UNIVERSIDAD PERUANA CAYETANO HEREDIA

Facultad de ESTOMATOLOGÍA

METÁSTASIS ORAL Y MAXILOFACIAL: UNA REVISIÓN SISTEMÁTICA

METASTASIS TO THE ORAL AND MAXILLOFACIAL REGION: A SYSTEMATIC REVIEW

TESIS EN LA MODALIDAD DE ARTÍCULO CIENTÍFICO PARA OPTAR POR EL TÍTULO DE SEGUNDA ESPECIALIDAD PROFESIONAL EN MEDICINA Y PATOLOGÍA ESTOMATOLÓGICA

AUTORA

DAYANA MAMANI CABEZAS

ASESOR

CARLOS VLADIMIR ESPINOZA MONTES

LIMA-PERÚ

2024

JURADO

Presidente: Mg. C.D. Roberto Antonio Leon Manco.

Vocal: C.D. Raul Rafferty Herrera Mujica.

Secretario: C.D. Carola Coronado Li.

Fecha de Sustentación: 13 de marzo de 2024

Calificación: Aprobado con Honores.

ASESOR DE TESIS

ASESOR

Mg. C.D. Carlos Vladimir Espinoza Montes

Departamento Académico de Medicina y Cirugía Bucomaxilofacial

ORCID: 0000-0003-3860-4486.

DEDICATORIA

A Dios por darme la vida junto a mi familia que es la fuerza para seguir adelante ante cualquier adversidad.

A los mejores padres Hugo y Lucia símbolos de constante trabajo, honestidad y perseverancias, quienes me enseñaron siempre a respetar, luchar, vivir y a mis hermanos Ruddy y Melvi.

AGRADECIMIENTO

A mis profesores, por su paciencia, por compartir sus conocimientos de manera profesional e invaluable, por su dedicación perseverancia y tolerancia, los llevaré conmigo en mí transitar profesional.

Y a todas las personas que de una y otra forma me apoyaron en la realización de este proyecto.

FUENTES DE FINANCIAMIENTO

Los autores declaran no tener fuentes de financiamiento.

DECLARACIÓN DE CONFLICTOS DE INTERÉS

- Los autores declaran no tener conflictos de interés.

RESULTADO DEL INFORME DE SIMILITUD

METÁSTASIS ORAL Y MAXILOFACIAL: UNA REVISIÓN SISTEMÁTICA

INFORME DE ORIGINALIDAD

25%	20%	21%	7%
INDICE DE SIMILITUD	FUENTES DE INTERNET	PUBLICACIONES	TRABAJOS DEL ESTUDIANTE

FUENTES PRIMARIAS

1	ikee.lib.auth.gr Fuente de Internet	3%
2	bhslibrary.tamhsc.edu Fuente de Internet	3%
3	Francesca Spirito, Mariateresa Ambrosino, Federica Morrone, Roberto Duraccio, Lorenzo Lo Muzio, Antonio Della Valle. "Challenging Differential Diagnosis of Mandible Angle Metastasis from Breast Cancer", Case Reports in Dentistry, 2024 Publicación	2%
4	Alberto Jose Peraza Labrador, Luciano Hermios Matos Valdez, Nestor Ricardo Gonzalez Marin, Karem Annelise Rodriguez Ibazetta et al. "Gnathic Schwannomas: A Report of Two Cases and Systematic Review of the Literature", Head and Neck Pathology, 2023 Publicación	1%

TABLA DE CONTENIDOS

RESUMEN

Objetivo: La metástasis en la región oral y maxilofacial (MROMF) es un hallazgo inusual; representa entre el 1 y el 1,5% de todas las neoplasias malignas en la región maxilofacial. Se presenta una revisión sistemática para determinar las tendencias en la presentación, las características diagnósticas y la evolución de los pacientes.

Métodos: Se realizaron búsquedas en bases de datos de artículos que informaran sobre MROMF. Las variables fueron demografía, síntomas del paciente, localización del tumor, tamaño del tumor, histopatología, origen del tumor, estudios inmunohistoquímicos, seguimiento y supervivencia. **Resultados:** Se identificaron 696 casos; 391 varones y 305 mujeres. La raza más frecuente fue la blanca. El tumor primario más frecuente en las mujeres fue el de mama 31,1% (n = 95), y en los hombres el de pulmón 20,5% (n = 143). La localización más frecuente fue la mandíbula 44,9% (n = 313), seguida del tejido blando gingival 16,8% (n = 117). Un síntoma clínico frecuente fue el dolor con un 17,5% (n = 122). La presentación clínica más frecuente fue una masa o tumor 37,4% (n = 260). La edad media era de 58,8 años. El tiempo medio antes del diagnóstico fue de 10,3 meses, el seguimiento medio después del diagnóstico fue de 13,1 meses y la supervivencia media fue de 9,8 meses. **Conclusiones:** La MROMF muestra una fuerte predilección por la mandíbula posterior, siendo una masa o tumor la presentación clínica más frecuente. Con frecuencia son dolorosos, y muestran un mal pronóstico.

Palabras claves: Neoplasias gingivales; Inmunohistoquímica; Neoplasias mandibulares; Enfermedades bucales; Neoplasias bucales; Metástasis de neoplasias.

ABSTRACT

Objective: Metastasis to oral and maxillofacial region (MOMFR) is an unusual finding; representing between 1 and 1.5% of all malignancies in the maxillofacial region. A systematic review is presented to determine trends in presentation, diagnostic features, and patient outcome. **Methods:** Searches of databases were carried out for papers reporting MOMFR. The variables were demographics, patient symptoms, tumor location, tumor size, histopathology, origin of the tumor, immunohistochemical studies, follow-up and survival. **Results:** 696 cases were identified; 391 males, and 305 females. The most common race was white. The most common primary tumor for females was from breast 31.1% (n = 95), for males from lung 20.5% (n = 143). The most common location was the mandible 44.9% (n = 313), followed by gingival soft tissue 16.8% (n = 117). A frequent clinical symptom was pain with 17.5% (n = 122). The most common clinical presentation was a mass or tumor 37.4% (n = 260). The mean age was 58.8 years. The average time before diagnosis was 10.3 months, the mean follow-up after diagnosis was 13.1 months, and the average survival was 9.8 months. **Conclusion:** MOMFR shows a strong predilection for the posterior mandible, with a mass or tumor being the most common clinical presentation. They are frequently painful, and demonstrate a poor prognosis.

Keywords: Gingival neoplasms; Immunohistochemistry; Jaw neoplasms; Mouth diseases; Mouth neoplasms; Neoplasm metastasis.

ARTICLE IN PRESS
JID: JORMAS [m5G;December 23, 2021;18:41]
J Stomatol Oral Maxillofac Surg 000 (2021) 1–10
Available online at ScienceDirect www.sciencedirect.com
Elsevier Masson France EM|consulte www.em-consulte.com

Review

Metastasis to the oral and maxillofacial region. A systematic review.

Alberto Jose Peraza Labrador[a,*], Nestor Ricardo Gonzalez Marin[b], Luciano Hermios Matos Valdez[c], Katman Bear Toledo Sanchez[d], Wil Zabarburu[e], Karem Annelise Rodriguez Ibazetta[f], Alejandra Elvia Ruiz Garcia[g], Dayana Mamani Cabezas[h], Leonardo Romero[i], Aldo Manzur Conte[j], John M Wright[k]

[a] Oral surgeon and oral pathologist director centro de odontologia integral acarigua, Mailing address: av 5 de diciembre cc metropolitan local 6, Venezuela
[b] Professor of Department of Otolaryngologist Military Hospital Bogota, Colombia
[c] Oral Pathology director. Diagnocentro bucal, Mailing address: Las Colondrinas Mz. B lote 9, las Olivos, Lima, Peru
[d] Resident oral pathology program cayetano Heredia peru. Oral and maxillofacial pathology and medicine clinics, Mailing address: Av. El Olivar, 3879 San Martin de Porres, Lima, Peru
[e] Director of Dental healthcare clinic, Av principal lote 7. Micaela Bastidas 2, Lima, Peru
[f] Associated of Oral and maxillofacial pathology and medicine clinics department. Mailing address: Av. Pablo Carriquiry 705, San Isidro, Lima, Peru
[g] Director Oral and maxillofacial pathology and medicine clinics. Mailing address: Cooperativa Santa Polonia Mz. N lote 15, San Martin de Porres, Lima, Peru
[h] Director associated. Oral and maxillofacial pathology and medicine clinics. Mailing address: Av. Petrolera km 4 Zona Sud OTB Villa San Miguel, Cochabamba, Bolivia
[i] Director of the Oral prosthodontic department. Romerdent dental clinic, Bogotá, Colombia
[j] Director of endodontic department. Savanna Dental Group, 1135 Adelaide St. North suite 303, London, Ontario N5Y 5K7, Canada
[k] Department of Diagnostic Sciences, Texas A&M University College of Dentistry, 3302 Gaston Ave, Dallas, TX 75246, United States

ARTICLE INFO

Article History:
Received 26 November 2021
Accepted 15 December 2021
Available online xxx

Keywords:
Neoplasm metastasis
Gingival neoplasms
Jaw neoplasms
Mouth diseases
Mouth neoplasms
Immunohistochemistry

ABSTRACT

Objective: Metastasis to oral and maxillofacial region (MOMFR) is an unusual finding; representing between 1 and 1.5% of all malignancies in the maxillofacial region. A systematic review is presented to determine trends in presentation, diagnostic features, and patient outcome.
Methods: Searches of databases were carried out for papers reporting MOMFR. The variables were demographics, patient symptoms, tumor location, tumor size, histopathology, origin of the tumor, immunohistochemical studies, follow-up and survival.
Results: 696 cases were identified; 391 males, and 305 females. The most common race was white. The most common primary tumor for females was from breast 31.1% (n = 95), for males from lung 20.5% (n = 143). The most common location was the mandible 44.9% (n = 313), followed by gingival soft tissue 16.8% (n = 117). A frequent clinical symptom was pain with 17.5% (n = 122). The most common clinical presentation was a mass or tumor 37.4% (n = 260). The mean age was 58.8 years. The average time before diagnosis was 10.3 months, the mean follow-up after diagnosis was 13.1 months, and the average survival was 9.8 months.
Conclusion: MOMFR shows a strong predilection for the posterior mandible, with a mass or tumor being the most common clinical presentation. They are frequently painful, and demonstrate a poor prognosis.

1. Introduction

Metastasis to the oral and maxillofacial region (MOMFR) is reported to account for 1% to 1.5% of all oral and maxillofacial malignancies [1–2]. MOMFR has been the first clinical evidence of a primary tumor in almost 31% of the cases [3], emphasizing that a significant number of primary tumors are unknown at the time of oral presentation [4]. The presence of oral lesions is generally a manifestation of advanced-stage disease, with high probability of multiples metastases in other locations [5]; which leads to a poor prognosis [6], with as high as 90% mortality [7]. The diagnosis of a metastatic tumor requires objective documentation including that the primary tumor must be clinically and histologically verified, and the metastatic tumor must be of the same histological subtype as the primary tumor [8]. Immunohistochemistry can be invaluable, particularly when dealing with a metastatic lesion of unknown primary [9]. Additionally, molecular characterization is used increasingly to further verify the primary and metastatic lesion [10].

Oral metastases can present in the jawbones, oral mucosa, or in both osseous and soft tissue [3]. Metastasis to bone is considerably more common than to soft tissue, and in the jaws, the mandible and

* Corresponding author at: Oral surgeon and oral pathologist director centro de odontologia integral acarigua, Mailing address: av 5 de diciembre cc metropolitan local 6, Venezuela.
E-mail address: ajp216@yahoo.com (A.J.P. Labrador).

https://doi.org/10.1016/j.jormas.2021.12.009

specifically body and posterior area, are the preferred site, while in soft tissue, gingiva is most commonly affected [1–3]. Patients with oral metastases are frequently between the 4th and 7th decades [3–6]. The most common clinical presentation is progressive swelling, discomfort, pain, paresthesia, and bleeding, often with increased tooth mobility, or delayed healing of extraction sockets [11].

MOMFR of oral soft tissue can mimic reactive overgrowths and other malignancies, including squamous cell carcinoma as well as mesenchymal tumors, lymphomas and when in bone, primary bone malignancies [11–13]. Radiographic features are more characteristic for malignancy, but not specifically for metastatic disease; a lytic ill-defined radiolucent image is most commonly observed [14]. However, some metastases most notably prostate tumors; can illicit an osteoblastic response and be seen as a mixed or radiopaque image [1,14-15].

The origin of the primary differs by gender, the most common metastatic tumor in males is from the lung affecting the jawbones and soft tissues, followed by renal cell carcinomas. In females, breast is the most common primary source for oral metastases to both jawbones and soft tissues, followed by the female genital organs respectively [1].

The current systematic review incorporates specific information reported in English studies published on metastasis in the oral and maxillofacial area, with emphasis on demographic data, race, clinical and radiographic features regarding the most common area for the most common metastatic tumors by gender, histopathology, immunohistochemical confirmation, and outcome.

2. Materials and methods

A systematic review of the published literature on cases of MOMFR was performed. According to the guidelines set forth by the Institutional Review Board of Dental comprehensive center Acarigua-Venezuela this study met criteria for nonhuman subject research, and as a result board approval was not required.

2.1. Search strategy

A systematic review was performed according to the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [17]. Electronic search until January 2021 from PUBMED, EMBASE, SCOPUS and SCIENCE-DIRECT were made, papers after 1977 were selected, the MeSH terms were "oral metastasis" OR " oral cancer" OR "TMJ metastatic tumor" OR " Jaws lesion" OR "immunohistochemistry" AND "head and neck metastasis" a manual search was also made from referenced paper. Only human studies published in English were included, letters to the editor, *in vitro* studies, tonsil metastasis studies, and publications with insufficient data or incomplete information were excluded. Authors with manuscripts with important data were contacted to obtain an additional information. A protocol was enrolled and recorded with the International Prospective Register of Systematic Reviews (PROSPERO-241,398).

2.2. Selection criteria

Studies with individual data for the diagnosis and demographics of patients with MOMFR were included. Exclusion criteria included not English-language, animal, cadaveric, as well as no obtainable full-text studies, review studies and systematic review, also irrelevant studies, and studies with insufficient or aggregated data. Studies with metastasis located in the oral and maxillofacial area, limited to mouth soft tissue, jawbones, and parotid were included, outside these areas were excluded. Two investigators (A.P.L. and L.M.) independently performed the search review to determine that all appropriate articles were included in the analysis. Any disagreements were resolved through discussion with all authors. The strength of evidence of the included articles was assessed with the Johanna Briggs Institute (JBI) for Evidence-Based Medicine score analyzed by two reviewers and adjudicated score of 5.49 for case reports, and 5.65 for case series and retrospective studies, for a maximum of 8 points score. (Table 1) Concerning the missing data, for each of the variables studied with the Listwise deletion method [220], when some cases had missing values of a particular variable; only cases with all or almost all variables in the analyses were used.

2.3. Data extraction

Variables included author, publication year, study type, sample size, patient demographics, presenting symptoms, tumor characteristics, imaging, immunohistochemistry, follow-up time, recurrence, and outcome. Data analyses were performed with Microsoft Excel 2018 (Microsoft Corp, Redmond, Washington).

2.4. Data analysis

The analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 ©Copyright IBM (SPSS Inc., Chicago, IL, USA).

3. Results

Our initial PubMed, Web of Science, MEDLINE, Science-Direct and EMBASE search identified 933 articles (flowchart Fig. 1). A total of 190 articles were analyzed with a total of 696 patients. There were 17 retrospective studies [5,10,15,16,188–200], 8 case series [14,181–187] and 165 case reports [2,6,8,19-180] included in the analysis. (Table 1).

3.1. Demographics

Sex: Data were available for 696 patients, of whom 56.24% ($n = 391$) were males and 43.86% ($n = 305$) were females. (Table 2)

Age: Data for all patients were found, with an average age of 58.8 years, and a range from 6 months to 90 years. The mean age for females was 56.3 years and for males 60.9 years. (Table 2)

Race: Data were available for 386 patients, where white patients were the most common 27.7% ($n = 193$), followed by Asian patients with 15.4% ($n = 107$), there were 43.4% ($n = 302$) not reported cases about race.

Size: Mean size of the lesion was mentioned in 472 cases, in total measuring 2.3 cm; for females 2.33 cm and males 2.36 cm. (Table 2)

Evolution: The mean evolution time of the tumor before diagnosis was reported in 352 cases, with 10.35 months; the average for females was 14.76 months and for males 6.9 months. The mean follow up for patients was found for 410 cases with a total of 13.1 months, for females 16.2 months and males 10.8 months. The mean survival time was found in 317 cases, totaling 9.8 months after diagnosis, for females 10.58 months and for males 9.2 months. (Table 2)

Localization: The information was found for 463 cases for both genders, the jawbones were the most common site with 56.3%, and for soft tissues 38.3%. The mandible was the most common location with (313 cases) 44.9% followed by the maxillary bone ($n = 72$) 10.3%. For the mandible the posterior zone was the most common 30.7% ($n = 214$), for females 35.1% ($n = 107$) cases, and males 27.4% ($n = 107$). Interestingly 1% ($n = 7$) of cases metastasized to both jaws at the same time of the evaluation. Soft tissue metastasis for both genders represented a total of 38.3% ($n = 267$) cases, were the gums or gingiva was the most common with 16.8% ($n = 117$), for females 16.4% ($n = 50$), for males 17.1% ($n = 67$), followed by tongue with a total of 7.2% ($n = 50$). (Table 3)

Knowledge of primary tumor at time of MOMFR: The evidence of metastatic disease was found in all 696 cases, were the most common

Table 1
JBI critical appraisal quality score. *earliest paper selected.

Year	Author	Study	Evidence value	Year	Author	Study type	Evidence value
2010	Kumar G.[2]	Case report	5.5	2013	Ahmadnia.[111]	Case report	6
2020	Rocha B.A.[8]	Case report	5.5				
2006	Rivero.[9]	Case report	6.5	1986	Tideman.[112]	Case report	6
2009	Uchiyama.[19]	Case report	4.5	1997	Koyama.[113]	Case report	6
2017	Dodo.[20]	Case report	6	1990	Anderson RS.[114]	Case report	5
2012	Gonzalez-P.[21]	Case report	6.5	2006	Mojica-M.[115]	Case report	6
2020	Patel S.[22]	Case report	6	2010	Soda.[116]	Case report	6.5
2011	Seaerborn.[23]	Case report	6.5	2007	Otmani.[117]	Case report	6
2006	Park.[24]	Case report	6	2011	Parker.[118]	Case report	6
2002	Yoshii.[25]	Case report	7.5	2010	Rivera.[119]	Case report	6
1979	Kim BY.[26]	Case report	5	2005	Taguchi.[120]	Case report	6.5
1993	Kerpel.[27]	Case report	5.5	1998	Heler.[121]	Case report	6.5
2017	Erkilic.[28]	Case report	5	2012	Nikitakis.[122]	Case report	6.5
2016	Ali R.[29]	Case report	7.5	2005	Mason.[123]	Case report	6
2016	Selvi.[30]	Case report	6.5	2011	Arvin.[124]	Case report	4.5
2015	Jatti.[31]	Case report	6	2004	Hoshino.[125]	Case report	6
2014	Nakanishi.[32]	Case report	3.5	2010	Huang.[126]	Case report	4
2013	Umashankar.[33]	Case report	5.5	2004	Smolka.[127]	Case report	5
2016	Kim IK.[34]	Case report	6	1988	Nardi.[128]	Case report	4
2013	Menezes J.[35]	Case report	5.5	2008	Lutz.[129]	Case report	7
2011	Soares.[36]	Case report	6	1988	Webster.[130]	Case report	5
2012	Freudlsperger.[37]	Case report	4	2007	Dib LL.[131]	Case report	6
2012	Villa.[38]	Case report	7	1985	Spott.[132]	Case report	7
1990	Kadokura.[39]	Case report	6.5	2001	Ogitsu-T.[133]	Case report	4.5
2000	Makos.[40]	Case report	7	2011	Orhan.[134]	Case report	5
2013	Sikka.[41]	Case report	4.5	2013	Kim DW.[135]	Case report	6
2012	Schwab.[42]	Case report	5.5	2013	Vazifeh M.[136]	Case report	4
2011	Yoshitomi.[43]	Case report	7	2012	Bhadage.[137]	Case report	4
2012	Gantini.[44]	Case report	6.5	2010	Nishikawa.[138]	Case report	6
2000	Maestre R.[45]	Case report	5	2011	Tatlidil.[139]	Case report	5.5
2013	Nakano.[46]	Case report	7	1999	Bhattacharyya.[140]	Case report	6
1987	Tsiaros III.[47]	Case report	4	1999	Dusoretz.[141]	Case report	5
2008	WEITA.[48]	Case report	6.5	1998	Galea.[142]	Case report	6
2010	Zhang Y.[49]	Case report	6.5	1980	Wolujewicz.[143]	Case report	6
1984	Luttrawaga.[50]	Case report	6.5	2010	Tanaka.[144]	Case report	6.5
2013	Ray.[51]	Case report	3.5	2008	Ikman PR.[145]	Case report	6
2008	Azam.[52]	Case report	6.5	2004	Elkhoury.[146]	Case report	4.5
2013	Wang.[53]	Case report	6.5	1991	Davidson.[147]	Case report	6.5
2011	Tesada.[54]	Case report	6	2001	Tomikawa.[148]	Case report	6
2000	Maiorano.[55]	Case report	6.5	1989	Naylor GD.[149]	Case report	5.5
2003	Ramirez.[56]	Case report	7	2011	Singh T.[150]	Case report	6
1991	Marker.[57]	Case report	6.5	2008	Kawamura.[151]	Case report	7
2012	Goldaracena.[58]	Case report	6.5	2011	Hassan.[152]	Case report	6.5
2004	Pires.[59]	Case report	6	2013	Fernandez-B.[153]	Case report	6.5
2008	Li R.[60]	Case report	4.5	2004	Nishida.[154]	Case report	3.5
2008	Tanaka.[61]	Case report	6.5	2005	Colombo.[155]	Case report	5
2004	Perrotti.[62]	Case report	6.5	1995	Altintas A.[156]	Case report	5.5
2012	Compilato.[63]	Case report	6	2009	Munakata.[157]	Case report	7
2014	Alves M.G.[64]	Case report	6	1989	Kanazawa.[158]	Case report	6
2004	Shimoyama.[65]	Case report	6.5	2003	Alves FA.[159]	Case report	5
2004	Marioni.[66]	Case report	6.5	1985	Sherr.[160]	Case report	4
2013	Manamatti.[67]	Case report	6.5	1991	Taicher.[161]	Case report	5.5
1982	Delfino.[68]	Case report	6.5	1991	Wang C.[162]	Case report	6.5
2010	Soares AB.[69]	Case report	7	1980	Ord.[163]	Case report	5.5
1980	Jones DC.[70]	Case report	6	2016	Gutierrin.[164]	Case report	6.5
1986	Sokolosky.[71]	Case report	5.5	1977*	Ciola.[165]	Case report	5
1985	Tsiaros.[72]	Case report	3.5	2010	Katsetsikon.[166]	Case report	7
2006	GPSpinelli.[73]	Case report	6.5	2008	Bonicllo.[167]	Case report	5.5
2001	Gaurten.[74]	Case report	6.5	1995	Takinami I.[168]	Case report	6
2012	Lee HS.[75]	Case report	6.5	1988	Mudrinll.[169]	Case report	5.5
2006	Schlozzi.[76]	Case report	6.5	1993	Barrera-E.[170]	Case report	6.5
2012	Lee L.[77]	Case report	6	2020	Gholami.[171]	Case report	7
2007	Gurlen.[78]	Case report	6	2018	Salvador.[172]	Case report	6.5
2007	Sadat S.[79]	Case report	6	2014	Takahashi.[173]	Case report	7
2010	Chaturvedy.[80]	Case report	5	2013	Peacock.[174]	Case report	7
2013	Li M.[81]	Case report	6.5	2009	Kim SM.[175]	Case report	7
2011	Moser.[82]	Case report	5	2009	Davies.[176]	Case report	6.5
1980	Suzuki K.[83]	Case report	6.5	2000	Plattell.[177]	Case report	5
2006	Kesting.[84]	Case report	6.5	2001	Thomas G.[178]	Case report	6.5
2013	Sahoo NK.[85]	Case report	6.5	2009	Ismail SB.[179]	Case report	4.5
2010	Beyer.[86]	Case report	6.5	2011	Nassin.[180]	Case report	4
2008	Moreda A.[87]	Case report	5	2017	Iu SY.[181]	Case series	6
2005	Pereira.[88]	Case report	6.5	2016	Cai.[14]	Case series	6.5
2012	Dumpala.[89]	Case report	5.5	2011	Simon.[182]	Case series	6.5

(continued)

Table 1 (Continued)

Year	Author	Study	Evidence value	Year	Author	Study type	Evidence value
2006	Chen YK.[90]	Case report	5.5	2007	Suarez Mde.[183]	Case series	7
2010	Rochal L.[91]	Case report	5.5	2009	Salerno.[184]	Case series	7
1990	Geist.[92]	Case report	4.5	2010	Kruse AL.[185]	Case series	5
2008	McElderry.[93]	Case report	5	1984	Rusthoven.[186]	Case series	4.5
1984	El Dihemy.[94]	Case report	5	2020	Capodiferro.[187]	Case series	4.5
2013	Erickson.[95]	Case report	6.5	2019	Kaplan.[10]	Retrospective	5
2012	Kechagias.[96]	Case report	6.5	2017	Andabaki R.[188]	Retrospective	5.5
2005	Adelson.[97]	Case report	6.5	2016	Owosho.[189]	Retrospective	6
2013	Jain S.[98]	Case report	5	2013	Murillo.[190]	Retrospective	5.5
1985	Sweet.[99]	Case report	5	2003	Van der Waal.[9]	Retrospective	5.5
2011	Poulias.[100]	Case report	6.5	2013	McClure.[15]	Retrospective	5.5
2012	Chierelli.[101]	Case report	6.5	2006	Lim SY.[191]	Retrospective	6.5
1994	McCarty.[102]	Case report	4.5	2009	Shen.[16]	Retrospective	4.5
2001	Poulopoulos.[103]	Case report	6	2011	Jham.[192]	Retrospective	6
2008	Pozzi.[104]	Case report	7	2013	Marchino.[193]	Retrospective	5.5
2011	Murray.[105]	Case report	4.5	2011	Irani.[194]	Retrospective	4.5
2008	Watanabe.[106]	Case report	5	2010	Pires.[195]	Retrospective	6.5
2011	Orlandi I.[107]	Case report	6	1984	Patton.[196]	Retrospective	6.5
2010	Yokoe.[108]	Case report	5.5	2009	Jalil.[197]	Retrospective	4.5
2000	Bately.[109]	Case report	3.5	2008	Antunes.[198]	Retrospective	5.5
2012	Novak.[110]	Case report	7	2010	Friedrich.[199]	Retrospective	5.5
				2011	Muttagi.[200]	Retrospective	5.5
	Adjudicated score for case reports		5.49		Adjudicated scores for C. series and retrospectives		5.65

primary metastatic tumor depends on gender, for females the most common primary was from breast with 31.1% ($n = 95$) cases of 305 female cases, followed by lung 12.5% ($n = 35$), for males, from 391 cases the most common was from the lung with 26.9% ($n = 105$) cases, followed by kidney with 12.8% ($n = 50$) cases. And without knowledge of the primary metastatic disease was 5.7% ($n = 40$), for females 3.6% ($n = 11$) and for males 7.4% ($n = 29$) cases. (Table 3)

Regarding the time of diagnosis of metastasis, for the oral lesion occurring first was 18.4% ($n = 128$) cases, at the same time as the diagnosis of the primary tumor 9.1% ($n = 63$) and with previous diagnosis of a primary tumor 37.5% ($n = 261$). There were 35.1% ($n = 244$) not reported cases. (Table 2)

Origin of the tumor: The most common cell of origin of the tumor was epithelial with 605 cases 87.06%, (Table 2)

Clinical presentation and symptom: The most common clinical presentation was mass/ tumor/swelling with a total of 37.4% ($n = 260$), 33.4% ($n = 102$) for females, 40.4% ($n = 158$) for males, and the principal clinical symptom was pain ($n = 122$) 17.5%, followed by discomfort ($n = 37$) 5.3% and numb chin syndrome with ($n = 32$) 4.6%. (Table 2)

4. Discussion

Metastatic disease to the oral and maxillofacial region occurs infrequently. It can involve both hard and soft tissues, and it is characterized by a poor prognosis. The present systematic review analyzed trends, and demographics, with emphasis on tumor localization, and radiographic features correlated with the most common metastatic tumors by gender. We used data from 1977 to 2021, according with the inclusion criteria. We chose those dates because immunohistochemistry and CBCTs were not available before 1977 and many of the older cases are poorly described and did not have the benefit of immunohistochemistry.

For MOMFR in our study the mean age of patients was 58.8 years (range: 6 months to 90 years), and this compares favorably with studies by Kirschnick et al. [3], where the mean age was 58.29, by Hirshberg et al., 49.1years [1], and Kaplan 67.7 years [10]. The most affected age-group found was 49 to 66 years, followed by patients over 66 years, between the 6th and 7th decade of life. This compares similarly with the reported cases by Hirshberg A, et al. in 1993 [11]. Concerning young patients, this study found 21 cases, with a range from 6 months to 17 years [5,10,16,117,118, 120,140,159,162,181,189,194,196,198,200]. These patients were more likely to have metastatics arcomas with a better survival time after 5 to 10 years, compared with adults ($p \leq 00,1$). An interesting feature was the race, where white patients were the most commonly affected, with 193 reported cases [8,21,23,36][38,42,36,45], 48,52,54,56,58,59,62–65,68,71,7376,78,82_84,86,92,93,96,97,99,100, 103,107,110,112_117,119,126,129,131_134,138,140,142_144,147_ 149,153,156,162_165,167_171,183_190,196], followed by Asian patients with 107 reported cases [20,25,39,43,46,47,49], 61,108,125,135,158,170,175,190,191,197]. (Table 1) These results were similar to a large study from the Surveillance, Epidemiology, and End Results (SEER) database from 2004 to 2010 to assess stage of cancer at diagnosis, and overall survival, in patients with cancer from different racial/ethnic groups, were white patients were the most common in all types of malignant tumors [201]. However, clearly publication bias has a significant effect on the race of the patients reported and may not reflect true incidence of metastasis by race, and yet the references are from all over the world. In our study there were 43.4% ($n = 302$) cases where race was not reported, although we tried unsuccessfully to contact the authors to determine the race of their patients.

Regarding symptomatology, the principal clinical symptom was pain ($n = 122$) 17.5%, different from that reported by Kirschnick LB, et al., with 60.56% in 109 of 180 cases reported with symptoms, but their total cases were 345 [3], so for that quantity the percentage would be 31%, although still higher than our results. One of the reasons is that they did not mention other symptoms, which in our review we reported discomfort (5.3%) numb chin syndrome (4.3%) paresthesia (4%) bone pressure (3%) and if we include this symptomatic data as "pain" our 17.5% would increase to 34% of the 696 total cases. In this regard, it is important to mention that almost 66% of the patients did not have symptoms at the beginning of metastasis. Pain and metastasis are controlled by the endothelin axis, a pathway comprised of the endothelin A and B receptors (ETAR and ETBR). The ETAR activation and silenced ETBR expression result in increased pain [216]. Tumor cells and associated inflammatory (immune) cells stimulates several chemical mediators, including prostaglandins (PGE2), nerve growth factor (NGF), endothelins (ET-1) and bradykinin (BK), which can directly activate or sensitize nociceptors, promoting pain [217].

Concerning clinical signs, a mass, tumor or swelling was the most common with ($n = 260$) cases, which in our cases this sign showed a male female ratio of 2:1. Relating to the evolution time before diagnosis for MOMFR, our study found a total of 10.3 months with 352

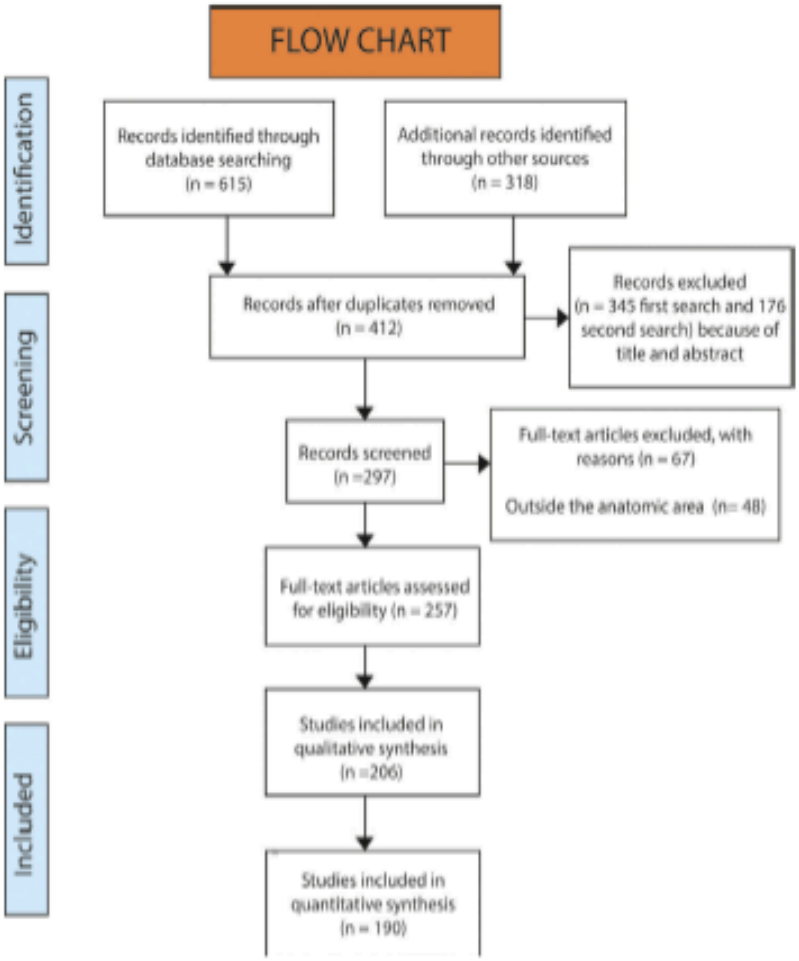

Fig. 1. Flowchart.

reported cases, but this varied depending on the primary, with a range from 1 month to 316 months, with emphasis that the development of symptoms is a function of time [22,37,46,47]98–136–142,188–200]. All these findings, are in concordance with advance disease. In addition the survival time for both genders was 9.8 months, for females 10.5 months ($n = 136$), and for males 9.2 months ($n = 181$), but slightly different from Hirshberg et al., who found a 7 months average[1], and 8 months for Kirschnick et al, and Vasilyeva et al. [3,202].

In relation to radiographic features, this study evaluated the nature of radiographic presentation, correlated with gender and the type of tumor for the most common primary malignancies, perhaps allowing for a more accurate presumptive diagnosis. Most of the previous retrospective studies combined primary tumors types in their radiographic analysis, without using the same amount of data weight for that purpose. Other important issues which can affect registration is that radiographic analyses of the jaws are not standardized; and the jaws are rarely examined during autopsy [37]. Relating to location, the posterior mandible was the most common site for both genders 41% for females and 30.7% for males, although for condylar lesions, the ratio was 2:1 for males compared with females. One hypothesis for the preference for the mandibular bone could be because it contains more red bone marrow (mainly in the posterior area ascending ramus and angle), than the maxilla which contains predominantly fatty marrow [205]. In addition, according to Fornetti et al, a process mediated by bone morphogenetic proteins (BMPs), endothelin-1, Wnt family ligands, and platelet-derived growth factor (PDGF) which are osteoblast stimulating factors, promote osteoblastic metastasis [206]. Moreover, a disturbance of the homeostatic RANK-RANKL, where metastatic prostate carcinomas can secrete high amounts of the RANKL inhibitor osteoprotegerin, decreasing osteoclastic activity [218]. On the other hand factors like insulin-like growth factor (IGF) and transforming growth factor-β (TGF-β) stimulate the induction of osteoclast promoting factors [206], and the osteolytic response of cancer cells triggers proteases that activates RANKL initiating a higher osteoclasts response [219] Thus, metastatic bone lesions produce a variability of radiographic images. As an important feature, most MOMFR are suspected on periapical or panoramic images, and these patients are then referred, where additional imaging like CT-scan, adds value of seeing the extent of the lesion in all dimensions. And for unknown primary, a PET scan can aid in revealing the primary.

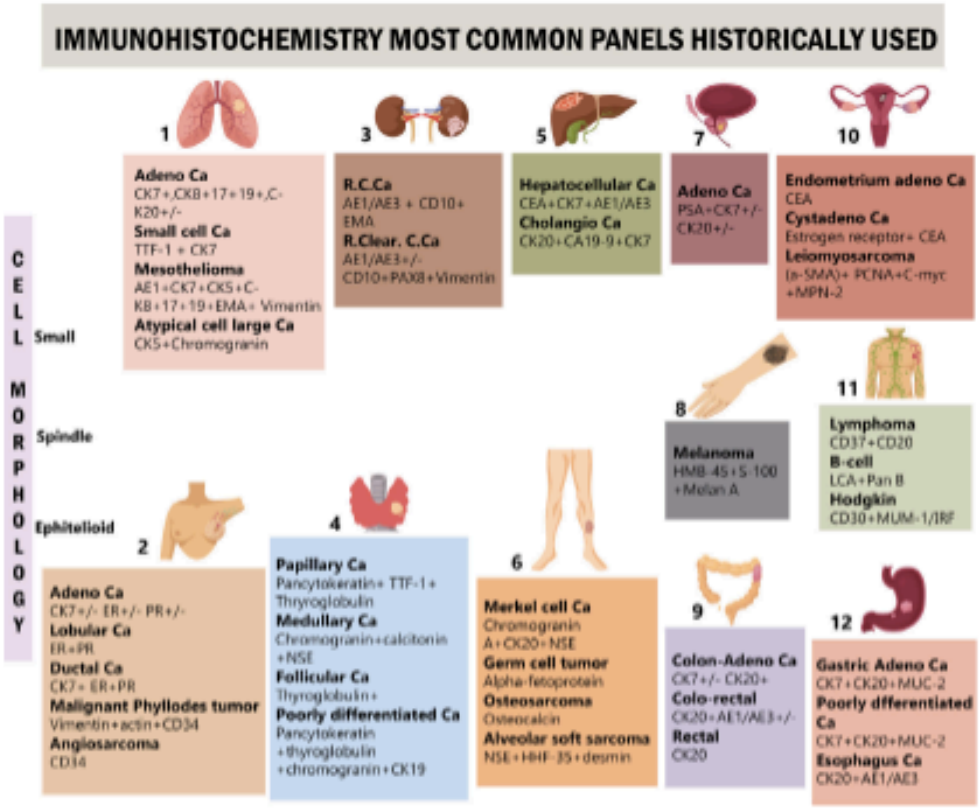

Fig. 2. Historical immunohistochemistry most used. 1 Lung, 2 Breast, 3 Kidney, 4 Thyroid, 5 Liver, 6 Lower extremity tumors, 7 Prostate, 8 Melanoma of skin, 9 Colo-rectal tumors, 10 Uterus tumors, 11 lymphomas, 12 Gastric. Immunohistochemistry positivity + 100% +/- 50 to 60%. Immunonomenclature, (CK) Cytokeratin, (TTF-1) thyroid transcription factor, (AE1/AE3) Monoclonal Mouse Anti-Human Cytokeratin, (EMA) Epithelial membrane antigen, (ER) Estrogen, (PR) Progesterone, (PAX) Paired-box gene, (NSE) Neuron-specific enolase, (HHF-35) monoclonal muscle Actin antibody, (PSA) prostate-specific antigen, (CEA) Cardioembryonic antigen, (LCA) leukocyte common antigen, (MUM-1/IRF) multiple myeloma oncogene 1/r, lymphocyte-specific interferon regulatory factor 1/r (MUC-2) Apomucines.

We believe we are the first systematic study evaluating the radiographic feature regarding the primary tumor in an extensive pool of cases ($n = 154$), where besides the anatomic area, the most common correlated image type was from lung metastasis, with 54 radiographic cases, showing in the body of the mandible an osteolytic image (OI) with ($n = 5$) cases [14,184,191,193], and ill-defined radiolucent image (IDRI) ($n = 10$) [15,24,27,126,125,190,195], for the posterior mandibular zone, OI was ($n = 10$) [15,16,184,188,190,191] and IDRI ($n = 10$) [24,125,181,182,185,190,193,197], leading to a different result from Lim SY et al. [191], Barr CE, et al. [207], and Staalsen NH et al. [208], where lung carcinomas commonly metastasize to the soft tissue. Also we found a combination of soft tissue and bone involvement for 19 cases and it is often impossible to determine whether these are primarily soft tissue or bone lesions. For breast metastasis we found ($n = 29$) cases for the jaw mostly in the posterior area, were OI was ($n = 10$) [15,96,100,181,188], and IDRI ($n = 7$) [21,99,130,133,181,197]. Regarding the kidney, there were ($n = 18$) cases, for the body of the mandible OI ($n = 4$) [28,109,195], and for the posterior area IDRI ($n = 5$) [28,111,163,187,188], very similar with the result by Pires et al., where it was found that oral metastatic renal clear cell carcinomas CCRCCs affect more bone than gingiva [195]. So it appears that bone involvement precedes soft tissue involvement in some metastatic tumors of the jaw bones [200]. For radiopaque image (RPI) this study found ($n = 15$) cases, for the most common primary tumors in table 4.

For lung there were 5 RPI cases in the mandible, 2 anterior, 1 in the body, and 2 posterior [16,38,195], for breast 4 RPI cases, in the anterior and body of the mandible [95,98,134]. For kidney 3 RPI mandible cases, anterior, posterior and condyle, [49,111,195], thyroid 4 RPI cases [14,138,198], for liver 1 posterior case [16], prostate 2 cases one for posterior and one for condyle [143,173], It is important to mention that no radiopaque image was found in the maxillary bone. Hirshberg found 413 radiographic cases, higher than our study ($n = 392$) were approximately 5% of his cases did not show any pathological changes, and 17% showed osteoblastic lesions, as either pure or mixed radiopacity [1]. Our study found more than 94% of metastatic cases to bone produced osteolysis and for radiopaque images a 4%, being exclusively for mandibular bone. On the other hand, this study found a considerable difference between bone and soft tissue metastasis. We found that bone tissue was involved with a 56.3% ($n = 392$) reported cases, and 267 were for soft tissues, and 37 cases not report data, similar to what Barnes reported, which found

Table 2
Demographic, race, age, (CI) confidence interval, (SD) standard deviation, (E-S) extraction socket, (R) range.

	Female	Male	Total	
Sample size	43.8% (n = 305)	56.2% (n = 391)	100% (n = 696)	
Age (years)	Mean ± SD (Min/Max)	Mean ± SD (Min/Max)	Mean ± SD	[CI95%]
	56.32 ± 17.58 (0.0/87)	60.9 ± 15.1 (0.6/90)	58.8 ± 16.4	[57.6 - 60]
Race				
White	28.5% (n = 87)	27.1% (n = 106)	27.7% (n = 193)	[24.4 - 31]
Asian white	16.7% (n = 51)	14.3% (n = 56)	15.4% (n = 107)	[12.7 - 18.1]
Brown	13.4% (n = 41)	10.5% (n = 41)	11.8% (n = 82)	[9.4 - 14.2]
Latin-Hispanic	0.7% (n = 2)	1.5% (n = 6)	0.6% (n = 4)	[0 - 1.2]
No report race	40% (n = 122)	46% (n = 180)	43.4% (n = 302)	NA
Clinical sign / symptomatology				
Mass/tumor/swelling	33.4% (n = 102)	40.4% (n = 158)	37.4% (n = 260)	[33.8 - 41]
Pain	21% (n = 64)	14.8% (n = 58)	17.5% (n = 122)	[14.7 - 20.3]
Bleeding	4.9% (n = 15)	5.6% (n = 22)	5.3% (n = 37)	[3.6 - 7]
Discomfort	5.2% (n = 16)	5.6% (n = 22)	5.5% (n = 38)	[3.8 - 7.2]
Numb chin syndrome	4.3% (n = 13)	4.9% (n = 19)	4.6% (n = 32)	[3 - 6.2]
Ulcer	3.9% (n = 12)	4.3% (n = 17)	4.2% (n = 29)	[2.7 - 5.7]
Paresthesia	4.3% (n = 13)	3.8% (n = 15)	4% (n = 28)	[2.5 - 5.5]
Pain less lesion	2.3% (n = 7)	4.6% (n = 18)	3.6% (n = 25)	[2.2 - 5]
Non healing E-S	2.3% (n = 7)	3.6% (n = 14)	3% (n = 21)	[1.7- 4.3]
Bone pressure	3% (n = 9)	3.1% (n = 12)	3% (n = 21)	[1.7- 4.3]
Dental mobility	2.3% (n = 7)	1.8% (n = 7)	2% (n = 14)	[1 - 3]
Pigmented lesion	1.3% (n = 4)	1% (n = 4)	1.1% (n = 8)	[0.3 - 1.9]
No report	11.8% (n = 36)	6.4% (n = 25)	8.7% (n = 61)	NA
Diagnosis of the primary tumor				
At first (oral)	16.7% (n = 51)	19.7% (n = 77)	18.4% (n = 128)	[15.5 - 21.3]
At the same time	9.2% (n = 28)	9% (n = 35)	9.1% (n = 63)	[7 – 11.2]
Previous cancer diagnosis	38.4% (n = 117)	36.8% (n = 144)	37.5% (n = 261)	[33.9 - 41.1]
No Report	35.7% (n = 109)	34.5% (n = 135)	35.1% (n = 244)	NA
Cell origin of the tumor				
Epithelial	87.5% (n = 267)	86.7% (n = 339)	87% (n = 606)	[84.5 - 89.5]
Mesenchymal	9.5% (n = 29)	10.2% (n = 40)	9.9% (n = 69)	[7.7 - 12.1]
From cell blood	3% (n = 9)	3.1% (n = 12)	3% (n = 21)	[1.7 - 4.3]
	Mean ± SD (n) (Min - Max)	Mean ± SD (n) (Min - Max)	Mean ± SD (n) (Min - Max)	[CI95%]
Size of the lesion (cm)	2.3 ± 0.9 (n = 198) (0.5 – 7)	2.3 ± 0.9 (n = 274) (0.3 –6)	2.3 ± 0.9 (n = 472) (0.3– 7)	[2.2 - 2.4]
Evolution time before diagnosis (months)	14.7 ± 43.3 (n = 154) 8 (1– 316)	6.9 ± 11.9 (n = 198) (1– 104)	10.3 ± 30.2 (n = 352) (1 –316)	[7.1 - 13.5]
Follow-up after diagnosis (months)	16.2 ± 28.4 (n = 175) 8 (1– 233)	10.8 ± 13.5 (n = 235) (1– 88)	13.1 ± 21.3 (n = 410) (1 –233)	[11 -15.2]
Survival time (months)	10.5 ± 16.9 (n = 136) 8 (1– 142)	9.2 ± 11.2 (n = 181) (1– 65)	9.8 ± 13.9 (n = 317) (1 –142)	[8.3 - 11.3]

metastatic lesions involving more commonly the jaws (65–75%) than the oral soft tissues (25–35%) [12].

Relating to soft tissue metastasis, our study found a total of 38.3% (n = 267) cases, where the gums or gingiva was the most common site with a 43.85%, followed by tongue 18.68% relatively similar with Hirshberg A, et al, with 219 cases, where gingiva was the most common affected site 54% (n = 118) cases, followed by the tongue 22.5% (n = 49) [1], and higher than Kirschnick LB et al., for 140 total cases, being the gingiva 23.25% (n = 80), the most common, followed by tongue with 6.68% (n = 23) [3]. This may be due in part that metastatic tumor cells may be attracted by the presence of teeth with chronically inflamed gingiva and rich capillary networks [209]. Furthermore, according to Chambers et al., there is a degree of inflammation in the gingival tissues, and the capillary vessels in chronically inflamed gingiva constantly proliferate and eventually progress with fragmentation of basement membranes with the immature capillaries facilitating exit for tumor cells [210]. The microvasculature environment of the target organ facilitates the growth of metastatic cells, allowing them to invade, where angiogenesis, and nutrients are essentials for cell proliferation [213]. According to Allon et al., in 138 of the 156 cases of soft tissue metastasis (88.5%), occurred in patients with teeth and in 18 (11.5%) in patients without teeth [214]. So the presence of teeth was found to be significantly related to the progress of gingival metastases.

Concerning the origin of the primary metastatic tumor in terms of gender, this study found for female patients, the breast was the most common, similar results to Hirshberg et al. [1], our results for the second MOMFR for females was the kidney, different from Hirshberg et al., where genital organ was the second most common [1]. Siegel et al., 2019 reported thyroid was the most common for females, and lung for males [215]. However Lim et al., reported prostate was the most common metastatic tumor [191], this may result because of the geographic area, and the number of patients of these studies. It is important to mention that this study found 5.7% (n = 40) cases of unknown primary tumor, different results from the 23% for an undiscovered malignancy at a distant site by Hirshberg 2008 [1].

Previous studies have shown almost 20 to 33% of oral metastases have been found to be the first sign of the metastatic process [1,4,10,13,200,203,204,211,212]. In contrast, surprisingly our study found that the metastatic lesion was the first sign of MOMFR in 18.4% (n = 128) [5,8,10,15,16,18,22,26,51,69,72,81,111–113,117,118, 156,158,170–173,182,184,185,188–190,191–193,196,197,199,200]. Interestingly in 9.1% (n = 63) the diagnosis of MOMFR was made at the same time [5,10,14,15,19,21,23,29,34,38,41,43,54,85,105,106, 108,114,129,137,139,142,143,148,149,152,163,166–169,187–189, 190,191,193,200], remarkably this is not mentioned in earlier studies. If we include this data we would reach a 27.5% of MOMFR. In this regard with 37.5% (n = 261) cases, the majority of patients had a

Table 3
Relation between sex, metastatic site and primary tumor origin.* Confidence interval calculated by sample size of each gender. (N.A) Not apply. (M.T) mesenchymal tumor.

	Female	Male	Total CI	
Area of the lesion	(n = 305)	(n = 391)	100% (n = 696)	[CI95%]
Soft Tissue	34.4% (n = 105)	41.43% (n = 162)	38.3% (n = 267)	[34.7 – 41.9]
Gums or gingiva	16.4% (n = 50)	17.1% (n = 67)	16.8% (n = 117)	[14 – 19.6]
Tongue	5.6% (n = 17)	8.4% (n = 33)	7.2% (n = 50)	[5.3 – 9.1]
Buccal mucosa	3.0% (n = 9)	3.6% (n = 14)	3.3% (n = 23)	[2 – 4.6]
Palate	1.6% (n = 5)	3.8% (n = 15)	2.9% (n = 20)	[1.7 – 4.1]
Lip	2.3% (n = 7)	4.1% (n = 16)	3.3% (n = 23)	[2 – 4.6]
Floor of the mouth	1.3% (n = 4)	1.5% (n = 6)	1.4% (n = 10)	[0.5 – 2.3]
Parotid	1% (n = 3)	1.3% (n = 5)	1.1% (n = 8)	[0.3 – 1.9]
Cheek	1.6% (n = 5)	1.3% (n = 5)	1.4% (n = 10)	[0.5 – 2.3]
Submandibular area	1.6% (n = 5)	0.3% (n = 1)	0.9% (n = 6)	[0.2 – 1.6]
Bone	60.7% (n = 185)	52.9% (n = 207)	56.3% (n = 392)	[52.6 – 60]
Mandible				
Anterior	10.8% (n = 33)	8.2% (n = 32)	9.3% (n = 65)	[7.1 – 11.5]
Posterior				
Ramus				
Angle				
	35.1% (n = 107)	27.4% (n = 107)	30.7% (n = 214)	[27.3 – 34.1]
	3.9% (n = 12)	4.9% (n = 19)	4.5% (n = 31)	[3 – 6]
	–	0.8% (n = 3)	0.4% (n = 3)	[−0.1 – 0.9]
Maxilla				
Anterior	6.2% (n = 19)	5.1% (n = 20)	5.6% (n = 39)	[3.9 – 7.3]
Posterior				
Both jaws				
	3.9% (n = 12)	5.4% (n = 21)	4.7% (n = 33)	[3.1 – 6.3]
	0.7% (n = 2)	1.3% (n = 5)	1% (n = 7)	[0.3 – 1.7]
No Report	4.9% (n = 15)	5.6% (n = 22)	5.3% (n = 37)	NA
Primary tumor origin				
Lung	12.5% (n = 38)	26.9% (n = 105)	20.5% (n = 143)	[17.5 – 23.5]
Breast	31.1% (n = 95)	1% (n = 4)	14.2% (n = 99)	[11.6 – 16.8]
Kidney	12.1% (n = 37)	12.8% (n = 50)	12.5% (n = 87)	[10 – 15]
Thyroid	9.8% (n = 30)	1.5% (n = 6)	5.2% (n = 36)	[3.6 – 6.8]
Liver	2.6% (n = 8)	6.4% (n = 25)	4.7% (n = 33)	[3.1 – 6.3]
Lower extremity M.T	3.3% (n = 10)	4.9% (n = 19)	4.2% (n = 29)	[2.7 – 5.7]
Prostate	NA	8.1% (n = 32)	4.6% (n = 32)	[5.5 –10.9]*
Melanoma	3.6% (n = 11)	5.4% (n = 21)	4.6% (n = 32)	[3 – 6.2]
Colon-rectal	2.3% (n = 7)	2.8% (n = 11)	3.6% (n = 25)	[2.2 – 5.0]
Uterus	6.6% (n = 20)	NA	2.9% (n = 20)	[1.8 – 0.4]
Lymphoma	2.6% (n = 8)	3.1% (n = 12)	2.9% (n = 20)	[1.7 – 4.1]
Colon	2.6% (n = 8)	2.8% (n = 11)	2.7% (n = 19)	[1.5 – 3.9]
Stomach	1% (n = 3)	2.8% (n = 11)	2.0% (n = 14)	[1 – 3]
Esophagus	0.3% (n = 1)	2.8% (n = 11)	1.7% (n = 12)	[0.7 – 2.7]
Adrenal gland	2.3% (n = 7)	0.8% (n = 3)	1.4% (n = 10)	[0.5 – 2.3]
Chest mesenchymal tumor	0.7% (n = 2)	1.3% (n = 5)	1% (n = 7)	[0.3 – 1.7]
Ureter	1% (n = 3)	1.3% (n = 5)	1.1% (n = 8)	[0.3 – 1.9]
Malignant histiocytoma of skin	0.3% (n = 1)	1% (n = 4)	0.7% (n = 5)	[0.1 – 1.3]
Pancreas	0.3% (n = 1)	0.8% (n = 3)	0.6% (n = 4)	[0 – 1.2]
Testes	NA	1% (n = 4)	0.6% (n = 4)	[0 – 2]
Cerebellum	0.3% (n = 1)	0.3% (n = 1)	0.3% (n = 2)	[−0.1 – 0.7]
Myeloma	0.3% (n = 1)	0.3% (n = 1)	0.3% (n = 2)	[−0.1 – 0.7]
Nasal	0	0.5% (n = 2)	0.3% (n = 2)	[−0.1 – 0.7]
Leukemia	0.3% (n = 1)	0	0.1% (n = 1)	[−0.1 – 0.3]
Unknown primary	3.6% (n = 11)	7.4% (n = 29)	5.7% (n = 40)	[4 – 7.4]

previous cancer diagnosis [2,5,6,10,14,15,24-28,30-33,35,37,39,40,42,44,46,48-50,52,53,55,56,58–62,65–68,70,73–75,79,81–84,88–104,109,110,115,116,119–128,130–136,138,140,141,144,145,147,150,151,153–155,157,159–162,164,165,174–178,180,183–191,193,195,196,200] On the other hand, in our study the 35.1% (n = 244) did not report this information.

Our study has several limitations, including the quality of the studies, the lack of complete information on mostly all the case series and retrospective studies. Unpublished data were not identified even though we tried to reach some of the authors. This suggests that publication bias cannot be absolutely excluded even though no significant publication bias was observed and analyzed with the JBI codification system. It was impossible to completely exclude the influence of confounding factors, and heterogeneity inherent in these included studies, however to date this is the most comprehensive study in this topic.

Metastatic disease creates both clinical and pathological challenges. Since about a fourth of patients with MOMFR occur in patients without a known primary malignancy, rarely is metastatic disease a likely consideration clinically. Since two thirds of metastatic lesions are to bone, the metastatic tumor infiltrates like any primary malignancy and most patients have clinical signs and symptoms and radiographic images suggesting a malignant process. It is important to remember that the most common malignancy seen in the jaws is metastatic disease, considerably more common that primary bony malignancies. Soft tissue metastases by contrast, often do not have clinical features of malignancy, particularly when the metastasis is to gingiva. While biopsy is critical and will often lead to the correct

Table 4
Principals' primary tumors, with the most common radiographic image, in the most common anatomic jawbone location. Primary tumor (PT) Osteolytic Image (OI), Ill-defined radiolucent image (IDRI) Radiopaque image (RPI) * seven patients were found to have both jaws.

P.T. Total (n = 154) *	Mandible (n = 130) *					Maxilla (n = 16) *	
	Anterior	Body	Posterior	Condyle	Angle	Anterior	Posterior
Lung (n = 54)							
OI	9.6% (n = 5)	9.6% (n = 5)	19.2% (n = 10)	0	0	1.9% (n = 1)	0
IDRI	7.7% (n = 4)	19.2% (n = 10)	19.2% (n = 10)	3.8% (n = 2)	1.9% (n = 1)	1.9% (n = 1)	0
RPI	3.8% (n = 2)	0.19% (n = 1)	3.8% (n = 2)	0	0	0	0
Breast (n = 20)							
OI	10.3% (n = 3)	3.4% (n = 1)	34.5% (n = 10)	6.9% (n = 2)	0	3.4% (n = 1)	3.4% (n = 1)
IDRI	6.9% (n = 2)	13.8% (n = 4)	24.1% (n = 7)	3.4% (n = 1)	0	3.4% (n = 1)	0
RPI	6.9% (n = 2)	6.9% (n = 2)	0	0	0	0	0
Kidney (n = 18)							
OI	11.1% (n = 2)	16.7% (n = 4)	11.1% (n = 2)	0	0	0	11.1% (n = 2)
IDRI	5.5% (n = 1)	11.1% (n = 2)	27.7% (n = 5)	5.5% (n = 1)	0	0	5.6% (n = 1)
RPI	5.5% (n = 1)	0	5.5% (n = 1)	5.5% (n = 1)	0	0	0
Thyroid (n = 14)							
OI	0	0	7.1% (n = 1)	7.1% (n = 1)	0	7.14% (n = 1)	0
IDRI	18.8% (n = 3)	14.3% (n = 2)	7.1% (n = 1)	0	0	7.14% (n = 1)	7.14% (n = 1)
RPI	7.1% (n = 1)	7.1% (n = 1)	14.3% (n = 2)	0	0	0	0
Liver (n = 15)							
OI	6.7% (n = 1)	6.7% (n = 1)	6.7% (n = 1)	13.3% (n = 2)	0	6.7% (n = 1)	6.7% (n = 1)
IDRI	6.7% (n = 1)	13.3% (n = 2)	40% (n = 6)	6.7% (n = 1)	6.7% (n = 1)	6.7% (n = 1)	0
RPI	0	0	6.7% (n = 1)	0	0	0	0
Prostate (n = 14)							
OI	7.1% (n = 1)	7.1% (n = 1)	21.4% (n = 3)	21.4% (n = 3)	0	0	14.2% (n = 2)
IDRI	0	0	14.2% (n = 2)	0	0	0	7.1% (n = 1)
RPI	0	0	7.1% (n = 1)	7.1% (n = 1)	0	0	0
Uterus (n = 10)							
OI	0	20% (n = 2)	10% (n = 1)	0	10% (n = 1)	0	10% (n = 1)
IDRI	0	10% (n = 1)	30% (n = 3)	0	0	10% (n = 1)	20% (n = 2)
RPI	0	0	0	0	0	0	0

diagnosis of metastatic disease, metastasis is generally a feature of advanced disease, often with metastasis to other sites as well, and is typically treated with palliation, or limited surgery, but the overall prognosis is poor.

Declaration of Competing Interest

No conflicts of interest.

Financial support

Not financial support for this paper.

Data Availability

Yes, we have all the information that was used to perform the manuscript. Data analyses were performed with Microsoft Excel 2018 (Microsoft Corp, Redmond, Washington).

Code availability

Statistical Package for the Social Sciences (SPSS) software, version 20.0 ©Copyright IBM (SPSS Inc., Chicago, IL, USA)

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Ethical statement

This study met criteria for nonhuman subject research, and as a result board ethics approval was not required. No datasets were generated or analyzed during the current study.

Acknowledgment

We want to dedicate this research to Dr Roman Carlos II, an oral and maxillofacial pathologist from Guatemala, who always was an extremely wonderful professional. Paz a su Alma.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jormas.2021.12.009.

References

[1] Hirshberg A, Shnaiderman-Shapiro A, Kaplan I, Berger R. Metastatic tumours to the oral cavity – pathogenesis and analysis of 673 cases. Oral Oncol 2008;44 (8):743–52 Aug. doi: 10.1016/j.oraloncology.2007.09.012.
[2] Kumar G, Manjunatha B. Metastatic tumors to the jaws and oral cavity. J Oral Maxillofac Pathol 2013;17(1):71–5 Jan. doi: 10.4103/0973-029X.110737.
[3] Kinchnick LB, Schuch LF, Cademartori MG, Vasconcelos ACU. Metastasis to the oral and maxillofacial region: a systematic review. Oral Dis 2020 Aug 13. doi: 10.1111/odi.13611.
[4] Wu YT. [Metastatic carcinoma to the oral tissues and jaws: a study of 25 cases]. Zhonghua Kou Qiang Yi Xue Za Zhi 1990;25(5):258–61 Sep317. Chinese. PMID: 1964887.
[5] van der Waal RI, Buter J, van der Waal I. Oral metastases: report of 24 cases. Br J Oral Maxillofac Surg 2003;41(1):3–6 Feb. doi: 10.1016/s0266-4356(02)00301-7.
[6] Rocha BA, Paranaíba LM, Dantas CD, de Carvalho MG, de Melo-Filho MR, Lima LM, Souto GR, Horta MC. Two rare cases of oral metastasis arising from lung adenocarcinoma and esophageal carcinoma. J Clin Exp Dent 2020 Oct 1;12(10):e980–e1004. doi: 10.4317/jced.57125.
[7] Valastyan S, Weinberg RA. Tumor metastasis: molecular insights and evolving paradigms. Cell 2011 Oct 14;147(2):275–92. doi: 10.1016/j.cell.2011.09.024.
[8] Kwon MS, Ko SO, Cho NP, Kim OH, Shin HK, Baek JA, Jaem DH. Gastric signet-ring cell adenocarcinoma metastatic to the gingiva: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006 Jul;102(1):62–6. doi: 10.1016/j.tripleo.2005.08.029.
[9] Eskander A, Ghanem T, Agrawal A. Education Committee of American Head and Neck Society (AHNS). AHNS Series: do you know your guidelines? Guideline recommendations for head and neck cancer of unknown primary site. Head Neck 2018 Mar;40(3):614–21. doi: 10.1002/hed.25026.
[10] Kaplan I, Rabner V, Shuster A, Shlomi B, Rosenfeld E, Greenberg A, Hirshberg A, Yahalom R, Shnaiderman-Shapiro A, Vered M. Metastatic tumors in oral mucosa

and jawbones: unusual primary origins and unusual oral locations. Acta Histochem 2019;121(8):151448 Novdoi: 10.1016/j.acthis.2019.151448.
[11] Hirshberg A, Leibovich P, Buchner A. Metastases to the oral mucosa: analysis of 157 cases. J Oral Pathol Med 1993 Oct;22(9):385–90 doi: 10.1111/j.1600-0714.1993.tb00128.x.
[12] Barnes L. Metastases to the head and neck: an overview. Head Neck Pathol 2009 Sep;3(3):217–24 doi: 10.1007/s12105-009-0123-4. Epub 2009 Jul 5. PMID: 20596975; PMCID: PMC2811631.
[13] Irani S. Metastasis to the oral soft tissues: a review of 412 cases. J Int Soc Prev Community Dent 2016;6(5):393–401 Sep-Oct. doi: 10.4103/2231-0762.192935.
[14] Cai J, He B, Li X, Sun M, Lam AK, Qiao B, Qiu W. Regulation of tumorigenesis in oral epithelial cells by defined reprogramming factors Oct4 and Sox2. Oncol Rep 2016;36(2):651–8 Augdoi: 10.3892/or.2016.4851.
[15] McClure SA, Movahed R, Salama A, Ord RA. Maxillofacial metastases: a retrospective review of one institution's 15-year experience. J Oral Maxillofac Surg 2013;71(1):178–88 JanEpub 2012 Jun 16. doi: 10.1016/j.joms.2012.04.009.
[16] Shen ML, Kang J, Wen YL, Ying WM, Yi J, Hua CG, Tang XF, Wen YM. Metastatic tumors to the oral and maxillofacial region: a retrospective study of 19 cases in West China and review of the Chinese and English literature. J Oral Maxillofac Surg 2009;67(4):718–37 Apr. doi: 10.1016/j.joms.2008.06.032.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISMA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009 Jul 21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
[18] Wu Z, Tang J, Li Y, Lu H, Xu J, Lv D. Successful management of rare gingival metastasis from gastric adenocarcinoma: a case report and literature review. World J Surg Oncol 2017 Aug 1;15(1):141. doi: 10.1186/s12957-017-1215-3.
[19] Uchiyama Y, Murakami S, Kakimoto N, Nakatani A, Kishino M, Hamab Y, Furukawa S. Diagnostic imaging findings for mandibular metastasis from gastric adenocarcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107(6):e49–53 Jundoi: 10.1016/j.tripleo.2009.03.004.
[20] Dodo M, Kumagai M, Kato Y, Hirakawa H, Koseki T. Metastasis in the mandibular condyle: a case report. J Med Case Rep. 2017 Nov 16;11(1):323. doi: 10.1186/s13256-017-1450-9.
[21] Gonzalez-Perez LM, Infante-Cossio P, Crespo-Torres S, Sanchez-Gallego F. Mandibular metastases as first clinical sign of an occult male breast cancer. Int J Oral Maxillofac Surg 2012;41(10):1211–4 Octdoi: 10.1016/j.ijom.2012.02.018.
[22] Patel S, Barros J, Nwizu NN, Ogbureke KUE. Metastatic renal cell carcinoma to the oral cavity as first sign of disease: a case report. Clin Case Rep 2020 Jul 14;8(8):1517–21. doi: 10.1002/ccr3.2923.
[23] Sauerborn D, Vidakovic B, Baranovic M, Mahovne I, Daric P, Daric D. Gastric adenocarcinoma metastases to the alveolar mucosa of the mandible: a case report and review of the literature. J Craniomaxillofac Surg 2011;39(8):645–8 Dec. doi: 10.1016/j.jcms.2010.10.020.
[24] Park JY, Kim HS, Zo JI, Lee S, Choi SW. Initial presentation of lung sarcomatoid carcinoma as a metastatic lesion in the mandibular gingiva. J Periodontol 2006;77(4):734–7 Apr10.1902/jop.2006.050137.
[25] Yoshii T, Muraoka S, Sano N, Furudoi S, Komori T. Large cell carcinoma of the lung metastatic to the mandibular gingiva. J Periodontol 2002;73(5):571–4 Maydoi: 10.1902/jop.2002.73.5.571.
[26] Kim RY, Perry SR, Levy DS. Metastatic carcinoma to the tongue: a report of two cases and a review of the literature. Cancer 1979;43(1):386–9 Jandoi: 10.1002/1097-0142(197901)43:1<386::aid-cncr2820430154>3.0.co;2-g.
[27] Kerpel SM, Freedman PD. Metastatic mesothelioma of the oral cavity. Report of two cases. Oral Surg Oral Med Oral Pathol 1993;76(6):746–51 Dec. doi: 10.1016/0030-4220(93)90046-7.
[28] Erkilic S, Keskinruzgar A, Bozlag Z, Gunhan O. Metastasis of a Renal Collecting Duct Adenocarcinoma to the Oral Cavity After Tooth Extraction. J Craniofac Surg 2017;28(4):e398–9 Jun. doi: 10.1097/SCS.0000000000003799.
[29] Ali RA, Mohamed KE. Metastatic clear cell renal cell carcinoma presenting with a gingival metastasis. Clin Pract 2016 Jun 10;6(2):847. doi: 10.4081/cp.2016.847.
[30] Selvi F, Faquin WC, Michaelson MD, August M. Three Synchronous Atypical Metastases of Clear Cell Renal Carcinoma to the Maxillary Gingiva, Scalp and the Distal Phalanx of the Fifth Digit: a Case Report. J Oral Maxillofac Surg 2016;74(6):1286. June1-9doi: 10.1016/j.joms.2016.01.054.
[31] Jatti D, Puri G, Aravinda K, Dheer DS. An atypical metastasis of renal clear cell carcinoma to the upper lip: a case report. J Oral Maxillofac Surg 2015;73(2):371. Febe1-6doi: 10.1016/j.joms.2014.09.006.
[32] Nakanishi Y, Xu B, LeVea C. Oral floor and gingival metastasis of cholangiocarcinoma: a case report and review of the literature. Case Rep Pathol 2014;712912 2014. doi: 10.1155/2014/712912.
[33] Umashankar D, Srinath N, Bavle RM, Bhandari A. Anterior maxillary metastasis of gastric adenocarcinoma: a rare case. J Oral Maxillofac Pathol 2013;17(3):467–70 Sep. doi: 10.4103/0973-029X.125223.
[34] Kim IK, Lee DH, Cho HY, Seo JH, Park SH, Kim JM. Prostate adenocarcinoma mandibular metastasis associated with numb chin syndrome: a case report. J Korean Assoc Oral Maxillofac Surg 2016;42(5):301–6 Octdoi: 10.5125/jkaoms.2016.42.5.301.
[35] Menezes JD, Cappellari PF, Capelari MM, Gonçalves PZ, Toledo GL, Toledo Filho JL, et al. Mandibular metastasis of adenocarcinoma from prostate cancer: case report according to epidemiology and current therapeutical trends of the advanced prostate cancer. J Appl Oral Sci 2013;21(5):490–5 Sep-Oct. doi: 10.1590/1679-775720130148.
[36] Soares EC, Costa FW, Rocha-Filho FD, Ferreira FV, Alves AP. Metastatic prostate adenocarcinoma associated with numb chin syndrome. J Craniofac Surg 2011;22(6):2366–8 Nov. doi: 10.1097/SCS.0b013e318231e5a1.
[37] Freudlsperger C, Kurth R, Werner MK, Hoffmann J, Reinert S. Condylar metastasis from prostatic carcinoma mimicking temporomandibular disorder: a case report. Oral Maxillofac Surg 2012;16(1):79–82 Mar. doi: 10.1007/s10006-010-0256-3.
[38] Villa A, Mariani U, Villa F. Oral metastasis of lung cancer. A challenge for the clinician. Oral Maxillofac Surg 2012;16(1):133–5 Mar. doi: 10.1007/s10006-011-0273-x.
[39] Kadokura M, Yamamoto S, Kataoka D, et al. Pulmonary adenocarcinoma metastatic to the gingiva. Int J Clin Oncol 1999;4:253–5. doi: 10.1007/s101470050064.
[40] Makos CP, Psomaderis K. A literature review in renal carcinoma metastasis to the oral mucosa and a new report of an epulis-like metastasis. J Oral Maxillofac Surg 2009;67(3):653–60 Mar. doi: 10.1016/j.joms.2008.10.006.
[41] Sikka S, Sikka P, Kaur G, Shetty DC. A review of histopathological and immunohistochemical parameters in diagnosis of metastatic renal cell carcinoma with a case of gingival metastasis. J Cancer Res Ther 2013;9(1):105–7 Jan-Mar. doi: 10.4103/0973-1482.110395.
[42] Schwab B, Lee WT. Bilateral renal cell carcinoma metastasis in the oral cavity. Am J Otolaryngol 2012;33(1):154–5 Jan-Feb. doi: 10.1016/j.amjoto.2010.12.006.
[43] Yoshitomi I, Kawasaki G, Mizuno A, Nishikido M, Hayashi T, Fujita S, Ikeda T. Lingual metastasis as an initial presentation of renal cell carcinoma. Med Oncol 2011;28(4):1389–94 Dec. doi: 10.1007/s12032-010-9596-y.
[44] Ganini C, Lasagna A, Ferraris E, Gatti P, Paglino C, Imarisio I, Morbini P, Benazzo M, Porta C. Lingual metastasis from renal cell carcinoma: a case report and literature review. Rare Tumors 2012 Jun 26;4(3):e41. doi: 10.4081/rt.2012.e41. Epub 2012 Sep 4.
[45] Maestre-Rodríguez O, González-García R, Mateo-Arias J, Moreno-García C, Serrano-Gil H, Villanueva-Alcojol L, Campos-de-Orellana AM, Monje-Gil F. Metastasis of renal clear-cell carcinoma to the oral mucosa, an atypical location. Med Oral Patol Oral Cir Bucal 2009 Nov 1;14(11):e601–4. doi: 10.4317/medoral.14.e601.
[46] Nakano H, Naito K, Suzuki S, Naito K, Kubota T, Takizawa S. Metastatic renal cell carcinoma in the cheek: report of a case. J Oral Maxillofac Surg Med Pathol 2013;25(3):291–3. doi: 10.1016/j.ajoms.2012.09.005.
[47] Tsianos EB, Karentzos C, Papadopoulos NE. Metastatic renal cell carcinoma in the gingiva of the maxilla and mandible: report of a case. J Oral Maxillofac Surg 1987;45(11):975–7 Nov. doi: 10.1016/0278-2391(87)90453-8.
[48] Will TA, Agarwal N, Petruzzelli GJ. Oral cavity metastasis of renal cell carcinoma: a case report. J Med Case Rep 2008 Sep 29;2:313. doi: 10.1186/1752-1947-2-313.
[49] Zhang Y, Gu ZY, Tian Z, Yang C, Cai XY. Oral metastasis from primary transitional cell carcinoma of the renal pelvis: report of a case. Int J Oral Maxillofac Surg 2010;39(7):737–9 Juldoi: 10.1016/j.ijom.2010.02.018. Epub 2010 Mar 16.
[50] Lutcavage GJ, Branham GB, Winterholler BW, Wood DA. Renal cell carcinoma metastasis to the hard palate. J Oral Maxillofac Surg 1984;42(7):469–74 Jul. doi: 10.1016/0278-2391(84)90236-2.