

Review

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Posted Date: 26 February 2024

doi: 10.20944/preprints202402.1485.v1

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



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Review

Oro-Facial Metastases from Renal Cell Carcinoma: A Systemic Review of the Literature with Focus on the Clear Cell Variant

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Simple Summary: The current systemic review aims to collect data from literature about the incidence, site of occurrence, age, sex and survival in patients affected by Renal Cell Carcinoma, with peculiar attention to the cases diagnosed as metastases from Clear Cell Renal Cell Carcinoma, which represents the most frequent histological variant. Clinical differential diagnosis has been widely discussed to provide the clinicians all the possibly useful information for an early diagnosis, despite the effective difficulties in recognizing such rare and easily mis-diagnosable lesions.

Abstract. Background: Metastatic tumors to the oro-facial tissues are rare, with an incidence ranging between 1% and 8% of all oral malignant tumors. Generally reported with a peak of incidence in the 5th–7th decades, but possibly occurring at any age, metastases may represent the first sign of an occult cancer or manifest in patient with an already known history of a primary carcinoma, mostly from the lungs, kidney, prostate, and colon-rectum in males, or uterus, breast, lung, and ovary in females. In the oro-facial tissues the sites mostly involved are the oral mucosa, gingiva/jawbones, tongue, and the salivary glands. **Methods:** A systemic Review of the literature on the oro-facial metastases from Renal Cell Carcinoma has been conducted by searching the most used databases, also focusing the attention on the Clear Cell histological variant, representing the most frequent one. **Results:** Among the 160 analyzed studies, 211 cases of oral metastases of renal cancer were found (148 in males, 70.1%; 63 in females, 29.8%), with an average age of 59.8 years. In almost 40% of cases, metastasis represented the first clinical manifestation of the primary tumor and 122 were histologically diagnosed as ccRCCs (57.8%). The tongue was involved in most of the cases (26% - 55 cases), followed by mandible (18.9% - 40 cases), gingiva (18.4% - 39 cases), maxilla (10.9% - 23 cases), parotid gland (10.4% - 22 cases), buccal mucosa (5.2% - 11 cases), lips (3.3% - 7 cases), hard palate (2.8% - 6 cases), soft palate, masticatory space and submandibular gland (0.9% - 2 cases), lymph nodes, tonsil and oral floor (0.4% - 1 case). Among the 122 ccRCCs (84 were 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 involved site (25.4% - 31 cases), followed by the gingiva (17.2% - 21 cases), parotid gland (13.1% - 16 cases), mandibular bone (12.2% - 15 cases), maxillary bone (11.4% - 14 cases), buccal mucosa and lips (4.9% - 6 cases), hard palate (4% - 5 cases), submandibular gland and soft palate (1.6% - 2 cases), lymph nodes, tonsil, oral floor and masticatory space (0.8%. 1 case). The clinical presentation in soft tissues was represented by a fast-growing exophytic mass, sometimes accompanied by pain. Instead in bone appeared as radiolucent lesions, with ill-defined borders and cortical erosion. **Conclusions:** Our data focus the attention on the incidence of Renal cancer Metastases in the oro-facial tissues. Their early identification surely represents a diagnostic challenge, especially when the clinical work-up is limited to the cervico-facial region. Nevertheless, early diagnosis and recently introduced adjuvant therapies may represent the key for better outcomes. Therefore, general guidelines about clinical and radiological identification of oro-facial potentially malignant lesions should be part of the cultural background of any dentists.

Keywords: Metastases; Renal cell Carcinoma; Clear Cell Renal cell carcinoma; oral cavity; head and neck

1. Introduction

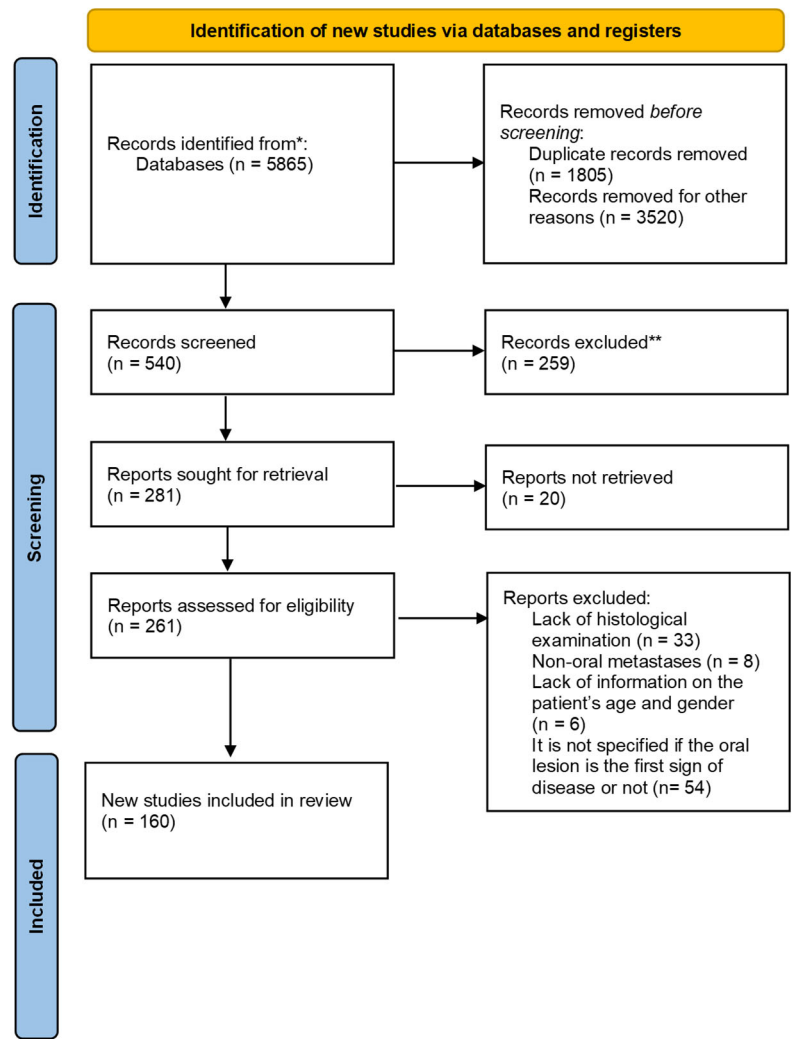
Metastatic dissemination of solid tumors may involve the Head and Neck, including the oral cavity, although infrequently and with an incidence between 1% and 8% of all oral malignant tumors (1–4) and a peak of incidence in the 5th–7th decades (2). Excluding the malignant tumors of the childhood, Oro-Facial Metastases (OFMs) may represent the first sign of an occult or still undiagnosed cancer or 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 and hard tissues or both synchronously, thus including the oral mucosa, jawbones, the salivary glands, the neck lymph nodes; the most frequent primary localization is represented by lung, kidney, prostate and colon-rectum in males, uterus, breast, lung and ovary in females (1,2,8,9), according to the overall incidence rate of each one among general population.

It is generally accepted that the metastatic diffusion shows a predilection for some specific sites in the oro-facial region, regardless the main tissue target of the primary tumor (e.g. bone for prostate cancer) and, additionally, it may be influenced by peculiar clinical conditions, mainly inflammatory conditions of the gingival-periodontal tissues or in edentulous individuals bearing removable prostheses. In such instances, the re-organization of the district blood flow related to the inflammation or induced by the pressure or trauma of the prosthesis, have been postulated to facilitate the metastatic growth (10). The jawbones and more specifically molar and premolar areas are frequently involved in view of their rich vascularization and high bone marrow content. In addition, metastases may develop in residual alveolus after tooth removal (post-extraction sites) probably as consequence of the increased blood flow related to the blood clot formation (1,2,8,10).

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. It occurs predominantly in males and, on average, around the age of 60 (11–17). Several risk factors have been claimed to favor RCC development, in particular an elevated body mass index (18), urinary stones in males (19), type 2 diabetes in females (20), chronic liver and kidney diseases (21) and long-term use of analgesics (22) in addition to environmental factors (23,24). On average, locoregional or distant metastases develop in one third of patients, and recurrence is observed in about 25% of cases with localized renal disease treated with nephrectomy. Metastases of RCC generally involve the lungs, regional lymph nodes, liver, bones, and brain (25). Localization to the oro-facial tissue has been seldom described in the literature. In this region, RCC metastases are relatively rare, with the tongue being predominantly involved, followed by the gingiva and maxillary bones (26,27).

RCC has several recognized histologic variants. In particular, clear cell RCC (ccRCC) (accounting for 70% of cases) (28,29), papillary RCC (pRCC) (10 to 15%), and chromophobe RCC (chRCC) (5%) are the most frequently encountered forms and represent 90% of RCCs (30). Among all, RCC, clear cell type, has a known propensity to metastasize, most commonly via direct invasion of the renal veins and vena cava, with subsequent hematogenous dissemination to the lungs; however, unusual metastatic sites or late metachronous metastases (>10 years) are not infrequent, and distant metastasis may be the first clinical presentation of the tumor (31). Metastatic ccRCC to the OFTs have been occasionally reported (1,2,28,32) and, in some instances, they may represent the initial manifestation of the disease (2,6,7,33), thus representing a true diagnostic dilemma both for clinicians (mainly for the rarity and the early diagnosis) and pathologist; in fact, due to the high glycogen and lipid content, the tumor cells of ccRCC display evident cytoplasmic vacuolization and clearing, mimicking other neoplasms of odontogenic or salivary gland origin that more commonly affect this area (2,28,29,32,34–36). Consequently, the oral localization of an occult ccRCC surely may represent a diagnostic challenge, especially when the clinical work up is still limited to the cervico-facial region (6,7,37–40).

The present study is 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 PRISMA guidelines for systemic review. (Graphic 1)



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

2. Materials and Methods

A systematic review of the literature was conducted intending to provide an overview of the available evidence in reliable databases. The terms “renal metastasis” or “renal metastases” or “clear cell renal cell carcinoma” AND “oral” o “Head and Neck” were alternatively used in searching, restricting their presence to the title of the article in the PubMed, Scopus, Web of Sciences and Google Scholar databases. The search was only limited to the studies on humans. All kind of papers were collected, thus including case report, case series, review of the literature, systematic review of the literature. After introducing the keywords in the databases, a total of 5865 results were obtained. First, the titles of the articles were read, and 540 articles were selected for reading the abstract as all papers reporting duplicate cases were deleted. Of these, 261 articles were chosen for full-text reading. 101 were removed because the lesion was not confirmed as metastasis at theanatomopathological examination or because the metastasis was outside the limits of the Head and Neck, because the gender and the age of the patients were not specified or because it was not proven whether the oral manifestation was the first sign of disease or not. Thus, 160 articles were chosen for inclusion in the present systematic review of the literature. The reading, selection, and analysis of the articles included in this systematic review were performed by a single clinician.

3. Results

In the 160 analyzed studies, 211 cases of oral metastases of renal cancer were found, of which 122 were histologically demonstrated to be ccRCCs (57.8%) at the final diagnosis. The tongue was involved by renal metastases in most of the cases (26% - 55 cases), followed by the mandibular bone (18.9% - 40 cases), gingiva (18.4% - 39 cases), maxillary bone (10.9% - 23 cases), parotid gland (10.4% - 22 cases), buccal mucosa (5.2% - 11 cases), lips (3.3% - 7 cases), hard palate (2.8% - 6 cases), soft palate, masticatory space and submandibular gland (0.9% - 2 cases), lymph nodes, tonsil and oral floor (0.4% - 1 case). Of the 211 total cases, 148 involved males (70.1%) and 63 females (29.8%). Average age was 59.8 years. Average male age was 61.8; average female age was 55.3 (Table 2). In almost 40% of cases, the development of an oral metastasis represented the first clinical manifestation of the primary tumor, which was previously unknown. Data have been globally collected in Table 1, listing Author/authors name, year of publication, site/sites, histological histotype, sex, age, occurrence as first sign of metastatic disease or not.

Table 1. METASTASES OF RENAL CARCINOMA TO THE ORAL CAVITY: REVIEW OF LITERATURE.

AUTHORS	Years	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
Pritchuk et al (50)	2002	Lip	RCC	M	70	Yes
		Maxillary bone	RCC	F	53	
		Tongue	RCC	M	60	
Göğüş et al (51)	2004	Parotid	ccRCC	F	59	No
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
Mazon 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
Nifosi 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
Syrylo 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
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	RCC RCC	F	61	yes
		Gingiva	Transitionalcell	M	72	yes
		Mandibular	cR	M	61	no
		bone	RCC	F	36	yes

Mandibular bone						
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	RCC	M	48	No
		Maxillary bone	RCC	F	73	No
		Mandibular bone	Reticulumcell sarc.	M	43	No
		Mandibular bone	RCC	M	57	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	ccRCC	F	61	yes
		Hard palate	ccRCC	F	43	
Susan et al (118)	1979	Hard palate	ccRCC	M	53	yes
		Hard palate	ccRCC	M	62	yes
Matsumoto and Yanagihara (119)	1982	Maxillary bone	ccRCC	M	73	yes
		Maxillary bone	ccRCC	M	48	yes
Pick et al (120)	1986	Mandibular bone	ccRCC	M	71	Yes
Florine et al (121)	1988	Mandibular bone	Clear cell sarcoma	M	15 m.	No
Zachariades et al (122)	1989	Mandibular bone	RCC	M	78	No
Jones and al (123)	1990	Mandibular bone	ccRCC	F	62	yes
		Mandibular bone	ccRCC	F	52	yes
Fandella et al (124)	1992	Maxillary bone	ccRCC	M	62	Yes
Lee et al (125)	1998	Maxillary bone	RCC	M	76	Yes
Guyot et al (126)	1999	Mandibular bone	RCC	M	83	No
Toranzo-Fernandez et al (127)	2000	Mandibular bone	Clear cell sarcoma	M	8	Yes
Honig (128)	2000	Maxillary bone	RCC	M	46	No
Shetty et al (129)	2001	Mandibulr bone	RCC	M	62	Yes
Heinroth et al (130)	2006	Maxillary bone	ccRCC	F	53	yes
Đanić et al (26)	2018	Tongue	RCC	M	51	yes
Madison and Frierson (131)	1988	Tongue	ccRCC	M	29	No
		Tongue	ccRCC	M	63	No
Kishore et al (132)	2018	Lip	ccRCC	M	54	No

Abro et al (133)	2019	Tongue	RCC	M	54	No
Netto et al (134)	2019	Gingiva	RCC	M	68	Yes
Walsh et al (135)	2022	Tongue	ccRCC	M	63	No
Mrena et al (136)	2008	Parotid	ccRCC	F	58	Yes
		Parotid	RCC	F	76	No
		Parotid	RCC	F	62	No
Aljawad et al (137)	2023	Parotid	ccRCC	M	65	No
Migliorelli et al (138)	2023	Maxillary bone	ccRCC	F	54	Yes
Maschino et al (139)	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 (140)	2022	Soft palate	ccRCC	M	50	No
Ludwig et al (141)	2020	Mandibular bone	ccRCC	M	78	Yes
Melnick et al (142)	1989	Parotid	ccRCC	M	72	Yes
Borghi et al (143)	1995	Parotid	ccRCC	M	68	No
Seijas et al (144)	2005	Parotid	ccRCC	M	67	Yes
Goel et al (145)	2003	Tongue	ccRCC	M	62	Yes
Lenkeit et al (146)	2020	Tongue	RCC	M	71	No
Ruiz-Oslé et al (147)	2017	Parotid				
		Mandibular	RCC	M	72	yes
		bone	RCC	M	55	yes
		Gingiva	RCC	M	62	yes
		Masticatory space	RCC	F	52	no
Doykos (148)	1969	Mandibular bone	Wilm’s Tumor	F	9	Yes
Schwab and Lee (149)	2012	Maxillary bone	ccRCC	M	63	No
Erkilic et al (150)	2017	Gingiva	Collecting duct adenocarcinoma	F	54	Yes
Lee and Lee (151)	2017	Mandibular bone	RCC	M	62	No
Guimarães et al (152)	2016	Gingiva	ccRCC	F	31	No
Owosho et al (153)	2016	Mandibular bone	RCC	F	61	No
		Mandibular bone	RCC	F	63	No
		Mandibular bone	RCC	F	18	No
		Gingiva	RCC	M	75	No
		Buccal mucosa	RCC	M	70	No
		Buccal mucosa	RCC	M	59	No
		Gingiva	RCC	M	66	No
		Buccal mucosa				
Nisi et al (154)	2020	Tongue	ccRCC	M	61	yes
		Buccal mucosa	ccRCC	M	71	yes
Lang et al (155)	2003	Tongue	ccRCC	M	45	No
Bucin et al (156)	1982	Gingiva	RCC	M	65	No
Marioni et al (157)	2004	Tongue	ccRCC	F	87	No
Van der Wall et al (158)	2003	Soft palate	ccRCC	F	62	No
		Maxillary bone	ccRCC	F	64	No
		Mandibular bone	ccRCC	M	48	No
			ccRCC	M	67	No

Buccal mucosa						
Fukuda et al (159)	2002	Mandibular bone	RCC	M	76	No
Makos and Psomaderis (27)	2009	Gingiva	ccRCC	M	63	No
Dehner (160)	1973	Mandibular bone	Wilm’s Tumor	F	6	No
Morii (161)	1975	Buccal mucosa	ccRCC	M	63	No
Sidhu (162)	1982	Mandibular bone	RCC	F	32	Yes
Sánchez Aniceto et al (163)	1990	Mandibular bone	RCC	M	54	Yes
Maestre-Rodríguez et al (164)	2009	Gingiva	ccRCC	M	52	Yes
Will et al (165)	2008	Floor of mouth	ccRCC	M	63	no
Nesbitt et al (166)	2019	Gingiva	Sarcomatoid RCC	M	59	Yes
Patel et al (167)	2020	Gingiva	ccRCC	F	59	yes
Narea-Matamala et al (168)	2008	Gingiva	RCC	M	74	yes
Massaccesi et al (169)	2009	Tonsil	ccRCC	M	76	yes
Shinozaki et al (170)	2009	Mandibular bone	ccRCC	F	76	No
Ohmura et al (171)	1981	Mandibular bone	ccRCC	M	53	No
Nakano et al (172)	2013	Gingiva	ccRCC	M	72	No
Ficarra et al (173)	1996	Wharton’s duct	ccRCC	M	73	No
Tunio et al (174)	2012	Tongue	ccRCC	M	35	No
Milner et al (175)	2014	Hard palate	ccRCC	M	67	Yes
Santana et al (176)	2000	Gingiva	ccRCC	M	63	Yes
Kizaekka et al (177)	2019	Tongue	ccRCC	M	77	No
Paraskevopoulos et al (178)	2021	Mandibular bone	ccRCC	M	72	Yes
Morita et al (179)	2018	Buccal mucosa	ccRCC	M	75	No
Prol et al (180)	2019	Mandibular bone	ccRCC	M	55	No
		Gingiva	ccRCC	M	62	No
		Gingiva	ccRCC	F	52	No
		Mandibular bone	chRCC	M	56	No
		Masticatory space	ccRCC	M	65	No
Shimono et al (181)	2021	Mandibular bone	RCC	M	62	Yes
		Maxillary bone	RCC	M	89	No
		Tongue	RCC	M	63	no
Ali and Mohamed (182)	2016	Gingiva	ccRCC	M	60	Yes
Selvi et al (183)	2016	Gingiva	ccRCC	M	51	No
Jatti et al (184)	2015	Lip	ccRCC	M	60	No
Sikka et al (185)	2013	Gingiva	ccRCC	M	73	Yes
Ganini et al (186)	2012	Tongue	ccRCC	M	70	No

Lutcavage et al (187)	1984	Hard palate	RCC	M	55	No
Azam et al (188)	2008	Tongue	ccRCC	M	78	Yes
Basely et al (189)	2009	Tongue	ccRCC	F	46	No
Ahmadnia et al (190)	2013	Mandibular bone	ccRCC	M	57	Yes
Ord et al (191)	1990	Maxillary bone	RCC	M	58	
		Maxillary bone	RCC	M	73	yes
Capodiferro et al (192)	2020	Gingiva				
		Tongue	ccRCC	F	69	No
		Mandibular bone	ccRCC	M	56	No
			ccRCC	M	45	No
		Mandibular bone	ccRCC	M	63	No
			ccRCC	M	55	No
		Parotid	ccRCC	F	55	No
		Parotid	ccRCC	M	60	No
Andabak Rogulj et al (193)	2018	Mandibular bone				
		Maxillary bone				
		Maxillary bone	ccRCC	M	65	No
		Mandibular bone	ccRCC	M	58	No
			RCC	F	64	No
		Maxillary bone	RCC	M	61	No
Derakhshan et al (194)	2018	Mandibular bone	RCC	F	68	No
		Maxillary bone	ccRCC	M	54	yes
		Maxillary bone	ccRCC	M	51	yes
Altuntaş et al (195)	2014	Tongue	pRCC	M	70	No
Amiruddin and Yunus (196)	2013	Tongue	ccRCC	M	66	No

Table 2. DATA ANALYSIS OF ORO-FACIAL METASTASES OF RENAL CELL CARCINOMA.

SITE	CASES	
tongue	55	26%
mandibular bone	40	18.9%
gingiva	39	18.4%
maxillary bone	23	10.9%
parotid gland	22	10.4%
buccal mucosa	11	5.2%
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	148	70.1%

female	63	29.85%
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Focusing on the numbers of the most frequent histotype (ccRCC) we see that 122 cases of oral metastases of ccRCCs the tongue was involved in most cases (25.4% - 31 cases), followed by the gingiva (17.2% - 21 cases), parotid gland (13,1% - 16 cases), mandibular bone (12.2% - 15 cases), maxillary bone (11.4% - 14cases), buccal mucosa and lips (4.9% - 6 cases), hard palate (4% - 5 cases), submandibular gland and soft palate (1.6% - 2 cases) and lymph nodes, tonsil, oral floor and masticatory space (0.8%. 1 case). It is clear that soft tissues are more affected by ccRCC metastases than hard tissues.

Focusing on the numbers of the most frequent histotype (ccRCC) we found the tongue was involved in most cases (25.4% - 31 cases), followed by the gingiva (17.2% - 21 cases), parotid gland (13,1% - 16 cases), mandibular bone (12.2% - 15 cases), maxillary bone (11.4% - 14cases), buccal mucosa and lips (4.9% - 6 cases), hard palate (4% - 5 cases), submandibular gland and soft palate (1.6% - 2 cases) and lymph nodes, tonsil, oral floor and masticatory space (0.8%. 1 case). It is clear that soft tissues are more affected by ccRCC metastases than hard tissues. Of the 122 total cases, 84 are male (68.8 %) and 38 are female (31.1%). Average age is 60.8 years. Average male age is 61.7; average female age is 59. In almost 33.6% of cases, the development of an oral metastasis is the first clinical manifestation of the primary tumor. Clinical presentations vary depending on the affected tissue: at the level of soft tissues, metastases frequently present as fast-growing and exophytic masses, accompanied or not by pain; bone’s 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.

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	-
Mazon 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	-
Nifosi 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	Hemorrhagic mass	-
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
Mallet (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	F	61	yes	Swelling	Osteolytic area
	Hard palate	F	43		Palate's perforation	NA
Susan et al (118)	Hard palate	M	53	yes	Swelling	NA
	Hard palate	M	62	yes	Pedunculated lesion	NA
Matsumoto and Yanagihara (119)	Maxillary bone	M	73	yes	Cheek's swelling epistaxis	Osteolytic area
	Maxillary bone	M	48	yes		NA
Pick et al (120)	Mandibular bone	M	71	Yes	Swelling	mixed radiolucent and radiopaque lesion
Jones and al (123)	Mandibular bone	F	62	yes	Swelling	osteolytic area
	Mandibular bone	F	52	yes	Swelling	osteolytic area
Fandella et al (124)	Maxillary bone	M	62	Yes	epistaxis	NA
Heinroth et al (130)	Maxillary bone	F	53	yes	Painful swelling	opacity in the maxillary sinus
Madison and Frierson (131)	Tongue	M	29	No	NA	-
	Tongue	M	63	No	NA	-
Kishore et al (132)	Lip	M	54	No	swelling	-
Walsh et al (135)	Tongue	M	63	No	Pedunculated lesion	-
Mrena et al (136)	Parotid	F	58	Yes	Non-tender nodule	-
Aljawad et al (137)	Parotid	M	65	No	Non-tender mass	-
Migliorelli et al (138)	Maxillary bone	F	54	Yes	Facial pain	Bone erosion
Maschino et al (139)	Maxillary bone	M	73	No	Exophytic mass	Osteolytic lesion
	Maxillary bone	F	84	No	Pain, discomfort	NA
	Parotid	M	78	No	Rapid growth mass	NA
Wallace et al (140)	Soft palate	M	50	No	Globular lesion	-
Ludwig et al (141)	Mandibular bone	M	78	Yes	Painful swelling and paresthesia	NA
Melnick et al (142)	Parotid	M	72	Yes	Parotid mass	-
Borghi et al (143)	Parotid	M	68	No	Painless swelling	-
Seijas et al (144)	Parotid	M	67	Yes	Painless mass	-
Goel et al (145)	Tongue	M	62	Yes	Swelling	-
Schwab and Lee (149)	Maxillary bone	M	63	No	Bilateral, friable masses with a foul odor	NA
Guimarães et al (152)	Gingiva	F	31	No	Painful growth	Enlargement of the periodontal ligament
Nisi et al (154)	Tongue	M	61	yes	Swelling	-
	Buccal mucosa	M	71	yes	Large mass	-
Lang et al (155)	Tongue	M	45	No	Pedunculated mass	-
Marioni et al (157)	Tongue	F	87	No	Exophytic, ulcerated mass	-
Van der Wall et al (158)	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 (161)	Buccal mucosa	M	63	No	NA	-
Maestre-Rodríguez et al (164)	Gingiva	M	52	Yes	Granulomatous gingival lesion	-
Will et al (165)	Floor of mouth	M	63	no	Indurated mass	-
Patel et al (167)	Gingiva	F	59	yes	pink-red, oval, ulcerated lesion with a white pseudomembranous surface	-
Massaccesi et al (169)	Tonsil	M	76	yes	dysphagia	-
Shinozaki et al (170)	Mandibular bone	F	76	No	swelling	Multilocular bone destruction
Ohmura et al (171)	Mandibular bone	M	53	No	NA	NA
Nakano et al (172)	Gingiva	M	72	No	swelling	-
Ficarra et al (173)	Wharton's duct	M	73	No	Movable mass in the floor of the mouth	-
Tunio et al (174)	Tongue	M	35	No	Painless swelling	-
Milner et al (175)	Hard palate	M	67	Yes	Irregularly shaped lump	none
Santana et al (176)	Gingiva	M	63	Yes	Double lobe nodule	Radiolucent lesion
Kizaekka et al (177)	Tongue	M	77	No	Pedunculated lesion	-
Paraskevopoulos et al (178)	Mandibular bone	M	72	Yes	NA	-
Morita et al (179)	Buccal mucosa	M	75	No	Swelling and facial asymmetry	-
Prol et al (180)	Mandibular bone	M	55	No	Mass	NA
	Gingiva	M	62	No	Mass	-
	Gingiva	F	52	No	NA	-
	Masticatory space	M	65	No	Mass	NA
Ali and Mohamed (182)	Gingiva	M	60	Yes	Gingival mass	Erosive bone changes
Selvi et al (183)	Gingiva	M	51	No	Rapidly progressive, painless exophytic lesion	Destruction of the alveolar bone
Jatti et al (184)	Lip	M	60	No	Ulcerated nodule	-
Sikka et al (185)	Gingiva	M	73	Yes	Multiple painless swelling	-
Ganini et al (186)	Tongue	M	70	No	Ulcerated lesion	-

Azam et al (188)	Tongue	M	78	Yes	Pedunculated lesion, difficulty in swallowing solid	-
Basely et al (189)	Tongue	F	46	No	Swelling on the left side of the neck	-
Ahmadnia et al (190)	Mandibular bone	M	57	Yes	Swelling, trismus	Radiolucent lesion
Capodiferro et al (192)	Gingiva	F	69	No	Large fungating mass	Bone rarefaction
	Tongue					
	Mandibular bone	M	56	No	Large fungating mass	-
	Mandibular bone	M	45	No	-	Osteolytic area
	Parotid	M	63	No	-	Osteolytic area
	Parotid	F	55	No	growing mass	-
	Parotid	M	55	No	growing mass	-
	Mandibular bone	M	60	No	-	Osteolytic area
Andabak Rogulj et al (193)	Maxillary bone	M	65	No	Mobility of tooth	NA
	Maxillary bone	M	58	No	Exophytic lesion	NA
Derakhshan et al (194)	Maxillary bone	M	54	yes	Pain and swelling	intraosseous
	Maxillary bone	M	51	yes	Polypoid mass	radiolucency
Amiruddin and Yunus (196)	Tongue	M	66	No	Painless mass	-

4. Discussion

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. (114,158) 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 (28,33,197). According to the recent review of Kase AM et al. (198) statistic data a 70% five-year survival for patient with regional disease which drastically decreased to 13% for those showing distant metastases. Such data highlights the importance of the early detection of metastatic lesions which can be difficult in absence of signs and/or symptoms in the whole organism with the exclusion of the oro-facial tissue which, conversely are relatively affordable due to the facility of clinical exploration and/or the frequent use of dental panoramic radiogram and/or CT for dental therapies over the life, at least in the occidental countries.

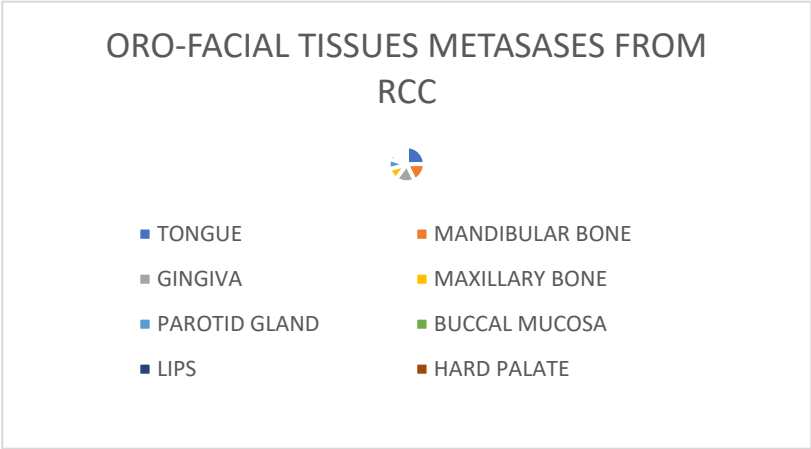
Generally, in the oral cavity, large and/or rapidly growing swellings in the tongue and periodontal tissue, as well unpredictable tooth mobility or gingiva-periodontal inflammation (including the peri-implant hard and soft tissues) surely represent clinical signs of possible malignancy (and consequently 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 the anatomopathological confirmation by hard or soft biopsy which represent the true key for the early and the differential diagnosis. In fact, data reported by Schütz V. et al. in a recent review on Stage T1N0M1 RCC, evaluate by comparison the long-term survival of 27 patients with ccRCC stage T1N0M1 in comparison to 18 patients without distant metastases also by using the immunohistochemistry staining for CD8+ tumor infiltrating lymphocytes; authors concluded, as

expected, that, at the same T1N0 conditions, M1 patients showed a significantly worse median cancer specific survival of 2.8 years, in contrast to the M0 patients with a value of 17.7 years and, additionally, number of CD8+ TILs was substantially higher in stage M1 compared to M0 ccRCC patients, thus obviously suggesting a more aggressive tumor biology; but, interesting, they also described a survival rate much higher than average (over five years) in the 29.6% of their T1N0M1 patients (eight patients) and three of those survived over a decade thanks to an intensified and multimodal treatment including metastasis-directed therapy (199).

Therefore, along with the targeted therapies which significantly impact positively both in treatment and prognosis of metastatic RCC patients, the early diagnosis surely plays a key rule too, as reported also by The International Metastatic Renal Cell Carcinoma Database Consortium risk model listing it among the risk factor (diagnosis to systemic therapy< 1 year), together with Karnofsky performance status < 80%, corrected calcium > normal, hemoglobin < normal, neutrophil > normal, and platelet count > normal, which globally may help to prognosticate survival in such patients. To date, this model indicated a median OS of 43.2 months in 0 risk factors group, 22.5 months in the 1–2 risk factors group, and 7.8 months in the poor risk group exhibiting 3 or more risk factors (200).

This model continues to be used widely today in clinical practice and as a predictive tool for responses to new combinations of immunotherapies. VEGFR axis has proven to be a key therapeutic target in metastatic RCC leading to improved outcomes in these risk categories. As translational work advanced, it was demonstrated that RCC has a unique immunogenicity that would forever change the treatment landscape (Figure 2).

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 gingiva and frequently the tongue as emerging from the current review with a prevalence of 26 % (Graphic 2).



Graphic 2 showing the prevalence of lesions by site of involvement.

The correct diagnosis of metastatic lesions of the oral cavity represents a challenge for the clinician, 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 the primary tumor.

The gingival lesions are more complex to diagnose a 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, and ossifying fibroma, 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, the Fibrous Hyperplasia is surely very common accounting for up to 40% of mucosal pathology in large series reported and occurring in a wide age range (201).

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

The most common Peripheral Odontogenic Tumors frequently involving the gingiva, peripheral odontogenic fibroma and peripheral ameloblastoma are the most frequent (PA) occurring most commonly; their occurrence in young-adults, the slow growth, and the clinical presentation mostly as gingival swelling with intact overlying mucosa surely represent important criteria for the differential diagnosis from malignancy; some suspicion may arise with peripheral ameloblastoma which can have a variable clinical presentation showing a granular or erythematous surface (202).

Among malignancies with gingival localization, the verrucous carcinoma surely represent the most frequent, although its clinical presentation usually as white plaque or verrucous lesion helps clinicians in diagnosing it; nevertheless, the occurrence of most aggressive squamous cell carcinoma in the periodontal tissue should be consider too mainly when occurring with granular or erythematous aspect often associated to periodontal and bone invasion and the related clinical (bleeding, teeth mobility, pain) and radiological signs (enlargement of the periodontal space, radio-transparencies). Additionally, the AIDS-related type of Kaposi's Sarcoma may show gingival manifestation generally with reddish appearance (thus mimicking mainly hemangioma, pyogenic granuloma and giant cell epulis especially when nodular in appearance) but also ulcerated when of larger dimension leading to a differential diagnosis obviously including other malignancies. Lastly, the head and neck represent the second most common extra-nodal site 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 (203, 204).

Additionally, the gingiva is frequently affected in patients with acute myeloid leukemia (205). Although Lymphoma and leukemia have a non-specific clinical presentation in the periodontal tissue, 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 swellings are localized) while advanced cases may show sign of malignancy as accompanied by alveolar bone loss and tooth mobility; in such cases patients have frequently a well-recognized history of generalized/systemic disease but when still undiagnosed surely represent a challenging situation for the clinicians with the differential diagnosis is likely to include several non-neoplastic and neoplastic conditions depending on the extent of disease at presentation.

Also the intraosseous presentation of metastasis in the jaws is extremely variable and consequently the early diagnosis of jawbone metastasis both as first sign diffuse neoplastic or not disease is more difficult than their counterpart of the soft tissues; the frequent association with decayed or unvital teeth or residual root fragments, periodontitis, peri-implant inflammatory conditions, the possible periapical localization, the un-specificity of the clinical symptoms (pain, anesthesia, paresthesia, swelling, teeth mobility, gingival bleeding, etc.) and the highly variable combination of them, the un-specificity of the radiological signs (as usually appearing as 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 the potential differential diagnosis extremely wide (206).

Metastasis occurrence in the major salivary glands and especially in the parotid gland (as the most frequent site of inflammatory and neoplastic salivary gland lesions) also represents a true diagnostic dilemma mainly because the majority of patients manifest the metastasis first and undergo parotid surgery before the primary tumor diagnosis and staging; also, a further complication is the

constant increasing of their overall incidence along with the un-specific characteristics on the radiological examination, generally MRI and US (207).

Probably, the tongue involvement by metastatic disease represents the most challenging situation to differently diagnose, first for the rarity generally reported in literature but mainly for the variability of the clinical presentation as they typically remain asymptomatic, but alternatively could present as painful hard masses with or without superficial ulceration due to biting trauma; as so, the differential diagnosis is very challenging and the histological examination of sample tissue should be performed soon to define the tumor and its origin. Also, tongue lesions frequently required treatment as may interfere with vital function (swallowing, biting, breathing, drinking) which generally is a total or partial surgical excision combined to adjuvant radiotherapy for local and general disease control (208). Of note is the data about ccRCC occurrence in the tongue among patients list in the current review as its incidence represents the 25.4% - 31 cases.

The 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 diagnosis of clear cell neoplasms includes 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 diagnosis of jawbone metastases also includes 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 diagnosis with clear cell salivary and odontogenic neoplasms (144). ccRCC consistently express positivity for CD10, cytokeratins AE1/AE3, Epithelial Membrane Antigen (EMA), PAX-8, Renal Cell Carcinoma Antigen (RCCAg) and vimentin. Conversely, ccRCC do not express cytokeratin 7, calretinin, CD117, muscle markers (smooth muscle actin, calponin, myosin) and Glial Fibrillary Acidic Protein (GFAP). Comparatively, all salivary gland tumors show immunoreactivity for cytokeratin 7, cytokeratins AE1/AE3 and EMA, with fainter and less diffuse positivity for cytokeratin 7 in epithelial-myoepithelial carcinoma (EMEC), hyalinizing clear cell carcinoma (HCCC) and myoepithelioma, for cytokeratins AE1/AE3 in myoepithelioma, and for EMA in HCCC and myoepithelioma. Muscle markers (smooth muscle actin, calponin, myosin) may be expressed in adenoid cystic carcinoma, EMEC, myoepithelioma and pleomorphic adenoma. CD117 is usually expressed in a strong and diffuse manner in adenoid cystic carcinoma and EMEC and, with a lower extension, in mucoepidermoid carcinoma and pleomorphic adenoma. GFAP is diffusely expressed in pleomorphic adenoma and only focally observable in EMEC and myoepithelioma. Calretinin may be occasionally expressed in a minority of acinic cell carcinomas, usually in few tumor cells. As regards odontogenic tumors, cytokeratins AE1/AE3, cytokeratin 7 and EMA are observable in odontogenic carcinoma, while cytokeratins AE1/AE3 and calretinin in ameloblastoma. However, CD10, PAX8 and RCCAg are consistently negative in all salivary glands and odontogenic tumors showing clear cell features, allowing certain differential diagnosis with ccRCC metastasis (192). Furthermore, though for speculative purposes only, clear cell sarcoma of the kidney should be considered in the differential diagnosis, at least in pediatric patients, being the second most common malignant tumor in children. This tumor may be easily ruled out by immunohistochemistry, because is negative for cytokeratins, EMA and CD10 (121,127). Consequently, it is important to highlight that the final diagnosis, together with the exclusion of all the possible differential diagnosis, is only made with certainty after histopathological examination. Hence, the biopsy is always mandatory, and role of the anatomical pathologist is vital in the clinical work up of patients with oral metastases from ccRCC.

From the literature over the past 100 years, we identified that the age at diagnosis ranged from 18 to 89 years. Metastases are more common in men than women (148 versus 63 cases, respectively), mirroring the male predominance of RCC more generally. The majority of RCC are clear cell type. Oral metastases from renal cell carcinoma can involve soft tissues and jawbones almost equally. The most affected sites are tongue and mandibular bone (Graphic 1, Table 2). The mass or nodule was the

most common clinical manifestation, while pain was the most prevalent symptom. In cases where 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

The current review of the literature confirms the well-recognized data about the low incidence of metastases in the oro-facial tissues and that the occurrence is mostly related to an advanced stage of disease. We found that in almost the 40% of cases the oro-facial tissues, metastases represented the first clinical manifestation of a still unknown clear cell renal cell carcinoma; this data is higher than the overall general incidence for all metastases to the head and neck presenting as first manifestation of an occult malignancy, generally accounting for about 20–35%. Hence, this tumor seems 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 metastasis from clear cell renal cell carcinoma in absence of an already known primary tumor (metastases as first sign of disease), despite the evident difficulties of their identification both by clinical examination and conventional (first grade) radiological investigations. The early clinical identification, with consequent histological definition and TNM staging, along with targeted therapies, may be vital in order to guarantee better outcomes for patients presenting with metastatic clear cell renal cell carcinoma.

Author Contributions: “Conceptualization, S.C.; methodology, V.G., A.L.F.; validation, C.C., G.F.; resources, M.F., D.D.V., G.I.; data curation, V.G., A.D.A., A.M.; writing—original draft preparation, S.C., V.G.; writing—review and editing, S.C., M.F.; supervision, S.C. All authors have read and agreed to the published version of the manuscript.

Funding: “This research received no external funding”.

Institutional Review Board Statement: Not applicable”.

Informed Consent Statement: Not applicable.”.

Data Availability Statement: Data collected in the current study have been downloaded by the following databases: PubMed, Scopus, Web of Sciences and Google Scholar.

Conflicts of Interest: “The authors declare no conflicts of interest”.

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