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Review

Metastatic Renal-Cell Carcinoma of the Oro-Facial Tissues: A Comprehensive Review of the Literature with a Focus on Clinico–Pathological Findings

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Abstract: Background: Metastatic tumors of the oro-facial tissuesare rare, with an incidence ranging between 1% and 8% of all oral malignant tumors. Generally reported with a peak of incidence in the 5–7th decades but possibly occurring at any age, metastases may represent the first sign of an occult cancer or manifest in patients with an already known history of a primary carcinoma, mostly from the lungs, kidney, prostate, and colon/rectum in males, and the uterus, breast, lung, and ovary in females. In the oro-facial tissues, the most involved sites are the oral mucosa, gingiva/jawbones, tongue, and salivary glands. Methods: A broad and deep literature review with a comprehensive analysis of the existing research on oro-facial metastases from renal-cell carcinoma (RCC) was conducted by searching the most used databases, with attention also paid to the clear-cell histological variant, which is the most frequent one. Results: Among the 156 analyzed studies, 206 cases of oro-facial metastases of renal cancer were found in patients with an average age of 60.9 years (145 males, 70.3%; 61 females, 29.6%). In almost 40% of the cases, metastasis represented the first clinical manifestation of the primary tumor, and 122 were histologically diagnosed as clear-cell renal-cell carcinoma (ccRCC) (59.2%). The tongue was involved in most of the cases (55 cases, 26.7%), followed by the gingiva (39 cases, 18.9%), mandible (35 cases, 16.9%), maxilla (23 cases, 11.1%), parotid gland (22 cases, 10.6%), buccal mucosa (11 cases, 5.3%), lips (7 cases, 3.3%), hard palate (6 cases, 2.8%), soft palate, masticatory space, and submandibular gland (2 cases, 0.9%), and lymph nodes, tonsils, and floor of the mouth (1 case, 0.4%). Among the 122 ccRCCs (84 males, 68.8%; 38 females, 31.1%), with an average age of 60.8 years and representing in 33.6% the first clinical manifestation, the tongue remained the most frequent site (31 cases, 25.4%), followed by the gingiva (21 cases, 17.2%), parotid gland (16 cases, 13.1%), mandibular bone (15 cases, 12.2%), maxillary bone (14 cases, 11.4%), buccal mucosa and lips (6 cases, 4.9%), hard palate (5 cases, 4%), submandibular gland and soft palate (2 cases, 1.6%), and lymph nodes, tonsils, oral floor, and masticatory space (1 case, 0.8%). The clinical presentation in soft tissues was mainly represented by a fast-growing exophytic mass, sometimes accompanied by pain, while in bone, it generally presented as radiolucent lesions with ill-defined borders and cortical erosion. Conclusions: The current comprehensive review collected data from the literature about the incidence, site of occurrence, age, sex, and survival of patients affected by oro-facial metastases from renal-cell carcinoma, with particular attention paid to the cases diagnosed as metastases from clear-cell renal-cell carcinoma, which is the most frequent histological variant. Clinical differential diagnosis is widely discussed to provide clinicians with all the useful information for an early diagnosis despite the effective difficulties in recognizing such rare and easily misdiagnosed lesionsTheir early identification represents a diagnostic challenge, especially when the

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clinical work-up is limited to the cervico–facial region. Nevertheless, early diagnosis and recently introduced adjuvant therapies may represent the key to better outcomes in such patients. Therefore, general guidelines about the clinical and radiological identification of oro-facial potentially malignant lesions should be part of the cultural background of any dentist.

Keywords: metastases; renal-cell carcinoma; clear-cell renal-cell carcinoma; oral cavity; head and neck

1. Introduction

The metastatic dissemination of solid tumors may involve the head and neck, including the oral cavity. However, this occurs infrequently, with an incidence rate between 1% and 8% of all oral malignant tumors [1–4], which peaks in the 5–7th decades [2]. Excluding the malignant tumors of childhood, oro-facial metastases (OFMs) may be the first sign of an occult or still undiagnosed cancer or may manifest during the clinical follow-up of a patient with an already diagnosed primary carcinoma [5–7]. Metastases to the oro-facial tissues can involve soft or hard tissues or both synchronously, including the oral mucosa, jawbones, salivary glands, and neck lymph nodes. The most frequent primary localizations, according to the overall incidence rates among the general population, are represented by the lung, kidney, prostate, and colon/rectum in males and the uterus, breast, lung, and ovary in females [1,2,8,9].

It is widely acknowledged that, regardless of the most frequent tissue target of the primary tumor (e.g., bone in the case of prostate cancer), metastatic diffusion also exhibits a preference for certain specific sites in the oro-facial region. In addition, very frequent particular clinical conditions, such as gingival–periodontal tissue inflammation, the presence of removable prosthesis in edentulous individuals, or gingival and alveolar bone remodeling after recent tooth removal, may also have an impact. In fact, in these cases, it has been hypothesized that the reorganization of the area of blood flow caused by inflammation, pressure, or damage from the prosthesis will promote the onset of the disease [10]. Because of their high bone marrow concentration and abundant vascularization, the jawbones, particularly the molar and premolar areas, are frequently affected. Furthermore, metastases may occur in the remaining alveoli after tooth extraction (post-extraction sites), most likely as a result of increased blood flow associated with blood clot development [1,2,8,10].

Renal-cell carcinoma (RCC) represents over 90% of all kidney malignancies in the adult population, making it the most prevalent kind of kidney cancer. It usually affects men and manifests itself around the age of 60 [11–17]. A number of risk factors have been suggested to favor the development of RCC. These include an elevated body mass index [18], urinary stones in men [19], type 2 diabetes in women [20], chronic liver and kidney illnesses [21], and long-term use of analgesics [22], in addition to environmental variables [23,24]. Patients with localized renal illness treated with nephrectomy often experience recurrence in around 25% of instances, and one third of patients develop locoregional or distant metastases. RCC usually metastasizes to the liver, brain, lungs, regional lymph nodes, and bones [25]. There are very few descriptions of localization to the oro-facial tissue in the literature. RCC metastases are very uncommon in this area, primarily affecting the tongue, gingiva, and maxillary bones in that order [26,27].

There are several histologic subtypes of RCC. The most common types, comprising 90% of cases, are chromophobe RCC (chRCC) (5%) and papillary RCC (pRCC) (10 to 15%); clear-cell RCC (ccRCC) accounts for 70% of cases [28,29]. Though unusual metastatic sites or late metachronous metastases (>10 years) have been reported, and distant metastasis may be the tumor's initial clinical manifestation, ccRCC has a known propensity to metastasize most frequently via direct invasion of the renal veins and vena cava, followed by hematogenous dissemination to the lungs [30,31].

A true diagnostic conundrum for clinicians and pathologists (primarily because of the rarity of early diagnosis) is presented by the occasional report of metastatic ccRCC to the

OFTs [1,2,28,32]. In fact, because of their high glycogen and lipid content, the tumor cells of ccRCC exhibit clear cytoplasmic vacuolization and clearing, mimicking other neoplasms of odontogenic or salivary gland origin that more frequently affect this area [2,28,29,33–36]. As such, the oral localization of an undetected ccRCC may undoubtedly pose a diagnostic problem, particularly if the cervicofacial region is still the exclusive focus of the clinical work-up [6,7,37–40]. The present study was proposed to systematically review case reports and case series of RCC's metastasis to the OFTs. Our primary aim was to perform a comprehensive review of all published cases of ccRCC metastases according to the PRISMA guidelines for systematic review (Figure 1).

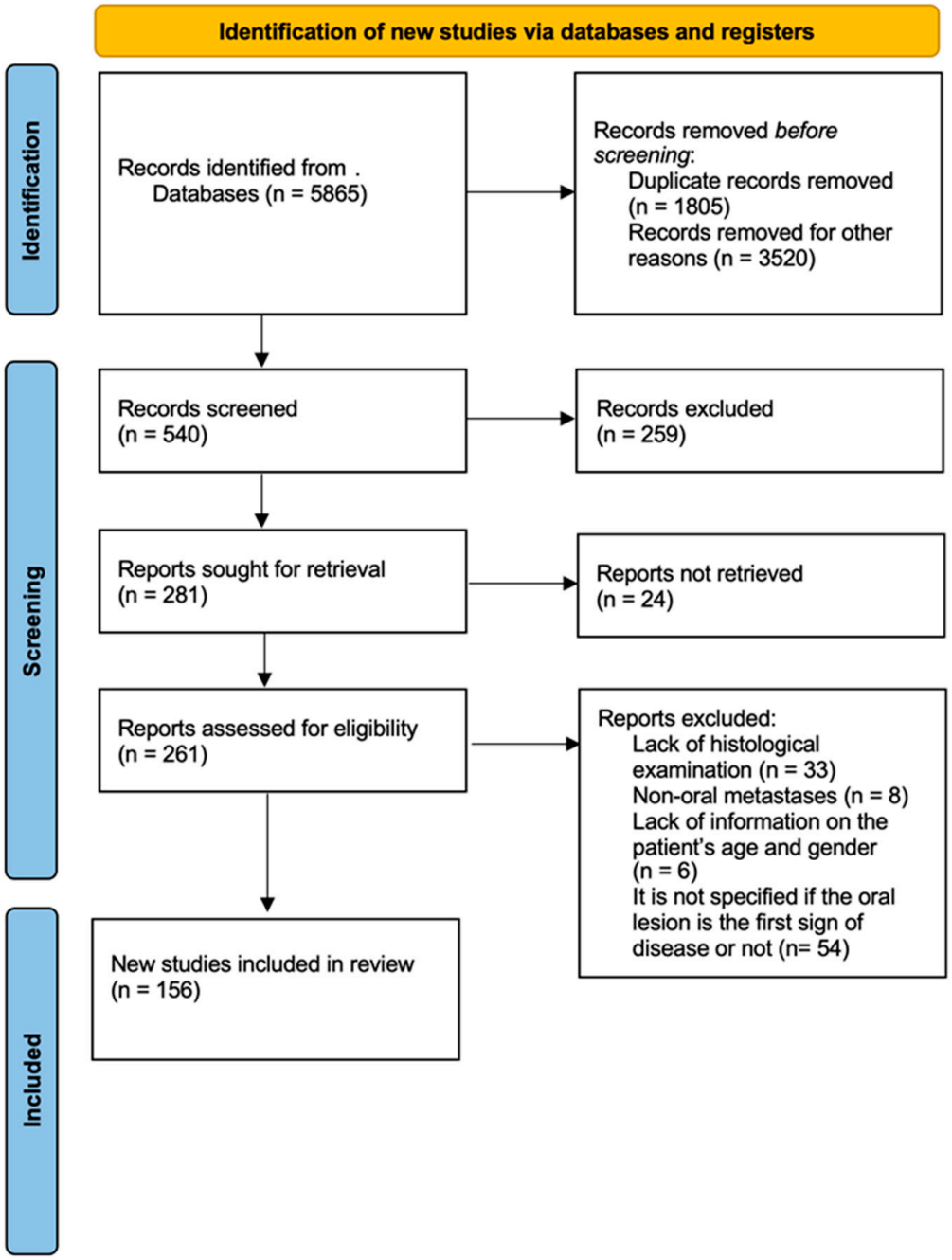

Figure 1. The PRISMA flow chart for reporting systematic reviews.

2. Materials and Methods

A comprehensive review of the literature was conducted according to the PRISMA guidelines for systematic reviews, with the intention of providing an overview of the available evidence in reliable databases. The terms "renal metastasis" or "renal metastases" or "clear-cell renal-cell carcinoma" AND "oral" or "Head and Neck" were alternatively used in the search, restricting their presence to the titles of the articles in PubMed, Scopus, Web of Sciences, Google Scholar, and Embase databases, in the period from September 2023 to January 2024. The search was limited to only studies on humans. All kinds of papers were collected, including case reports, case series, reviews of the literature, and systematic reviews of the literature. After applying the keywords to the databases, a total of 5865 results were obtained. Of these, only 156 articles were chosen for inclusion in the present review. The others were removed because the lesions were not confirmed as metastases at the anatomopathological examination, because the metastases were outside the limits of the head and neck, because the genders and ages of the patients were not specified, or because it was not proven whether the oral manifestation was the first sign of disease or not. The reading, selection, and analysis of the articles included in this review were performed by four reviewers (VG, AdA, SC, and MF).

3. Results

In the 156 analyzed studies, 206 cases of oral metastases of renal cancer were found, of which 122 were histologically demonstrated to be ccRCCs (59.2%) at the final diagnosis. The tongue was involved by renal metastases in most of the cases (55 cases, 26.7%), followed by the gingiva (39 cases, 18.9%), mandibular bone (35 cases, 16.9%), maxillary bone (23 cases, 11.1%), parotid gland (22 cases, 10.6%), buccal mucosa (11 cases, 5.3%), lips (7 cases, 3.3%), hard palate (6 cases, 2.8%), soft palate, masticatory space, and submandibular gland (2 cases, 0.9%), and lymph nodes, tonsils, and oral floor (1 case, 0.4%). Of the 206 total cases, 145 were males (70.3%) and 61 were females (29.6%). The average age was 60.9 years. The average male age was 62.2, and the average female age was 57.8. In almost 40% of cases, the development of oral metastasis represented the first clinical manifestation of the primary tumor, which was previously unknown. Data were globally collected and are presented in Table 1, listing the author(s) names, the year of publication, site/sites, histological histotype, sex, age, and occurrence as the first sign of metastatic disease or not, while clinical data in Table 2.

Table 1. Full list of the selected articles regarding metastases of renal-cell carcinoma to the oral cavity. For each article, the first author, year of publication, site, histological type, gender, age, and eventual presence of the first sign of diseases are described. RCC = renal-cell carcinoma. ccRCC: clear-cell renal-cell carcinoma. pRCC: papillary renal-cell carcinoma.

Authors	Year	Site	Histotype	Gender	Age	First Sign of Disease
Ray et al. [41]	2013	Tongue	RCC	M	65	Yes
Kalinin et al. [42]	2023	Tongue	ccRCC	F	58	yes
Nishii et al. [43]	2020	Maxillary bone	ccRCC	M	89	No
Zhang et al. [44]	2020	Mandibular bone	RCC	F	56	Yes
Jung et al. [45]	2023	Mandibular bone	RCC	F	22	Yes
Stojanovic et al. [46]	2020	Gingiva	RCC	M	53	Yes
Li et al. [47]	2001	Parotid	RCC	M	63	No
Kundu et al. [48]	2001	Parotid	ccRCC	M	61	Yes
Park and Hlivko [49]	2002	Parotid	ccRCC	F	83	No
Pritchyk et al. [50]	2002	Lip Maxillary bone Tongue	RCC RCC RCC	M F M	70 53 60	Yes
Göğüş et al. [51]	2004	Parotid	ccRCC	F	59	No

Table 1. *Cont.*

Authors	Year	Site	Histotype	Gender	Age	First Sign of Disease
Torres-Carranza et al. [52]	2006	Tongue	ccRCC	F	49	No
Newton et al. [53]	2007	Parotid	ccRCC	F	74	No
Yoshitomi et al. [54]	2011	Tongue	ccRCC	M	47	Yes
Morvan et al. [55]	2011	Tongue	ccRCC	F	48	No
Balliram et al. [56]	2012	Tongue	pRCC	M	72	Yes
Serouya et al. [57]	2012	Submandibular gland	ccRCC	M	60	No
Wadasadawala et al. [58]	2011	Tongue	RCC	M	48	No
Deeb et al. [59]	2012	Parotid	RCC	M	82	No
Özkiriş et al. [60]	2011	Cervical lymph nodes	ccRCC	F	56	No
Ghazali et al. [61]	2012	Tongue	ccRCC	F	64	No
Lau et al. [62]	2012	Parotid	ccRCC	F	79	No
Mazeron et al. [63]	2013	Tongue	ccRCC	M	66	Yes
Yanlan et al. [64]	2013	Parotid	ccRCC	F	44	Yes
Udager and Rungta [65]	2014	Parotid	ccRCC	M	64	No
Abbaszadeh-Bidokhty et al. [66]	2014	Tongue	ccRCC	M	80	No
Kotak and Merrick [67]	2014	Lip	ccRCC	M	64	No
Suojanen et al. [68]	2014	Lip	ccRCC	M	71	No
Kudva et al. [69]	2016	Buccal mucosa	ccRCC	F	36	Yes
Georgy et al. [70]	2017	Gingiva	ccRCC	M	63	Yes
Nifosì et al. [71]	2017	Gingiva	ccRCC	M	58	No
Raiss et al. [6]	2017	Tongue	RCC	M	55	Yes
Vasilyeva et al. [72]	2018	Gingiva	RCC	F	78	Yes
McNattin and Dean [73]	1931	Tongue	Tubular Adenocarcinoma	M	58	Yes
Altinel et al. [74]	2010	Tongue	ccRCC	M	67	Yes
Syryło et al. [75]	2010	Lip	ccRCC	M	59	Yes
Gil-Julio et al. [76]	2012	Buccal mucosa	ccRCC	M	65	No
Shirazian and Bahrami [77]	2016	Gingiva	ccRCC	M	45	Yes
Schrag and Jordan [78]	1945	Tongue	RCC	M	34	No
Carmen and Korbitz [79]	1970	Tongue	ccRCC	M	77	No
Friedlander et al. [80]	1978	Tongue	RCC	M	84	No
Fitzgerald et al. [81]	1982	Gingiva and Tongue	RCC	M	63	No
Inai et al. [82]	1987	Tongue	RCC	M	42	No
Ishikawa et al. [83]	1991	Tongue	RCC	F	58	No
Okabe et al. [84]	1992	Tongue	ccRCC	M	58	No
Shibayama et al. [85]	1993	Tongue	RCC	M	41	No
Ziyada et al. [86]	1994	Tongue	ccRCC	M	59	Yes
Airoldi et al. [87]	1995	Tongue	RCC	M	51	No
Aguirre et al. [88]	1996	Tongue	ccRCC	F	82	Yes
Konya et al. [89]	1997	Tongue	RCC	M	59	Yes
Tomita et al. [90]	1998	Tongue	ccRCC	M	50	No
Navarro et al. [91]	2000	Tongue	ccRCC	M	62	No
Mekni et al. [92]	2002	Tongue	ccRCC	M	63	No
Kyan and Kato [93]	2004	Tongue	ccRCC	M	66	No
Huang et al. [94]	2006	Tongue Parotid	RCC ccRCC	F F	76 56	No No
Cochrane et al. [95]	2006	Tongue	RCC	M	41	No
Del Rosario Regalado et al. [96]	2007	Tongue	RCC	M	81	No
Longo et al. [97]	2008	Tongue	RCC	M	68	No
Kella et al. [98]	2009	Tongue	ccRCC	F	67	Yes
Friedmann and Osborn [99]	1965	Maxillary bone	RCC	M	63	No

Table 1. *Cont.*

Authors	Year	Site	Histotype	Gender	Age	First Sign of Disease
Trinca and Willis [100]	1936	Tongue	RCC	M	57	Yes
Branch and Norton [101]	1928	Gingiva	ccRCC	F	64	Yes
Salman and Langel [102]	1954	Gingiva	RCC	F	62	No
Persson and Wallenius [103]	1961	Gingiva	ccRCC	F	60	No
Cranin et al. [104]	1966	Gingiva	RCC	M	72	No
Buchner and Begleiter [105]	1980	Gingiva	ccRCC	M	46	No
Nishimura et al. [106]	1982	Mandibular bone Gingiva Mandibular bone	RCC RCC RCC	F M F	61 72 36	yes yes yes
Fay and Weir [107]	1983	Gingiva	ccRCC	F	18	No
Zohar et al. [108]	1985	Gingiva	ccRCC	F	54	Yes
Tsianos et al. [109]	1987	Gingiva	RCC	M	78	No
Müller-Mattheis et al. [110]	1989	Gingiva	RCC	F	47	No
Hagen et al. [111]	1989	Gingiva	RCC	F	46	No
Corsi et al. [35]	1994	Lip	ccRCC	M	44	No
Salman and Darlington [112]	1944	Hard palate	ccRCC	F	54	No
Mallet [113]	1961	Mandibular bone	ccRCC	F	72	Yes
Meyer and Shklar [114]	1965	Parotid Maxillary bone Mandibular bone Mandibular bone	RCC RCC Reticulum cell RCC	M F M M	48 73 43 57	No No No No
Godby et al. [115]	1967	Gingiva	ccRCC	M	45	No
Milobsky et al. [116]	1975	Maxillary bone	RCC	F	66	Yes
Nagayama and Oka [117]	1979	Mandibular bone Hard palate	ccRCC ccRCC	F F	61 43	yes
Susan et al. [118]	1979	Hard palate Hard palate	ccRCC ccRCC	M M	53 62	yes yes
Matsumoto and Yanagihara [119]	1982	Maxillary bone Maxillary bone	ccRCC ccRCC	M M	73 48	yes yes
Pick et al. [120]	1986	Mandibular bone	ccRCC	M	71	Yes
Zachariades et al. [121]	1989	Mandibular bone	RCC	M	78	No
Jones and al [122]	1990	Mandibular bone Mandibular bone	ccRCC ccRCC	F F	62 52	yes yes
Fandella et al. [123]	1992	Maxillary bone	ccRCC	M	62	Yes
Lee et al. [124]	1998	Maxillary bone	RCC	M	76	Yes
Guyot et al. [125]	1999	Mandibular bone	RCC	M	83	No
Hönig [126]	2000	Maxillary bone	RCC	M	46	No
Shetty et al. [127]	2001	Mandibular bone	RCC	M	62	Yes
Heinroth et al. [128]	2006	Maxillary bone	ccRCC	F	53	yes
Đanić et al. [26]	2018	Tongue	RCC	M	51	yes
Madison and Frierson [129]	1988	Tongue Tongue	ccRCC ccRCC	M M	29 63	No No
Kishore et al. [130]	2018	Lip	ccRCC	M	54	No
Abro et al. [131]	2019	Tongue	RCC	M	54	No

Table 1. *Cont.*

Authors	Year	Site	Histotype	Gender	Age	First Sign of Disease
Netto et al. [132]	2019	Gingiva	RCC	M	68	Yes
Walsh et al. [133]	2022	Tongue	ccRCC	M	63	No
Mrena et al. [134]	2008	Parotid	ccRCC	F	58	Yes
		Parotid	RCC	F	76	No
		Parotid	RCC	F	62	No
Aljawad et al. [135]	2023	Parotid	ccRCC	M	65	No
Migliorelli et al. [136]	2023	Maxillary bone	ccRCC	F	54	Yes
Maschino et al. [137]	2013	Maxillary bone	ccRCC	M	73	No
		Maxillary bone	ccRCC	F	84	No
		Parotid	ccRCC	M	78	No
		Tongue	RCC	M	66	No
Wallace et al. [138]	2022	Soft palate	ccRCC	M	50	No
Ludwig et al. [139]	2020	Mandibular bone	ccRCC	M	78	Yes
Melnick et al. [140]	1989	Parotid	ccRCC	M	72	Yes
Borghi et al. [141]	1995	Parotid	ccRCC	M	68	No
Seijas et al. [142]	2005	Parotid	ccRCC	M	67	Yes
Goel et al. [143]	2003	Tongue	ccRCC	M	62	Yes
Lenkeit et al. [144]	2020	Tongue	RCC	M	71	No
Ruiz-Oslé et al. [145]	2017	Parotid	RCC	M	72	yes
		Mandibular bone	RCC	M	55	yes
		Gingiva	RCC	M	62	yes
		Masticatory space	RCC	F	52	no
Schwab and Lee [146]	2012	Maxillary bone	ccRCC	M	63	No
Erkilic et al. [147]	2017	Gingiva	Collecting duct carcinoma	F	54	Yes
Lee and Lee [148]	2017	Mandibular bone	RCC	M	62	No
Guimarães et al. [149]	2016	Gingiva	ccRCC	F	31	No
Owosho et al. [150]	2016	Mandibular bone	RCC	F	61	No
		Mandibular bone	RCC	F	63	No
			RCC	F	18	No
		Gingiva	RCC	M	75	No
		Buccal mucosa	RCC	M	70	No
		Buccal mucosa	RCC	M	59	No
		Gingiva Buccal mucosa	RCC	M	66	No
Nisi et al. [151]	2020	Tongue	ccRCC	M	61	yes
		Buccal mucosa	ccRCC	M	71	yes
Lang et al. [152]	2003	Tongue	ccRCC	M	45	No
Bucín et al. [153]	1982	Gingiva	RCC	M	65	No
Marioni et al. [154]	2004	Tongue	ccRCC	F	87	No
Van der Wall et al. [155]	2003	Soft palate	ccRCC	F	62	No
		Maxillary bone	ccRCC	F	64	No
		Mandibular bone	ccRCC	M	48	No
		Buccal mucosa	ccRCC	M	67	No
Fukuda et al. [156]	2002	Mandibular bone	RCC	M	76	No
Makos and Psomaderis [27]	2009	Gingiva	ccRCC	M	63	No
Morii [157]	1975	Buccal mucosa	ccRCC	M	63	No
Sidhu [158]	1982	Mandibular bone	RCC	F	32	Yes

Table 1. *Cont.*

Authors	Year	Site	Histotype	Gender	Age	First Sign of Disease
Sánchez Aniceto et al. [159]	1990	Mandibular bone	RCC	M	54	Yes
Maestre-Rodríguez et al. [160]	2009	Gingiva	ccRCC	M	52	Yes
Will et al. [161]	2008	Floor of mouth	ccRCC	M	63	no
Nesbitt et al. [162]	2019	Gingiva	Sarcomatoid RCC	M	59	Yes
Patel et al. [163]	2020	Gingiva	ccRCC	F	59	yes
Narea-Matamala et al. [164]	2008	Gingiva	RCC	M	74	yes
Massaccesi et al. [165]	2009	Tonsil	ccRCC	M	76	yes
Shinozaki et al. [166]	2009	Mandibular bone	ccRCC	F	76	No
Ohmura et al. [167]	1981	Mandibular bone	ccRCC	M	53	No
Nakano et al. [168]	2013	Gingiva	ccRCC	M	72	No
Ficarra et al. [169]	1996	Wharton's duct	ccRCC	M	73	No
Tunio et al. [170]	2012	Tongue	ccRCC	M	35	No
Milner et al. [171]	2014	Hard palate	ccRCC	M	67	Yes
Santana et al. [172]	2000	Gingiva	ccRCC	M	63	Yes
Kizaekka et al. [173]	2019	Tongue	ccRCC	M	77	No
Paraskevopoulos et al. [174]	2021	Mandibular bone	ccRCC	M	72	Yes
Morita et al. [175]	2018	Buccal mucosa	ccRCC	M	75	No
Prol et al. [176]	2019	Mandibular bone Gingiva Gingiva Mandibular bone Masticatory space	ccRCC ccRCC ccRCC chRCC ccRCC	M M F M M	55 62 52 56 65	No No No No No
Shimono et al. [177]	2021	Mandibular bone Maxillary bone Tongue	RCC RCC RCC	M M M	62 89 63	Yes No no
Ali and Mohamed [178]	2016	Gingiva	ccRCC	M	60	Yes
Selvi et al. [179]	2016	Gingiva	ccRCC	M	51	No
Jatti et al. [180]	2015	Lip	ccRCC	M	60	No
Sikka et al. [181]	2013	Gingiva	ccRCC	M	73	Yes
Ganini et al. [182]	2012	Tongue	ccRCC	M	70	No
Lutcavage et al. [183]	1984	Hard palate	RCC	M	55	No
Azam et al. [184]	2008	Tongue	ccRCC	M	78	Yes
Basely et al. [185]	2009	Tongue	ccRCC	F	46	No
Ahmadnia et al. [186]	2013	Mandibular bone	ccRCC	M	57	Yes
Ord et al. [187]	1990	Maxillary bone Maxillary bone	RCC RCC	M M	58 73	yes
Capodiferro et al. [188]	2020	Gingiva Tongue Mandibular bone Mandibular bone Parotid Parotid Mandibular bone	ccRCC ccRCC ccRCC ccRCC ccRCC ccRCC ccRCC	F M M M M F M	69 56 45 63 55 55 60	No No No No No No No

Table 1. *Cont.*

Authors	Year	Site	Histotype	Gender	Age	First Sign of Disease
Andabak Rogulj et al. [189]	2018	Maxillary bone Maxillary bone Mandibular bone Maxillary bone Mandibular bone	ccRCC ccRCC RCC RCC RCC	M M F M F	65 58 64 61 68	No No No No No
Derakhshan et al. [190]	2018	Maxillary bone Maxillary bone	ccRCC ccRCC	M M	54 51	yes yes
Altuntaş et al. [191]	2014	Tongue	pRCC	M	70	No
Amiruddin and Yunus [192]	2013	Tongue	ccRCC	M	66	No

Table 2. Data analysis of oro-facial metastases of renal-cell carcinoma. For each site, the total number and percentage of cases are described.

SITE	CASES	
Tongue	55	26.9%
Gingiva	39	18.9%
Mandibular bone	35	16.9%
Maxillary bone	23	11.1%
Parotid gland	22	10.6%
Buccal mucosa	11	5.3%
Lips	7	3.3%
Hard palate	6	2.8%
Soft palate	2	0.9%
Masticatory space	2	0.9%
Submandibular gland	2	0.9%
Lymph nodes	1	0.4%
Tonsil	1	0.4%
Oral floor	1	0.4%
GENDER	**CASES**	
Male	145	70.3%
Female	61	29.6%

Focusing on the numbers of the most frequent histotype (ccRCC), we found that the tongue was involved in most cases (31 cases, 25.4%), followed by the gingiva (21 cases, 17.2%), parotid gland (16 cases, 13.1%), mandibular bone (15 cases, 12.2%), maxillary bone (14 cases, 11.4%), buccal mucosa and lips (6 cases, 4.9%), hard palate (5 cases, 4%), submandibular gland and soft palate (2 cases, 1.6%) and lymph nodes, tonsils, oral floor, and masticatory space (1 case, 0.8%). It is clear that soft tissues are more affected by ccRCC metastases than hard tissues. Of the 122 total cases, 84 were male (68.8%) and 38 were female (31.1%). The average age was 60.8 years. The average male age was 61.7, and the average female age was 59. In almost 33.6% of cases, the development of oral metastasis was the first clinical manifestation of the primary tumor. Clinical presentations varied depending on the affected tissue: at the level of soft tissues, metastases frequently presented as fast-growing and exophytic masses, accompanied or not by pain; bone metastases radiologically appeared as radiolucent lesions, with ill-defined borders and cortical erosion. In addition,

some of them also expanded into the adjacent soft tissues, thus causing submucosal swelling on the gingiva (Table 3).

Table 3. Metastases of clear-cell renal-cell carcinoma to the oro-facial tissues and clinical radiological presentation. For each article, site, epidemiological features, clinical presentation, and radiological aspects are described.

Authors	Site	Gender	Age	First Sign of Disease	Clinical Presentation	Radiological Aspect
Kalinin et al. [42]	Tongue	F	58	yes	Painless nodule	-
Nishii et al. [43]	Maxillary bone	M	89	No	Swelling of the left maxillary ginguva	Osteolytic area
Kundu et al. [48]	Parotid	M	61	Yes	Facial weakness and post-auricular pain	-
Park and Hlivko [49]	Parotid	F	83	No	infra-auricular swelling	-
Göğüş et al. [51]	Parotid	F	59	No	pre-auricular swelling	-
Torres-Carranza et al. [52]	Tongue	F	49	No	Pedunculated painless mass	-
Newton et al. [53]	Parotid	F	74	No	Pre- auricular swelling	-
Yoshitomi et al. [54]	Tongue	M	47	Yes	mass	-
Morvan et al. [55]	Tongue	F	48	No	Painful mass	-
Serouya et al. [57]	Submandibular gland	M	60	No	Submandibular mass	-
Özkiriş et al. [60]	Cervical lymph nodes	F	56	No	Multiple mass in neck region	-
Ghazali et al. [61]	Tongue	F	64	No	Painless mass	-
Lau et al. [62]	Parotid	F	79	No	Parotid mass	-
Mazeron et al. [63]	Tongue	M	66	Yes	Exophytic mass	-
Yanlan et al. [64]	Parotid	F	44	Yes	Painless mass in parotid region	-
Udager and Rungta [65]	Parotid	M	64	No	Painless mass in parotid region	-
Abbaszadeh-Bidokhty et al. [66]	Tongue	M	80	No	Swelling	-
Kotak and Merrick [67]	Lip	M	64	No	Asymptomatic swelling	-
Suojanen et al. [68]	Lip	M	71	No	Spontaneously bleeding mass	-
Kudva et al. [69]	Buccal mucosa	F	36	Yes	Painful ulcer	Bone erosion
Georgy et al. [70]	Gingiva	M	63	Yes	Gingival nodule	-
Nifosì et al. [71]	Gingiva	M	58	No	small painful reddish indurated swelling	-
Altinel et al. [74]	Tongue	M	67	Yes	Tongue mass	-
Syryło et al. [75]	Lip	M	59	Yes	Upper lip nodule	-
Gil-Julio et al. [76]	Buccal mucosa	M	65	No	Discomfort in left cheek	-
Shirazian and Bahrami [77]	Gingiva	M	45	Yes	red-purple rubbery, sessile exophytic lesion with smooth surface	Saucer shape resorption of the crestal bone
Carmen and Korbitz [79]	Tongue	M	77	No	Painful mass	-
Okabe et al. [84]	Tongue	M	58	No	Painless mass	-
Ziyada et al. [86]	Tongue	M	59	Yes	Tongue mass	-
Aguirre et al. [88]	Tongue	F	82	Yes	swelling	-
Tomita et al. [90]	Tongue	M	50	No	Hemorragic mass	-

Table 3. *Cont.*

Authors	Site	Gender	Age	First Sign of Disease	Clinical Presentation	Radiological Aspect
Navarro et al. [91]	Tongue	M	62	No	Exophytic lesion	-
Mekni et al. [92]	Tongue	M	63	No	NA	-
Kyan and Kato [93]	Tongue	M	66	No	Tongue mass	-
Huang et al. [94]	Parotid	F	56	No	Bilateral enlarging mass in parotid region	-
Kella et al. [98]	Tongue	F	67	Yes	NA	-
Branch and Norton [101]	Gingiva	F	64	Yes	Epulis-like mass	-
Persson and Wallenius [103]	Gingiva	F	60	No	Rapidly growing swelling	-
Buchner and Begleiter [105]	Gingiva	M	46	No	Rapidly growing mass	-
Fay and Weir [107]	Gingiva	F	18	No	Soft, fluctuant mass	Demarcated radiolucency
Zohar et al. [108]	Gingiva	F	54	Yes	Soft, friable red mass	-
Corsi et al. [35]	Lip	M	44	No	NA	-
Salman and Darlington [112]	Hard palate	F	54	No	Ulcerated nodule	NA
Mallett [113]	Mandibular bone	F	72	Yes	Pain and swelling	Osteolytic area
Godby et al. [115]	Gingiva	M	45	No	Gingival mass	Bone resorption
Nagayama and Oka [117]	Mandibular bone Hard palate	F F	61 43	yes	Swelling Palate's perforation	Osteolytic area NA
Susan et al. [118]	Hard palate Hard palate	M M	53 62	yes yes	Swelling Pedunculated lesion	NA NA
Matsumoto and Yanagihara [119]	Maxillary bone Maxillary bone	M M	73 48	yes yes	Cheek's swelling epistaxis	Osteolytic area NA
Pick et al. [120]	Mandibular bone	M	71	Yes	Swelling	mixed radiolucent and radiopaque lesion
Jones and al [122]	Mandibular bone Mandibular bone	F F	62 52	yes yes	Swelling Swelling	osteolytic area osteolytic area
Fandella et al. [123]	Maxillary bone	M	62	Yes	epistaxis	NA
Heinroth et al. [128]	Maxillary bone	F	53	yes	Painful swelling	opacity in the maxillary sinus
Madison and Frierson [129]	Tongue Tongue	M M	29 63	No No	NA NA	- -
Kishore et al. [130]	Lip	M	54	No	swelling	-
Walsh et al. [133]	Tongue	M	63	No	Pedunculated lesion	-
Mrena et al. [134]	Parotid	F	58	Yes	Non-tender nodule	-
Aljawad et al. [135]	Parotid	M	65	No	Non-tender mass	-
Migliorelli et al. [136]	Maxillary bone	F	54	Yes	Facial pain	Bone erosion
Maschino et al. [137]	Maxillary bone Maxillary bone Parotid	M F M	73 84 78	No No No	Exophytic mass Pain, discomfort Rapid growth mass	Osteolytic lesion NA
Wallace et al. [138]	Soft palate	M	50	No	Globular lesion	-
Ludwig et al. [139]	Mandibular bone	M	78	Yes	Painful swelling and paresthesia	NA
Melnick et al. [140]	Parotid	M	72	Yes	Parotid mass	-

Table 3. *Cont.*

Authors	Site	Gender	Age	First Sign of Disease	Clinical Presentation	Radiological Aspect
Borghi et al. [141]	Parotid	M	68	No	Painless swelling	-
Seijas et al. [142]	Parotid	M	67	Yes	Painless mass	-
Goel et al. [143]	Tongue	M	62	Yes	Swelling	-
Schwab and Lee [146]	Maxillary bone	M	63	No	Bilateral, friable masses with a foul odor	NA
Guimarães et al. [149]	Gingiva	F	31	No	Painful growth	Enlargement of the periodontal ligament
Nisi et al. [151]	Tongue	M	61	yes	Swelling	-
	Buccal mucosa	M	71	yes	Large mass	-
Lang et al. [152]	Tongue	M	45	No	Pedunculated mass	-
Marioni et al. [154]	Tongue	F	87	No	Exophytic, ulcerated mass	-
Van der Wall et al. [155]	Soft palate	F	62	No	NA	-
	Maxillary bone	F	64	No	NA	-
	Mandibular bone	M	48	No	NA	-
	Buccal mucosa	M	67	No	NA	-
Makos and Psomaderis [27]	Gingiva	M	63	No	Epulis-like mass	-
Morii [157]	Buccal mucosa	M	63	No	NA	-
Maestre-Rodríguez et al. [160]	Gingiva	M	52	Yes	Granulomatous gingival lesion	-
Will et al. [161]	Floor of mouth	M	63	no	Indurated mass	-
Patel et al. [163]	Gingiva	F	59	yes	pink-red, oval, ulcerated lesion with a white pseudomembranous surface	-
Massaccesi et al. [165]	Tonsil	M	76	yes	dysphagia	-
Shinozaki et al. [166]	Mandibular bone	F	76	No	swelling	Multilocular bone destruction
Ohmura et al. [167]	Mandibular bone	M	53	No	NA	NA
Nakano et al. [168]	Gingiva	M	72	No	swelling	-
Ficarra et al. [169]	Wharton's duct	M	73	No	Movable mass in the floor of the mouth	-
Tunio et al. [170]	Tongue	M	35	No	Painless swelling	-
Milner et al. [171]	Hard palate	M	67	Yes	Irregularly shaped lump	none
Santana et al. [172]	Gingiva	M	63	Yes	Double lobe nodule	Radiolucent lesion
Kizaekka et al. [173]	Tongue	M	77	No	Pedunculated lesion	-
Paraskevopoulos et al. [174]	Mandibular bone	M	72	Yes	NA	-
Morita et al. [175]	Buccal mucosa	M	75	No	Swelling and facial asymmetry	-
Prol et al. [176]	Mandibular bone	M	55	No	Mass	NA
	Gingiva	M	62	No	Mass	-
	Gingiva	F	52	No	NA	-
	Masticatory space	M	65	No	Mass	NA

Table 3. *Cont.*

Authors	Site	Gender	Age	First Sign of Disease	Clinical Presentation	Radiological Aspect
Ali and Mohamed [178]	Gingiva	M	60	Yes	Gingival mass	Erosive bone changes
Selvi et al. [179]	Gingiva	M	51	No	Rapidly progressive, painless exophytic lesion	Destruction of the alveolar bone
Jatti et al. [180]	Lip	M	60	No	Ulcerated nodule	-
Sikka et al. [181]	Gingiva	M	73	Yes	Multiple painless swelling	-
Ganini et al. [182]	Tongue	M	70	No	Ulcerated lesion	-
Azam et al. [184]	Tongue	M	78	Yes	Pedunculated lesion, difficulty in swallowing solid	-
Basely et al. [185]	Tongue	F	46	No	Swelling on the left side of the neck	-
Ahmadnia et al. [186]	Mandibular bone	M	57	Yes	Swelling, trismus	Radiolucent lesion
Capodiferro et al. [188]	Gingiva Tongue Mandibular bone Mandibular bone Parotid Parotid Mandibular bone	F M M M M F M	69 56 45 63 55 55 60	No No No No No No No	Large fungating mass Large fungating mass - - growing mass growing mass -	Bone rarefaction - Osteolytic area Osteolytic area - - Osteolytic area
Andabak Rogulj et al. [189]	Maxillary bone Maxillary bone	M M	65 58	No No	Mobility of tooth Exophytic lesion	NA NA
Derakhshan et al. [190]	Maxillary bone Maxillary bone	M M	54 51	yes yes	Pain and swelling Polypoid mass	intraosseous radiolucency
Amiruddin and Yunus [192]	Tongue	M	66	No	Painless mass	-

4. Discussion

4.1. General Considerations

Metastatic tumors from distant organs and tissues to the oro-facial tissues are not encountered frequently. According to the literature, metastatic tumors comprise about only 1% of all oro-facial malignancies [114,155]. Renal-cell carcinoma (RCC) is the most common form of kidney malignancy, accounting for more than 90% of all renal malignancies in the adult population [11]. Distant metastases from RCC are very common and usually multiple to different organs, with a decreasing incidence, respectively, to the lungs (50–60%), bones and liver (30–40%), and head and neck (12–16%) [1,2]. Among the latter, 50% of the metastases were detected in the thyroid, nose, and paranasal sinuses and pharynx [28,33,193]. According to the recent review by Kase AM et al. [194], the statistical data show a five-year survival rate of 70% for patients with regional disease, which drastically decreases to 13% for those showing distant metastases. Such data highlight the importance of the early detection of metastatic lesions, which can be difficult in the absence of signs and/or symptoms of the whole organism. This excludes the oro-facial tissue, the diagnosis of which, conversely, is relatively accessible due to the ease of clinical exploration and/or the frequent use of dental panoramic radiogram and/or CT for dental therapies over one's lifetime, at least in occidental countries.

Generally, in the oral cavity, large and/or rapidly growing swellings in the tongue and periodontal tissue, as well unpredictable tooth mobility or gingiva-periodontal inflammation (including the peri-implant hard and soft tissues), surely represent clinical signs

of possible malignancy (and consequently also of metastatic diffusion), when the most common lesions of benign nature (mainly odontogenic abscess, periodontal or perimplant abscess) have been excluded. The early detection by well-addressed general dentists and their radiological evaluation always need anatomopathological confirmation by hard or soft biopsy, often supported by immunohistochemistry too, which represents the true key for the early and differential diagnosis [195].

Targeted therapies in renal-cell cancer have significantly advanced in recent years, offering more precise and effective treatment options for patients. These therapies often target specific molecules or pathways that play a crucial role in the growth and spread of cancer cells. For example, vascular endothelial growth factor (VEGF) inhibitors and mammalian target of rapamycin (mTOR) inhibitors are commonly used targeted therapies for renal-cell cancer [196,197]. Current treatments are mostly immunotherapy combinations with anti-VEGFR (vascular endothelial growth factor receptor) tyrosine kinase inhibitors (TKIs) [198]. By inhibiting these key pathways, targeted therapies can help slow down disease progression and improve patient outcomes. However, it is important to note that not all patients may respond to these therapies, and resistance can develop over time. Ongoing research efforts are focused on developing novel targeted therapies and combination approaches to overcome resistance mechanisms and improve treatment efficacy for patients with renal-cell cancer.

Therefore, along with the targeted therapies that significantly positively impact both the treatment and prognosis of metastatic RCC patients, early diagnosis certainly plays a key role too, as also reported by The International Metastatic Renal-Cell Carcinoma Database Consortium risk model, which lists it among the risk factors (diagnosis to systemic therapy < 1 year), together with a Karnofsky performance status <80%, corrected calcium > normal, hemoglobin < normal, neutrophil > normal, and platelet count > normal, which may globally help to prognosticate survival in such patients. To date, this model has indicated a median OS of 43.2 months in the group with 0 risk factors, 22.5 months in the group with 1–2 risk factors, and 7.8 months in the risk group exhibiting 3 or more risk factors [199].

This model continues to be used widely today in clinical practice and as a predictive tool for responses to new combinations of immunotherapies. The VEGFR axis has proven to be a key therapeutic target in metastatic RCC, leading to improved outcomes in these risk categories. As translational work has advanced, it has been demonstrated that RCC has a unique immunogenicity that could forever change the treatment landscape

RCC is the third most common malignancy to metastasize to the head and neck region, after lung and breast carcinomas. Oro-facial metastasis is the presenting complaint in 7.5% of patients with RCC [50]. Distant metastases to the oro-facial tissues may involve the jaws, especially the mandible, or the soft tissues, mostly the gingiva and, frequently, the tongue, with a prevalence of 26%, as shown in the current review (Figure 2).

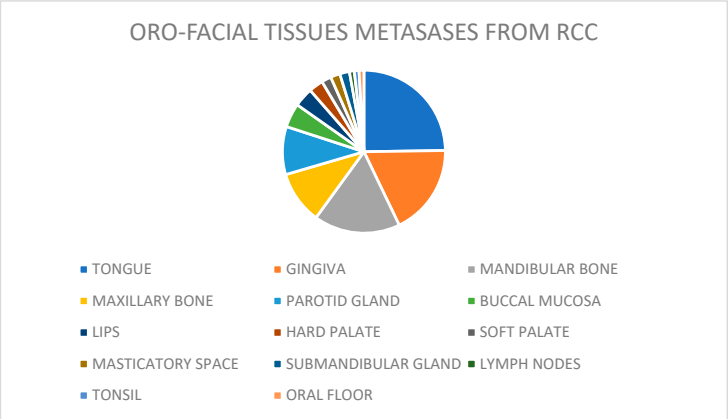

Figure 2. The prevalence of lesions by site of involvement.

4.2. Diagnostic Challenges and Clinical Work-Up

The correct diagnosis of metastatic lesions of the oral cavity represents a challenge for clinicians, especially when the patient has no history of malignant diseases. This literature review shows that in 36.4% of cases (77 of 211 patients affected by oral metastases), the development of an oral metastasis is the first clinical manifestation of a primary tumor.

Gingival lesions are more complex to diagnose because of the presence of several benign conditions that may be potentially included among the differential diagnoses (e.g., pyogenic granuloma, peripheral giant cell granuloma, ossifying fibroma, and fibrous hyperplasia), thus frequently leading to a diagnostic delay. However, clinical signs, such as rapid enlargement or invasion of the underlying bone, may support the diagnosis by excluding an inflammatory origin of the lesion [27]. Among the reactive lesions of the gingiva, fibrous hyperplasia is certainly very common, accounting for up to 40% of the mucosal pathologies in a large case series reported and occurring in a wide age range [200].

Additionally, vascular epulis, also called pyogenic granuloma, is a frequently occurring gingival lesion, usually presenting as soft, bright red swelling, with focal ulceration providing a grey/yellow appearance. It is usually related to trauma or chronic irritation and alterations in sex hormone levels (e.g., puberty, pregnancy, use of oral contraceptive drugs, or hormone replacement therapy). Its clinical presentation, along with easily provoked bleeding after trauma, broadens the spectrum of differential diagnosis, including malignant lesions (such as metastasis) and systemic causes of vascular expansion of the gingiva, such as leukemia and granulomatosis with polyangiitis.

The most common peripheral odontogenic tumors most frequently involve the gingiva, peripheral odontogenic fibroma, and peripheral ameloblastoma (PA). Their occurrence in young adults, slow growth, and clinical presentation (mostly as gingival swelling with intact overlying mucosa) represent important criteria for their differential diagnosis of malignancy. Some suspicion may arise with peripheral ameloblastoma, which can have a variable clinical presentation, showing a granular or erythematous surface [201].

Among malignancies with gingival localization, verrucous carcinoma is the most frequent, and its clinical presentation, usually as white plaque or verrucous lesions, helps clinicians diagnose it. Nevertheless, the occurrence of the most aggressive squamous cell carcinoma in the periodontal tissue should also be considered when occurring with a granular or erythematous appearance, often associated with periodontal and bone invasion and related clinical (bleeding, teeth mobility, and pain) and radiological signs (enlargement of the periodontal space and radio-transparencies). Additionally, the AIDS-related type of Kaposi's sarcoma generally shows gingival manifestation with a reddish appearance (thus mimicking hemangioma, pyogenic granuloma, and giant cell epulis, especially when nodular in appearance) and ulcerated when larger, leading to a differential diagnosis that obviously includes other malignancies. Lastly, the head and neck are the second most common extranodal sites for lymphoma occurrence (11–33%), especially diffuse large B-cell non-Hodgkin lymphoma, with the most common sites affected being the gingiva, mandible, palate, maxilla, and tongue [202,203].

Additionally, the gingiva is frequently affected in patients with acute myeloid leukemia [204]. Although lymphoma and leukemia have nonspecific clinical presentation in the periodontal tissue, they often present with swelling and reddening of the gingival tissues (mimicking gingivitis, periodontitis of different stages, and hyperplastic gingivitis of different etiology when generalized, and pyogenic granuloma or giant cell epulis when swelling is localized), while advanced cases may show signs of malignancy as accompanied by alveolar bone loss and tooth mobility. In such cases, patients frequently have a well-recognized history of generalized/systemic disease, but when still undiagnosed, they represent a challenging situation for clinicians, with the differential diagnoses likely to include several non-neoplastic and neoplastic conditions depending on the extent of the disease at presentation.

The intraosseous presentation of metastasis in the jaw is extremely variable, and consequently, the early diagnosis of jawbone metastasis is the first sign of widespread

neoplastic disease and is more difficult than its counterpart in soft tissues. Its frequent association with decayed or unvital teeth or residual root fragments, periodontitis, peri-implant inflammatory conditions, its possible periapical localization, the nonspecificity of its clinical symptoms (pain, anesthesia, paresthesia, swelling, teeth mobility, gingival bleeding, etc.) and the highly variable combination of them, and the nonspecificity of its radiological signs (usually appearing as a radiolucent area with ill-defined borders, but also as a radiopaque or mixed radiopaque–radiolucent lesion mostly when of prostatic origin) make the spectrum of potential differential diagnoses extremely wide [205].

Metastasis occurrence in the major salivary glands, especially the parotid gland (as the most frequent site of inflammatory and neoplastic salivary gland lesions), is also a true diagnostic dilemma, mainly because most patients manifest the metastasis first and undergo parotid surgery before the primary tumor diagnosis and staging. A further complication is the constant increase in its overall incidence, along with its nonspecific characteristics in radiological examination, generally MRI and US [39].

Metastatic disease of the tongue is likely the most challenging situation to diagnose differently, first due to its general rarity reported in the literature, but mainly for the variability in its clinical presentation. It typically remains asymptomatic but alternatively can present as painful hard masses with or without superficial ulceration due to biting trauma. Therefore, its differential diagnosis is very challenging, and histological examination of sample tissue should be performed quickly to define the tumor and its origin. Tongue lesions also frequently require treatment as they may interfere with vital function (swallowing, biting, breathing, or drinking). Treatment generally comprises total or partial surgical excision combined with adjuvant radiotherapy for local and general disease control [184]. It is worth noting the data on ccRCC occurrence in the tongue among the patients listed in the current review, as its incidence was 31 cases (25.4%).

4.3. Pathological Differential Diagnosis and Imaging

Clinical suspicion always needs to be supported by histology and immunohistochemistry to discriminate renal metastases from other lesions characterized by the histologic presence of clear cells. When occurring in major salivary glands, the differential diagnoses of clear-cell neoplasms include mucoepidermoid carcinoma (MEC) and other salivary gland tumors, such as epithelial–myoepithelial carcinoma, oncocytomas, hyalinizing clear-cell carcinoma (HCCC), and acinic cell carcinoma (ACC). All these tumors may display a clear-cell component [28,29,35]. The differential diagnoses of jawbone metastases include some histological types of odontogenic tumors, which may also display clear cells, such as clear-cell ameloblastoma (CCA), calcifying epithelial odontogenic tumor (CEOT), and clear-cell odontogenic carcinoma (CCOC) [8,10,29]. In particular, immunohistochemistry is extremely important to perform differential diagnoses with clear-cell salivary and odontogenic neoplasms [142]. ccRCC consistently expresses positivity for CD10, cytokeratins AE1/AE3, epithelial membrane antigen (EMA), PAX-8, renal-cell carcinoma antigen (RCCAg), and vimentin. Conversely, ccRCC does not express cytokeratin 7, calretinin, CD117, muscle markers (smooth muscle actin, calponin, and myosin), or glial fibrillary acidic protein (GFAP), usually expressed in salivary gland tumors. Regarding odontogenic tumors, cytokeratins AE1/AE3, cytokeratin 7, and EMA are observable in odontogenic carcinoma, while cytokeratins AE1/AE3 and calretinin are observable in ameloblastoma. However, CD10, PAX8, and RCCAg are consistently negative in all salivary glands, and odontogenic tumors show clear-cell features, allowing for certain differential diagnoses with ccRCC metastasis [184]. Furthermore, clear-cell sarcoma of the kidney may be easily ruled out using immunohistochemistry because it is negative for cytokeratins, EMA, and CD10. Consequently, it is important to highlight that the final diagnosis, together with the exclusion of all the possible differential diagnoses, is only made with certainty after histopathological examination. Hence, biopsy is always mandatory, and the role of the anatomical pathologist is vital in the clinical work-up of patients with oral metastases from ccRCC.

Radiology also plays a fundament role in the diagnosis and characterization of renal masses in the early and pretreatment identification of the most frequent histologic subtypes and the staging of metastatic RCCs. CT and MRI are conventionally used as the first choices in RCC characterization and staging, with the latter having the benefits of no radiation exposure and accuracy in the definition of cystic lesions

As recently reported by Bellin et al. in a 2024 update, remarkable advances in the imaging technology of RCC have been recently introduced, including dual-energy CT, photon-counting detector CT, radiomics, and high-resolution multiparametric MRI [206].

An overall aim is to continuously improve diagnostic performance (the detection of tumors at an earlier stage) both in the preoperative assessment of histologic subtypes and the differential diagnoses among malignant and benign lesions, also with a potential reduction in contrast use and radiation exposure. The use of artificial intelligence in the classification, grade, and prognosis of RCC has also shown encouraging results, leading to accurate detection and diagnosis in a reduced time and help in treatment management.

4.4. Summary of Clinico-Epidemiologic Aspects

From the literature over the past 100 years, we identified that the age at diagnosis ranges from 18 to 89 years. Metastases are more common in men than women (145 versus 61 cases, respectively), mirroring the male predominance of RCC more generally. The majority of RCCs are the clear-cell type. Oral metastases from renal-cell carcinoma involve the soft tissues and jawbones almost equally. The most affected sites are the tongue and gingiva (Figure 1, Table 2). A mass or nodule is the most common clinical manifestation, while pain is the most prevalent symptom. In cases where the bone was affected by metastasis, a radiolucent image was the most reported. Any mass present in the oral cavity should be biopsied and analyzed carefully, as metastatic lesions may resemble clinically benign lesions.

5. Conclusions and Future Directions

The current review of the literature confirms the well-recognized data on the low incidence of metastases in the oro-facial tissues and that their occurrence is mostly related to an advanced stage of disease. We found that in almost 40% of cases, metastases to the oro-facial tissues represented the first clinical manifestation of a still unknown clear-cell renal-cell carcinoma. These data are higher than the overall general incidence for all metastases to the head and neck presenting as the first manifestation of an occult malignancy, generally accounting for about 20–35%. Hence, these tumors seem to predilect oro-facial tissues more than others. Moreover, metastases to the head and neck from clear-cell renal-cell carcinoma can occur at any age, and the prognosis is generally poor.

All collected data highlight the importance of early diagnosis, especially for metastases from clear-cell renal-cell carcinoma in the absence of an already known primary tumor (metastases as the first sign of disease), despite the evident difficulties of their identification both via clinical examination and via conventional (first-grade) radiological investigations. Early clinical identification, with consequential histological definition and TNM staging, along with targeted therapies, may be vital to guarantee better outcomes for patients presenting with metastatic clear-cell renal-cell carcinoma.

Regarding future directions for research on oral metastases from renal-cell carcinoma, further investigation into the underlying mechanisms of metastasis development and progression is crucial. Understanding the specific molecular pathways involved could provide insights into potential targeted therapies. However, it is important to acknowledge the limitations of the current study, including the small sample sizes and lack of long-term follow-up data. To translate these findings into clinical settings, the next step would involve conducting larger-scale clinical trials to validate the effectiveness and safety of any potential treatments identified through research on oral metastases from renal-cell carcinoma. Collaborations among researchers, clinicians, and industry partners will be key to moving toward implementing tailored therapeutic strategies for patients in a clinical setting.

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