

Metastasis to the oral cavity: a systematic review

Metástase para a cavidade oral: uma revisão sistemática

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Abstract

The present study proposed to systematically review case reports of metastasis to the oral cavity and compile epidemiological, clinical, radiological, and histopathological features, intending to identify common aspects that may favor early diagnosis of such condition. Articles were found by searching the following databases: PubMed; EMBASE; LIVIVO; Web of Science; LILACS; Scopus and SciELO. The search was carried out in March 2021 by two independent researchers, with no restrictions of publication date or language. A total of 2379 studies were retrieved and 60 articles completely matched inclusion criteria, totalizing 65 cases from 19 countries. Metastasis to oral cavity cases were slightly frequent in males (1.7:1) in the sixth decade of life, manifesting in oral soft tissues (58%, 37/65), mostly originated from the lungs (20%, 13/65) as primary site. Adenocarcinoma was the most reported type of malignancy. In 51% of cases the oral metastatic lesion was the first sign of cancer and 60% of the patients already presented metastasis to other locations. In 23% of the reports, only benign lesions were considered as diagnostic hypothesis, due to a remarkable clinical resemblance to hyperplastic, reactive lesions and odontogenic infections. The survival probability at 6 months after oral metastasis diagnosis was 49%. Metastatic lesions to the oral cavity are often misdiagnosed as benign lesions; due to its severity and quick progression, they must be considered in the differential diagnosis process, conducted by a multidisciplinary healthcare team comprising an oral surgeon, especially for patients with history of cancer.

Keywords: Neoplasm metastasis; Mouth neoplasms; Systematic review.

Resumo

O presente estudo se propôs a revisar sistematicamente relatos de casos de metástase para cavidade oral e compilar características epidemiológicas, clínicas, radiológicas e histopatológicas, com o objetivo de identificar aspectos comuns que possam favorecer o diagnóstico precoce dessa condição. Os artigos foram encontrados por meio de busca nas seguintes bases de dados: PubMed; EMBASE; LIVIVO; Web of Science; LILACS; Scopus e SciELO. A busca foi realizada no mês de março de 2021 por dois pesquisadores independentes, sem restrições de data de publicação ou idioma. Um total de 2379 estudos foram recuperados e 60 artigos preencheram completamente os critérios de inclusão, totalizando 65 casos de 19 países. Os casos de metástase para a cavidade oral foram pouco frequentes no sexo masculino (1,7:1) na sexta década de vida, manifestando-se em tecidos moles orais (58%, 37/65), originando-se principalmente dos pulmões (20%, 13/65), como local primário. O adenocarcinoma foi o tipo de malignidade mais relatado. Em 51% dos casos a lesão metastática oral foi o primeiro sinal de câncer e 60% dos pacientes já

apresentavam metástase para outras localizações. Em 23% dos laudos, apenas lesões benignas foram consideradas como hipótese diagnóstica, devido à notável semelhança clínica com lesões hiperplásicas, reativas e infecções odontogênicas. A probabilidade de sobrevida em 6 meses após o diagnóstico de metástase oral foi de 49%. Lesões metastáticas para a cavidade oral são muitas vezes diagnosticadas erroneamente como lesões benignas; devido à sua gravidade e rápida evolução, devem ser considerados no processo de diagnóstico diferencial, conduzido por equipe multidisciplinar de saúde composta por cirurgião-dentista, principalmente para pacientes com história de câncer.

Palavras-chave: Metástase neoplásica; Neoplasias bucais; Revisão sistemática.

Resumen

El presente estudio se propuso revisar sistemáticamente reportes de casos de metástasis a la cavidad oral y recopilar características epidemiológicas, clínicas, radiológicas e histopatológicas, con la intención de identificar aspectos comunes que puedan favorecer el diagnóstico precoz de tal condición. Los artículos se encontraron buscando en las siguientes bases de datos: PubMed; EMBASE; LIVIVO; Web of Science; LILACS; Scopus y SciELO. La búsqueda fue realizada en marzo de 2021 por dos investigadores independientes, sin restricciones de fecha de publicación ni de idioma. Se recuperaron un total de 2379 estudios y 60 artículos cumplieron completamente con los criterios de inclusión, totalizando 65 casos de 19 países. Los casos de metástasis a la cavidad bucal fueron levemente frecuentes en el sexo masculino (1,7:1) en la sexta década de la vida, manifestándose en los tejidos blandos orales (58%, 37/65), en su mayoría originados en los pulmones (20%, 13/65) como sitio primario. El adenocarcinoma fue el tipo de malignidad más informado. En el 51% de los casos la lesión metastásica oral fue el primer signo de cáncer y el 60% de los pacientes ya presentaban metástasis en otras localizaciones. En el 23% de los reportes sólo se consideraron como hipótesis diagnósticas las lesiones benignas, debido a una notable similitud clínica con lesiones hiperplásicas, reactivas e infecciones odontogénicas. La probabilidad de supervivencia a los 6 meses del diagnóstico de metástasis bucales fue del 49%. Las lesiones metastásicas en la cavidad oral a menudo se diagnostican erróneamente como lesiones benignas; debido a su gravedad y rápida progresión, deben ser considerados en el proceso de diagnóstico diferencial, realizado por un equipo de salud multidisciplinario integrado por un cirujano bucal, especialmente en pacientes con antecedentes de cáncer.

Palabras clave: Metástasis de la neoplasia; Neoplasias de la boca; Revisión sistemática.

1. Introduction

Cancer is a leading public health burden worldwide, as it is the first or second cause of death before age 70 in 112 out of 183 countries, according to the World Health Organization (Sung et al., 2021). Although cancer mortality has declined over the past decades, only individuals diagnosed with localized or regional disease exhibited improvements in survival rates; in the meantime, patients diagnosed with metastatic lesions typically face terminal illness, and the prognosis is poor (Steeg, 2016).

Metastasis, by definition, is the dissemination of malignant cells from a primary tumor with later establishment of new colonies at distant sites (Lambert et al., 2017). The *invasion-metastasis cascade* is a complex multistep process that begins with the epithelial-mesenchymal transition of primary tumor cells, followed by the invasion of surrounding tissues. Those cells proceed to enter the bloodstream, either directly or through the lymphatic system, becoming circulating tumor cells (CTCs), able to travel both separately and in clusters. While being transported through the bloodstream, CTCs endure several adversities, such as immune attacks; however, due to specific interactions with other circulating cells, some of the CTCs can evade the defenses. Eventually, they are arrested by capillary beds and extravasate to distant sites. At that point, they may either be terminated by the tissue parenchyma, enter a state of dormancy as single disseminated tumor cells or small micrometastatic clusters, or start colonizing the area (Lambert et al., 2017; Steeg, 2016).

Several key aspects of the mentioned mechanisms remain unknown. Studies conducted to expand the understanding of the processes are limited, partially as a result of the broad diversity of cancer cell lines and their molecular profiles, leading to the difficulty to carry large-scale tests in experimental models or to reproduce *in vivo* complexity at *in vitro* experiments (Jin et al., 2020; Shibue & Weinberg, 2011). Furthermore, metastatic cells exhibit the competence to evade cytotoxic drug effects, representing a real challenge for the development of therapies. Accordingly, prevention and early detection still offer the best chance for a successful treatment (Bacac & Stamenkovic, 2008).

The oral cavity is well-established as an infrequent site for metastatic spread. The present study is proposed to systematically review case reports of metastasis to the oral cavity and compile epidemiological, clinical, imaging, and histopathological features in pursuance of identifying common aspects that may favor the early diagnosis of such condition.

2. Methodology

Study design

A systematic review was conducted intending to provide an overview of the available evidence in reliable databases. The study was carried out according to the PRISMA Statement for Reporting Systematic Reviews and registered at PROSPERO platform (CRD42021222914).

Search strategy

Articles were found by searching the following databases: PubMed; EMBASE; LIVIVO; Web of Science; LILACS; Scopus and SciELO.

The following keywords were defined using the Medical Subject Headings (MESH) terms from the National Library of Medicine Controlled Vocabulary Thesaurus: (“neoplasm metastases” OR “neoplasm metastasis” OR “metastases” OR “metastasis”) AND (“oral” OR “buccal” OR “jaw” OR “jaws” OR “mandible” OR “maxilla” OR “palate” OR “hard palate” OR “mouth” OR “oral cavity”) AND (“diagnostic”) AND (“immunohistochemistry” OR “immunohistochemical” OR “immunohistochemically”).

The search was carried out in June 2021 by two independent researchers. Results were not supplemented by hand search as it would mischaracterize the systematic review, possibly adding papers published in unreliable journals and, consequently, increasing risk of bias.

Inclusion/exclusion criteria

Published studies, with no restrictions of publication date or language, fulfilling the following criteria, were included: Case reports or case series assessing diagnosed metastatic tumors in humans manifesting in the oral cavity or salivary glands and originated from other sites different from the oral cavity.

Studies satisfying any of the following criteria were excluded: No clinical documentation available (clinical description, imaging assessment and histopathological evaluation); and primary site of malignancy not identified.

Data extraction

Data extracted from included reports comprehend location of primary site; time from diagnosis of primary site (if applicable); histopathological classification of the neoplasms; patient’s complaints; time since the patients first detected the oral manifestations; location of the metastasis; patients age and gender; clinical, radiological and immunohistochemical descriptions of the lesions; presence of metastasis to other sites; therapy of choice; and survival.

Risk of bias

Quality of Evidence was assessed applying the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports and Case Series (Moola et al., 2017).

Statistical analysis

Kaplan-Meyer Survival Curve was calculated for patients whose survival was reported, according to Glantz 2014 and Sullivan 2016.

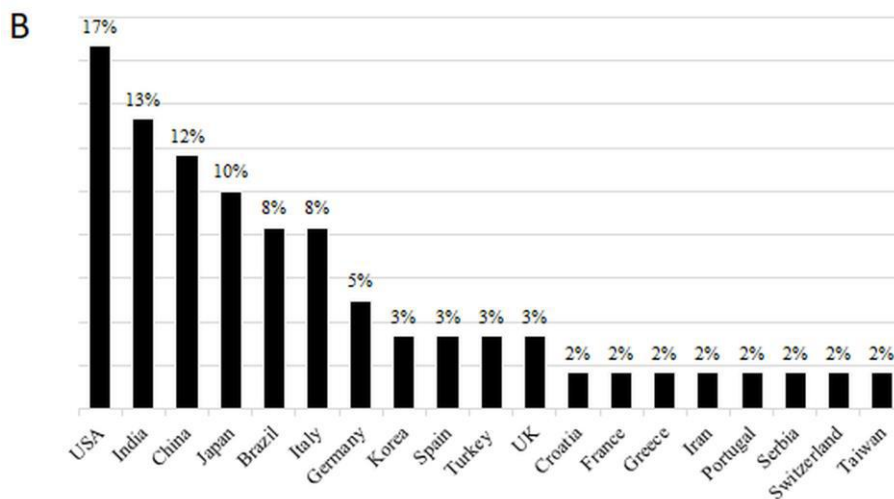
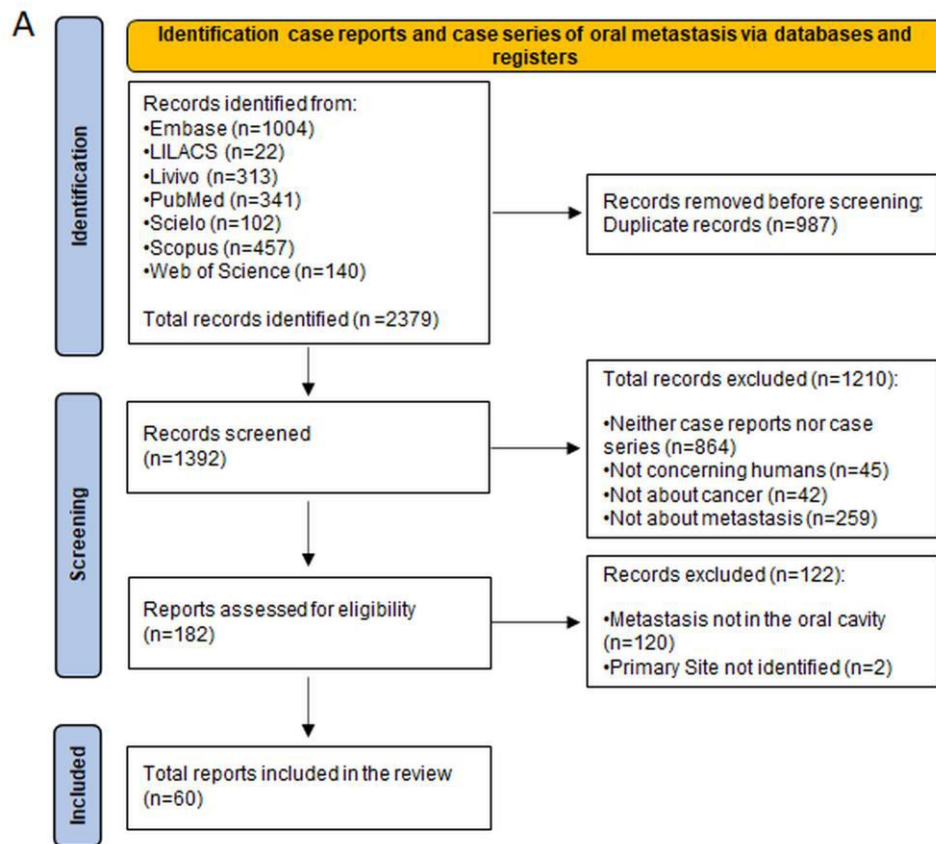
3. Results

Search, screening results and studies profile

It was possible to retrieve a total of 2379 studies from the initial search. A total of 60 articles (56 case reports and 4 case series) completely matched inclusion criteria, with a total of 65 cases. Complete analysis is displayed in the following PRISMA flow diagram (Figure 1A). They originated from 19 different countries (Figure 1B) and were published between 1996 and 2019.

Among the eligible cases, 63% (41/65) had at least one dental surgeon involved in the healthcare team, and 82% (53/65) were originated at or had contributions from Universities and Colleges.

Figure 1 - Research flow diagram and country origin of eligible studies. (A) Eligibility assessment of case reports based on PRISMA flow diagram. (B) Percentage of eligible case reports per country.



Source: Authors.

Risk of bias assessment of eligible articles

Risk of bias was assessed on all cases. 5% (3/60) of the studies exhibited high risk of bias – none of them described the patient’s demographic characteristics and clinical history, also ignoring follow-up description (Dominici et al., 2003; Huang et al., 2009; Lavanya et al., 2014). Other 46% (28/60) had moderate risk of bias, especially due to lack of description of treatment regimen implemented and post-intervention clinical condition of the patient, including survival report. Finally, 52% (29/60) showed low risk, presenting very few issues in the report, but also regarding inadequate follow-up information. The complete table with Risk of Bias assessment is available on Supplementary Table I.

Epidemiology and clinical aspects

Most of the patients were males (1.7:1), mostly at the sixth decade of life. The oral metastatic lesion was the first sign of cancer in 51% of all individuals. Additionally, after clinical evaluation, 60% of them already had metastasis to other locations.

The most common primary site (Figure 2A) of metastatic lesions in oral soft tissues were lungs; in the jaws, metastatic cancer was mostly reported as originated from lungs. The most frequent site of metastasis to the oral cavity (Figure 2B) were soft tissues (58%), especially manifesting in gingiva. Another 42% of metastasis to the oral cavity located in the jaws, with great prevalence for the mandible (89%).

67% of the patients reported the evolution of the oral lesion in up to three months, especially during the first month. The timeline of evolution of oral metastatic lesion based on information available in the articles are demonstrated on the Figure 2C.

Metastatic lesions developing in soft tissues were more likely to be associated with bleeding than lesions in the jaws. Concurrently, bone lesions were frequently associated with pain and paresthesia.

Most lesions (74%) were described as tumors, masses and swelling, mostly greater than 10mm in diameter. The color of the lesions was often reported as erythematous or normal. In soft tissues, the surface of the lesion was mostly described as irregular and/or ulcerated, and firm consistency. No alterations regarding lymph nodes were detected in most of the patients, and lesions were associated with a tooth extraction site in only 16,9% of the reports.

Differential diagnosis

23% of the reports only considered benign lesions among the diagnostic hypothesis; cited lesions included pyogenic granuloma (39,4%) and odontogenic infections (17,4%).

Imaging assessment

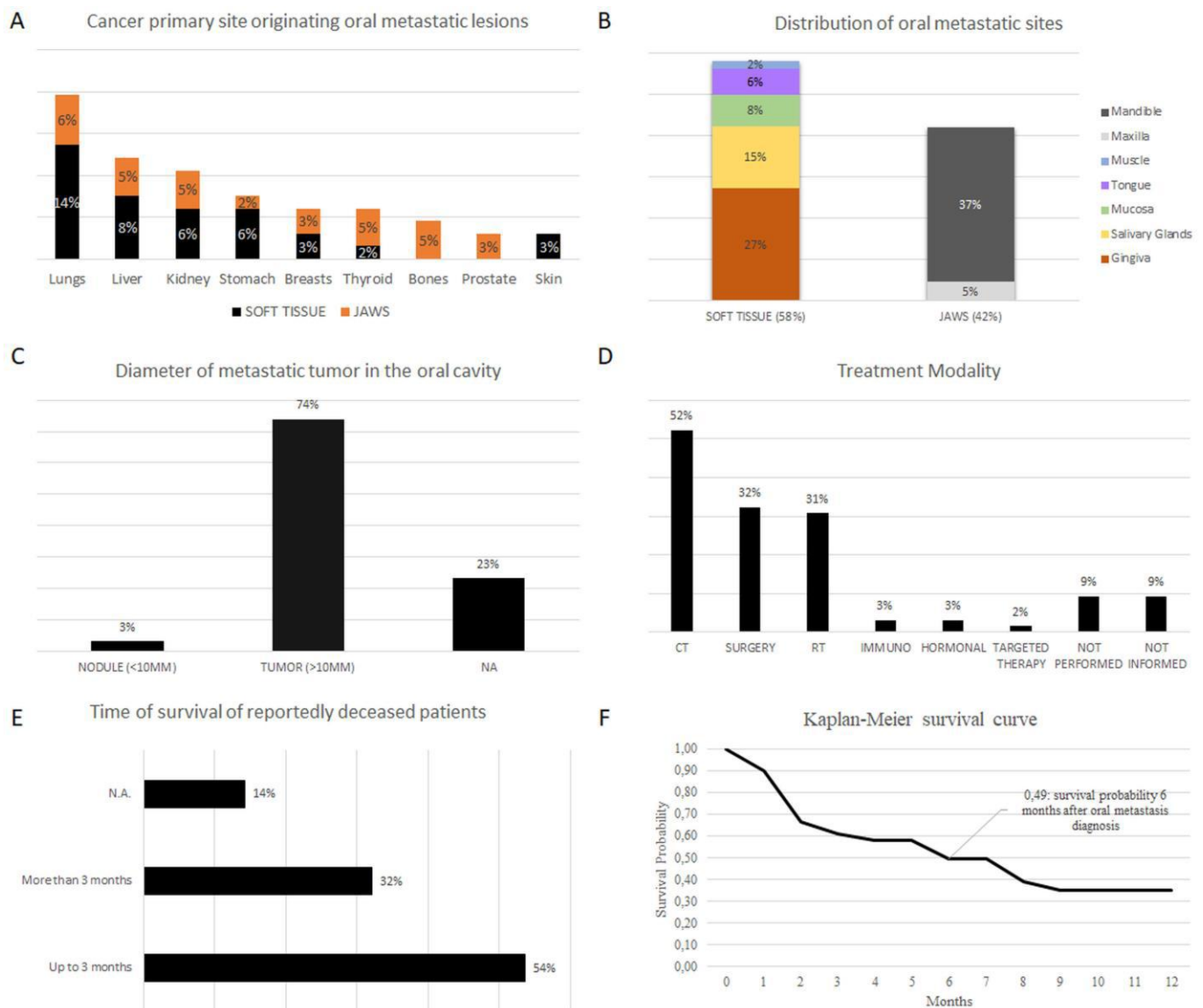
Positron emission tomography scan (PET-CT) alone or in combination with other imaging techniques was used in 53,9% of the cases. 75,4% of the cases presented at least one alteration of imaging findings related to the oral lesion. All imaging assessment per case report are presented on **Supplementary Table II**.

Treatment and survival

A combination of two or more modalities of treatment protocols were applied in 40% of all patients; 9% had no treatment performed. The distribution of cancer therapies is exhibited in Figure 2D.

Among the 39 reports with survival time described, 58,9% of the patients died in less than 03 months after the oral metastasis diagnosis. (Figure 2E) The Kaplan-Meier survival curve was calculated and the survival probability of 6 months after oral metastasis diagnosis was 49%, as exhibited in **figure 2F** and **supplementary table IV**.

Figure 2 - Percentage of reports according to primary tumor site (A), oral metastasis site (B), oral metastasis size (C), treatment modality (D), time of survival of reportedly deceased patients (E) and Kaplan-Meier Survival Curve (F).



Source: Authors.

4. Discussion

In recent literature, a few studies regarding metastatic lesions to the oral cavity have been published (Kirschnick et al., 2022). Our findings corroborate some of previous studies. Notwithstanding, our analysis suggest that the number of discoveries of primary tumors associated with the diagnosis of oral metastatic lesions might be higher than those previously reported in other papers. Additionally, our study had a higher number of patient follow-up reported (60%); and Kaplan-Meier estimates showed a mean survival time 2 months shorter than previous literature.

The present study is the only recent paper in the field that did not perform hand search or review of references lists, as it would mischaracterize the validity of the study and add risk of bias to the results (Vassar et al., 2016). Also, only confirmed metastasis diagnosis with clinical documentation and identification of primary site were included. Thus, it is ensured that the papers in our data collection were published by reliable sources and the cases conducted with the desirable criteria.

A few limitations were experienced during data extraction, mostly due to the absence of a standardized method to report clinical aspects of the lesions: 43% of the authors did not detail neither the size nor the color of the lesion observed and 37% of the cases did not describe the differential diagnosis. In spite of these limitations, data available on patients' follow-up was sufficient to calculate the Kaplan-Meier Survival Curve after oral metastasis diagnostic.

Despite classified as rare events, metastasis to the oral cavity must be included to the differential diagnosis process; this condition represents a challenging diagnosis, often mimicking benign, reactive lesions. Most of the reports did not include malignant lesions in the diagnostic hypothesis. As observed, 54% of the reportedly deceased patients died in less than 03 months after the oral metastasis diagnosis, validating the urgency for more research concerning such entities.

The oral surgeon must be aware of such occurrences and its clinical presentations in all oral tissues, conducting a detailed anamnesis to investigate the patient's medical history and perform a meticulous physical exam; then, after establishing diagnostic hypothesis, request the appropriate complimentary exams for each case, building a solid final diagnosis.

5. Conclusion

In such manner, oral assessment plays a pivotal role in those individuals' prognosis and life expectancy, as an early diagnosis may favor better treatment outcomes; thus, it is strongly advised for oncologists to work cooperatively to oral surgeons, integrated to the multidisciplinary healthcare team of oncology patients.

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