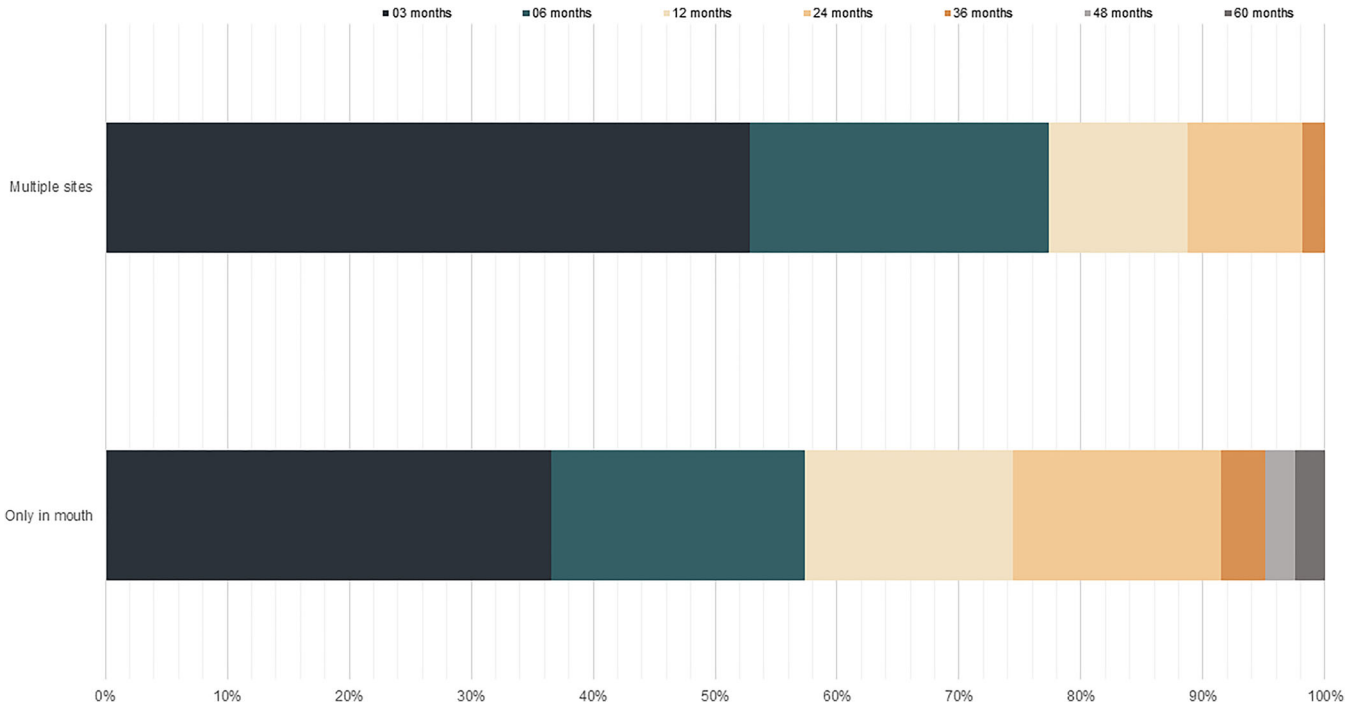

FIGURE 4 Survival rate (in months) according to the multiplicity of metastases [Color figure can be viewed at wileyonlinelibrary.com]

3.4 | Risk of bias among studies

In general, case reports and case series do not offer a high level of evidence. However, this is a rare entity, and we have used a large number of cases (381) extracted from 10 databases. We also applied adequate inclusion and exclusion criteria and analyzed the risk of bias and found that it was low in most of the studies. We hope that the errors have been averaged.

4 | DISCUSSION

The evidence suggests a strong association ($p < 0.05$) between certain factors and the diagnosis of metastases in the oral and maxillofacial region, including location of the primary tumor, sex of the patient, and some features of the metastatic lesions (location, symptomatology, paresthesia, bleeding, presence of cervical lymphadenopathy, size, clinical appearance, and radiolucency/radiopacity).

Based on "seed and soil" theory, we know that the metastatic process is not random.[14] Specific local conditions favor cell installation and tumor growth. This is known as metastatic tropism. In our sample, the lungs, kidney, liver, thyroid, and prostate glands were the most prevalent primary sites. The exact association between these organs and the maxillofacial region remains unknown. The literature indicates the involvement of the lungs, kidneys, liver, prostate glands, and breast, but not thyroid.[1,15,16] In this systematic review, this difference can be attributed to restricting the search to cases with occult primary tumors at the time of diagnosis, thus excluding the breasts and including the thyroid. Breast cancers tend to be significantly symptomatic, whereas thyroid cancers tend to be "asymptomatic."[17]

Most primary tumors from distant sites of the mouth, when they reach the oral and maxillofacial region, do so through the hematogenous route.[18] This almost always implies pulmonary involvement during the generalized spread, which includes the mouth and other multiple sites.[7] This may be one of the explanations for the fact that, when an oral metastatic lesion comes from the intestine/colon, uterus/endometrium, or breast, it is part of a disease that is already widely disseminated. In fact, cells of these primary sites tend to have pulmonary tropism.[18–22] On the other hand, thyroid cells seem to prefer the lymphatic pathway to reach the mouth.[23] Similarly, liver cells can use Batson's plexus for this purpose. In both cases, they would not pass through the lung, delaying the generalization of spread.[18] In addition, thyroid tumors tend to have a relatively indolent biological behavior; and oral lesions arising from liver tumors are quite bleeding, attracting attention.[23–26] These factors would increase the chances of oral metastatic lesions of both sites (thyroid and liver) being single foci of dissemination, at the time of diagnosis. Therefore, when we see oral metastatic lesions as an early or late sign of dissemination, we must consider that this is due not only to

chronology but also to biological characteristics of the primary site/tumor.

For metastatic lesions from the liver, we observed, in our sample of only positive cases, a marked predilection for males (91.3%), a result consistent with that of Wu et al.,[27] which was justified by behavioral and metabolic factors. In contrast, females seemed to be more likely to be affected by thyroid tumors (81.3%) than males, as also reported.[28] This high tendency toward females is associated with the high incidence of thyroid carcinoma in women.[23]

In the hard tissues, the mandible was predominantly the most affected site (91.0%), maybe because it contains more hematopoietic marrow.[29,30] Breasts, prostate glands, and thyroid have high tropism for bone tissues and, thus, are most likely to affect the jaws.[31] For the breasts and prostate glands, there seemed to be also an association with hormonal factors, which facilitated the interaction of malignant cells with osteoblasts and osteoclasts, both by mutual stimulation and imitation.[32] The growth factors present in the bone tissue may also be activated and contribute to the remodeling process induced by malignant cells.[32]

The most painful lesions were from the lungs, liver, intestine/colon, and prostate glands, probably because these tumors have a high affinity for bone tissues, and lytic bone metastases trigger pain. The acidic microenvironment produced by osteoclasts during the solubilization of hydroxyapatite may sensitize the nociceptors that innervate the medulla, mineralized portion, and periosteum.[33]

Although the lesions from the lungs were painful and the lesions from the kidneys were not, they were the least associated with paresthesia. Paresthesia, when present, is associated with perineural invasion. In the case of the maxillofacial region, the "numb chin syndrome" may arise because of infiltration/compression of the lower alveolar nerve sheath by tumor tissues.[34] The literature suggests that the tumors most prone to this behavior are lymphomas and carcinomas from the prostate glands, breasts, and head and neck,[34,35] which agrees with the results of our study, where the prostate glands were most affected.

Metastases from renal cell carcinomas were the least likely to cause paresthesia and pain. These primary tumors are unpredictable, with slow and silent initial growth. Frequently, its first manifestation arises at the point of or after dissemination,[36] secondary lesions seemed to mimic the corresponding primary lesions, showing that tumor biology overrides the local factors. The same happened with cervical lymphadenopathy, which was more frequently observed in association with oral lesions disseminated from lung primary tumors, known for lymphoid tropism.[37]

It is well recognized that malignant intraosseous lesions are more prone to bone reabsorption. Therefore, nearby teeth often have poor support. Thus, our attention was captured when we found only a few reports. Progressive osteolytic lesions are expected to cause tooth displacement (although malignant lesions can also keep them in position because of the speed at which they destroy bone). Similarly, malignant soft tissue lesions near the hard tissues may erode them; however, this has rarely been mentioned. It is important to note that swellings with normal surface and consistency are generally suggestive of benign lesions, but they can also represent oral and maxillofacial metastases.

There are divergences in clinical and radiographic presentations when comparing primary and secondary malignant oral lesions. It seems that not every principle that applies to primary oral malignancies (especially squamous cell carcinoma) also applies to metastatic oral malignancies. Sometimes, these do not fit the features of a suspicious condition. We must be alert and prepared to consider subtle clinical and radiographic presentations in order to establish an early diagnosis.

However, would early diagnosis influence survival rate? In the comparative analysis between oral lesions that were the sole focus of dissemination and those that were part of significantly advanced diseases, with multiple secondary sites, a positive association with survival was observed, which was greater in cases where the oral lesion was the only sign of dissemination ($p = 0.002$). This finding is critical, as it raises the dentist to a leading role in the diagnostic process since a better prognosis is dependent on oral findings. In addition to early diagnosis, time is saved with good tracking of the primary site. Hence, although positron emission tomography scans and immunohistochemical investigations are more useful, clinical, and imaging examinations may also be beneficial.

In our case reports and case series, due to failure to perform or even omission of reported metastatic foci tracking, oral lesions were confirmed (38.8%) and the suspected (61.1%) sole focus of dissemination, in contrast to the 20%–35% reported in the literature.[3] This difference may be explained by the restrictions applied to the search since one of the inclusion criteria was that the lesion still had an occult primary tumor, which presupposes a less widespread disease and increases the chance of the mouth being the single focus.

4.1 | Strengths and limitations

This comprehensive systematic review, which spanned almost 100 years of publication, is the first to provide evidence regarding the clinical and imaging characteristics of oral and maxillofacial metastases of occult primary tumors, including their association with the primary tumor location, patient data, and survival rate.

The search was broad, but language restrictions may have prevented some studies from being included.

Moreover, as already explained, case reports and case series offer an inherent publication bias. The variation in clinical and imaging descriptions and the frequent lack of information can affect the results. However, as the best evidence available for this subject was found in these descriptive observational studies, we circumvented the limitations by performing careful analysis of the results.

5 | CONCLUSION

Although oral and maxillofacial metastases are commonly observed in widespread disease, when it is the only focus of dissemination, early diagnosis can positively affect the prognosis. To aid clinicians in raising this diagnostic suspicion, some clinical and imaging features can contribute to and even relate to plausible primary tumors.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

Data are available in Supporting Information.

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