Review Article

Renal cell carcinoma metastasizing to salivary glands: Systematic review

ABSTRACT

Distant metastasis to salivary glands is a very rare event. Renal cell carcinoma (RCC) has been known for its high propensity of metastasis to unusual locations and salivary glands are one among those sites. Approximately 0.1% of all salivary gland metastatic neoplasms originate from renal malignancies Literature has reported several studies analysing the metastatic tumors to the oral region. However, very little research work has been published to date to analyse solely the RCC metastasizing to the salivary glands. Thus, this review was conducted to examine the published cases of RCC metastasizing to salivary glands in the literature to date and to learn about their characteristics. An electronic search of the published literature was performed without publication year limitation in PubMed/ Medline, Scopus, Google Scholar, Web of Science, Science Direct, Embase, and Research Gate databases, using mesh keywords like ('Renal cancer', OR 'Renal carcinoma' OR 'Renal cell cancer' OR 'Renal cell carcinoma'), AND ('Metastasis' OR 'Metastases'), And ('Salivary glands' OR 'Parotid gland' OR 'Submandibular gland' OR 'Sublingual gland'). We also searched all related journals manually. The reference list of all articles was also checked. Our research revealed a total of 83 relevant papers (1965-2022) with 100 patients. Parotid was the most predominant gland affected. 8% of patients died with a mean survival time of 1.3 yr. From this research, it can be concluded that RCC metastasizing to salivary glands is a rare occurrence. Careful evaluation of these cases is needed in order to raise awareness of these lesions and gain a better understanding of their characteristics for clinical as well as global implications.

Keywords: Metastasis, parotid, renal cell carcinoma, salivary glands

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INTRODUCTION

Distant metastasis to salivary glands (SG) is very uncommon and most often associated with primary malignancies of the skin. Only 1–4% of all salivary gland tumors (SGTs) manifest with metastasis.[1] Carcinomas of the breast, lungs, kidneys, and prostate are those primaries that may also potentially metastasize to SG. Renal cell carcinoma (RCC) is the seventh most common histological type of cancer in the Western world, originating from the proximal renal tubular epithelium. Worldwide, 403,000 new cases of RCC and 175,000 deaths due to this malignancy were recorded in 2018.[2] In India, the incidence of RCC among males is about 2/100,000 population, and among females is about 1/100,000 population.[3] One of the unique features of RCC is its long-term asymptomatic clinical behavior and high risk of distant organ metastasis in the advanced stages. Only in 10% of patients, the "classic

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triad" of symptoms, that is, hematuria, flank pain, and palpable masses has been noticed.[4] Approximately 18% of patients with RCC have metastasis at the time of diagnosis, and in >50% of cases, metastasis is detected during the follow-up period after nephrectomy.[5] The most common organs involved in distant metastasis of RCC are the lungs, bones, lymph nodes, liver, adrenal glands, and brain.[6] The head and neck are the rare sites of RCC metastasis (8–14%), and when it occurs, the thyroid is the most affected organ. RCC has been known for its high propensity of metastasis to unusual locations and SG is one among those sites. Approximately 0.1% of all SG metastatic neoplasms originate from renal malignancies and parotid is the most common SG involved.[1] Literature has reported several studies analyzing metastatic tumors in the oral region.[7,8] However, very little research work has been published to date to analyze solely the RCC metastasizing to the SG. Thus, this review was conducted to examine the published cases of RCC metastasizing to SG in the literature from 1965 to 2022 and learn about their characteristics. Thus, analyzing the occurrence of such cases in the general population will make clinicians and pathologists aware of the diagnosis of these cases, leading to timely management.

MATERIALS AND METHODS

The current research was carried out following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Owing to the nature of the current review, any ethical approval was not required.

Focused question

To conduct the study, CoCoPop (context, condition, population) framework, designed by Joanna Briggs Institute, was used focusing on the research question "How many cases of RCC metastasizing to SG have been documented in the literature, and what is the prognosis of these metastatic lesions?"

Pop (Population): Patients with RCC

Co (Condition): Salivary gland metastasis

Co (context): Characteristics of these patients.

Search strategy for identification of studies [Figure 1]

An electronic search of the published literature was performed without publication year limitation in PubMed/Medline, Scopus, Google Scholar, Web of Science, Science Direct, Embase, and Research Gate databases, using mesh keywords like ('Renal cancer', OR 'Renal carcinoma' OR ' Renal cell cancer' OR 'Renal cell carcinoma'), AND ('Metastasis' OR 'Metastases'), And ('Salivary glands' OR 'Parotid gland' OR 'Submandibular gland' OR 'Sublingual gland'). We also searched all related journals manually. The reference list of all articles was also checked.

Screening of studies

The current review involved three steps of screening the studies. In the first step, titles were reviewed by two authors (SG, KHAA) independently and duplicates were removed. Then the other four authors (RLOE, MP, JPSC, SS) reviewed the selected abstracts of all the reports independently. The reviewers were calibrated on the basis of their assessment of their titles and abstracts of the first 50 references retrieved. The kappa value of agreement between reviewers was 0.82. If the title/ abstracts met the eligibility rule, they were included in the study. In the final stage, the text of selected studies was screened by remaining two authors (KQ, ABY) separately. The full report was collected, discussed, and resolved for cases among all authors that appeared to fit the inclusion criteria or for which evidence was insufficient to make a clear determination.

Inclusion criteria

- Confirmed cases of RCC metastasizing to SG. The papers included were from 1965 to 2022.
- Type of studies: Case reports, case series, retrospective analysis, clinicopathological studies, prospective studies, original research, and systematic reviews
- Cases were selected beyond the restriction of limitations on parameters such as age, gender, ethnicity, and socioeconomic status.
- Articles published in any language were included.

Exclusion criteria

- Cases with no definite diagnosis of RCC metastasizing to SG.
- Publications reporting SG metastasis from any site other than the kidneys.
- Cases with RCC metastasizing to jaw bones were not included.
- Studies that did not provide individual patient data were excluded.
- Editorials, conference abstracts, hypothesis papers, web news, media reports, and animal studies.

Outcome measures

2.6.1. Primary outcome measures: To evaluate the number of cases of RCC metastasizing to SG reported in the literature and determine their prognosis.

2.6.2. Secondary outcome measures: To evaluate other factors such as worldwide distribution of cases, patient's demographic details, associated risk factors, predominant site of SG metastasis, clinical features of these metastatic

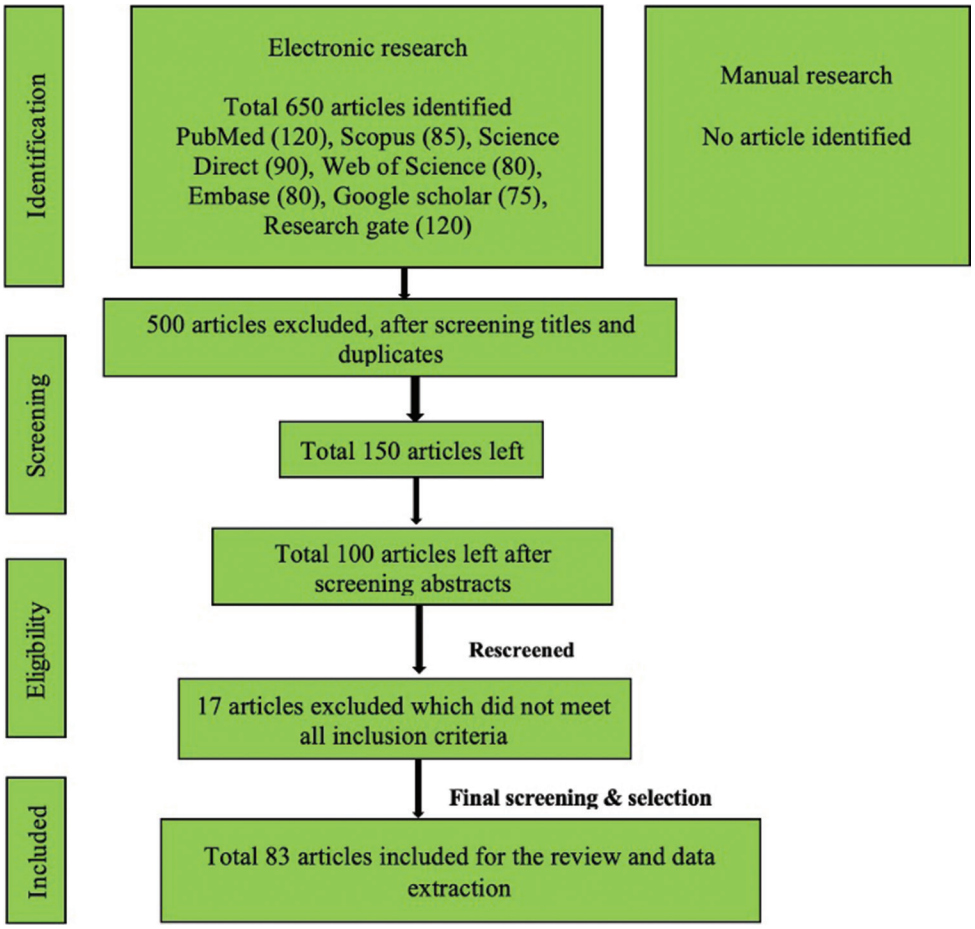

Figure 1: PRISMA flowchart showing search strategy

lesions, most prevalent type of metastatic RCC, and type of therapies used.

Risk of bias assessment

Most studies included in this review were case reports and case series. The risk of bias was appraised following the CARE and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklists.[9,10] In several papers, there was missing information regarding many parameters used for data extraction. We tried reaching the authors of those cases to clarify this bias; however, we were unable to recover the missing information.

Data extraction and analysis

After study selection, screening, and a thorough examination, the data were extracted. The information gathered was cross-checked and tabulated into three tables [Tables 1–3]. In case of missing data, 6 weeks' time was given to gather the information. If the information was still missing, we then indicated the missing data as "Not available (NA)" in the text and in the tables. The results are expressed in descriptive statistics. The overall survival rate was calculated by survival analysis using the Kaplan–Meier curves.

RESULTS

Results have been summarized in Table 4. Our research strategy revealed a total of 83 relevant papers published from 1965-2022 (a few references).[11-37] A total of 100 patients included 55 males and 35 females with a male to female ratio of 1.6:1. The maximum number of cases were from the USA (n = 17) followed by Poland (n = 11), Turkey = UK (n = 10), and Japan = Italy (n = 8). The patients' mean age was 65.1 years (range: 35–97). The mean age was 63.3 years in males and 68.4 years in females. Fifty-five of the 100 patients (55%) had a previous history of RCC, whereas 33 had none (33%). The parotid gland was the most predominant site of metastasis (85%), followed by the submandibular gland (SMG) (13%). In both glands, the right side was affected more than the left. In 37% of cases, SG was the initial and the only site of metastasis. Also, 40% of cases involved metastasis to other distant sites too. The most common type of RCC diagnosed was clear cell carcinoma (CCC). Major therapeutic aids included were surgery (39.5%), and combined therapies (22.1%), [Table 4]. Also, 8% of patients died with a mean survival rate of 1.3 years.

Table 1: Details of publications included in the current review (1965–2022)

S. No.	Authors	Year	Country	Type of study	Total no. of patients
1	Patey *et al*.	1965	UK	CP	1
2	Satomi *et al*.	1974	Japan	CS	1
3	Kucan *et al*.	1981	USA	CS	1
4	Percival *et al*.	1982	UK	CR	1
5	Sist *et al*.	1982	USA	CR	1
6	Bedrosian *et al*.	1984	USA	CR	1
7	Smits *et al*.	1984	Netherland	CR	1
8	Hessen *et al*.	1986	USA	CS	1
9	Zoltie *et al*.	1986	UK	CR	1
10	Harrison *et al*.	1987	UK	CR	1
11	Som *et al*.	1987	USA	RA	1
12	Gunbay *et al*.	1989	Turkey	CR	1
13	Melnick *et al*.	1989	USA	CR	1
14	Owens *et al*.	1989	USA	CS	2
15	Coppa *et al*.	1990	USA	CS	2
16	Pisani *et al*.	1990	Italy	CR	1
17	Tsuta *et al*.	1990	Japan	CR	1
18	Sarangi *et al*.	1991	UK	CR	1
19	Ravi *et al*.	1992	India	CR	1
20	Borghi *et al*.	1995	Italy	CR	1
21	Sykes *et al*.	1995	UK	CR	1
22	Stanley *et al*.	1995	UK	CR	2
23	Ficarra *et al*.	1996	Italy	CR	1
24	Gangopadhyay *et al*.	1998	Saudi Arabia	CR	1
25	Vara *et al*.	1998	Spain	CR	1
26	Adil *et al*.	1999	Turkey	CR	1
27	Li *et al*.	2001	Germany	CR	1
28	Ieva *et al*.	2002	Italy	CR	1
29	Park *et al*.	2002	USA	RA	1
30	Gogus *et al*.	2004	Turkey	CR	1
31	Seijas *et al*.	2005	Spain	CR	1
32	Moudouni *et al*.	2006	France	CR	1
33	Pomar Blanco *et al*.	2006	Spain	RA	1
34	Andreades *et al*.	2007	Greece	CR	2
35	Kondo *et al*.	2007	Japan	CR	2
36	Newton *et al*.	2007	UK	CR	1
37	Kalpan *et al*.	2008	Turkey	CR	1
38	Mrena *et al*.	2008	Finland	SR	3
39	Spreafico *et al*.	2008	Italy	CR	1
40	Choi *et al*.	2009	South Korea	CR	1
41	Laco *et al*.	2009	Czech Republic	CR	1
42	Lee *et al*.	2009	South Korea	CR	1
43	Miah *et al*.	2010	UK	CR	1
44	Wayne *et al*.	2010	USA	CR	1
45	Ito *et al*.	2011	Japan	CR	1
46	Sinha *et al*.	2011	India	CR	1
47	Deeb *et al*.	2012	USA	CR	1
48	Lau *et al*.	2012	Australia	CR	1
49	Lawlor *et al*.	2012	USA	CR	1
50	Serouya *et al*.	2012	USA	CR	1
51	Takiashi *et al*.	2012	Japan	CR	1
52	Vegara *et al*.	2013	Spain	CR	1
53	Yanlan *et al*.	2013	China	CR	1
54	Akatiken *et al*.	2014	Turkey	CR	1
55	Hosan - centenero *et al*.	2014	Spain	CR	1
56	Kwak *et al*.	2014	South Korea	CR	1
57	Maralani *et al*.	2014	Canada	CR	1
58	Tunio *et al*.	2014	Saudi Arabia	CR	1
59	Udagar *et al*.	2014	USA	CR	1
60	Bulguru *et al*.	2015	Turkey	CR	1
61	Kolokythas *et al*.	2015	USA	CR	1
62	Mellioni *et al*.	2015	Italy	CR	1
63	Piggati *et al*.	2015	Brazil	CR	1
64	Shi *et al*.	2015	China	CR	1
65	Balaban *et al*.	2016	Turkey	CR	1
66	Berkiten *et al*.	2016	Turkey	CR	1
67	Hussain *et al*.	2016	USA	CR	1
68	Majewska *et al*.	2016	Poland	CP	9
69	Renda *et al*.	2016	Turkey	CR	1
70	Leider	2017	Germany	RA	1
71	Rocca *et al*.	2017	Italy	CR	1
72	Franzen *et al*.	2018	Germany	CR	2
73	Higuera *et al*.	2018	Argentina	CR	1
74	Sydney *et al*.	2019	Turkey	CR	1
75	Albsoul *et al*.	2020	Jordan	CR	1
76	Halnony *et al*.	2020	Turkey	CR	1
77	Gopan *et al*.	2021	India	CR	1
78	Martire *et al*.	2021	Brazil	CR	1
79	Santana *et al*.	2021	Brazil	CR	1
80	Torchalla *et al*.	2021	Poland	CR	2
81	Krawczyk *et al*.	2022	Poland	CR	1
82	Parosanu *et al*.	2022	Romania	CR	1
83	Singla *et al*.	2022	India	PS	1

CP: Clinico-pathological study, CR: Case report, CS: Case series, PS: Prospective study, RA: Retrospective analysis, SR: Systematic review, UK: United Kingdom, USA: United states of America

DISCUSSION

RCC is one of the lethal neoplasms leading to approximately 2% of global cancer diagnoses and deaths, projecting to increase in burden worldwide. In the past few years, the cases of RCC have rapidly developed in developed countries, mostly USA.[38] In the current research also, the maximum number of cases were from the USA (17%) followed by Poland (11%), UK = Turkey (10%) > Japan = Italy (8%) > Spain (5%), and India (4%). Other regions involved a few cases [Table 4]. RCC occurs predominantly during the 5th–6th decades exhibiting a male predilection with a male–female ratio of 1.5:1. In the current study also, there was a male predominance, with M:F = 1.6:1. However, the age ranged between 3rd and 9th decades.[4]

Table 2: Clinical details of patients with renal cell carcinoma metastasizing to salivary glands (1965-2022)

PT NO.	Age (in years)	Gender	Previous history of RCC/ Side of Kidney	Medical history	Chief complaint	Site of metastasis
1	63	F	N	NA	Pulsatile facial mass for 1 Yr.	P (SNA)
2	66	M	Y/L	NA	Difficulty in eating	P (SNA)
3	55	M	N	N	Intraoral mass x 3-4 Mon	P (R)
4	71	F	N	N	MassBelow right angle of the mandible for 9 Mon	P (R)
5	62	M	N	N	Mass on left preauricular region	P (L)
6	61	M	N	N	Painless mass in mouth	SMG (L)
7	60	F	Y/NA	NA	Painful mass on Right preauricular region	P (R)
8	52	M	N	N	Mass. on the left preauricular region for 2 Mon.	P (L)
9	64	F	Y/NA	N	Mass on Right preauricular region for 2 Mon	P (R)
10	NA	NA	NA	NA	Pulsatile swellingFacial	SMG (SNA)
11	42	NA	N	NA	Rapidly growing facial mass	P (SNA)
12	60	M	NA	NA	Painful facial mass on left side of face	P (L)
13	72	M	NA	NA	Mass on left preauricular lesion for 2.5 yr.	P (L)
14	55	M	N	NA	Intraoral ass x 3mo.	P (R)
15	75	F	Y/L	NA	Pulsatile mass on left preauricular region for 10 weeks	P (L)
16	42	M	N	NA	Pulsatile mass on left side of face	P (L)
17	55	M	Y/R	NA	Painful preauricular mass for 6 weeks	P (R)
18	59	M	N	N	Mass. on left preauricular region for 2 Mon.	P (L)
19	51	M	Y/L	N	Swelling, facial weakness on right side of mouth	P (R)
20	71	M	Y/NA	NA	Mass in left side of mouth for 3 months	P (L)
21	55	F	Y/NA	NA	Bilateral facial masses for 3 Mon	P (BL)
22	63	M	N	NA	Right facial mass for 1 Yr.	P (R)
23	59	M	N	NA	Mass for 3 weeks on the left side of the mouth	P (L)
24	40	M	N	NA	Swelling on the right side of the face	P (R)
25	59	M	N	NA	Right preauricularswelling	P (R)
26	73	F	NA	NA	Difficulty in swallowing	Wharton duct (R)
27	48	M	N	NA	Mass on left side neck for 3 Mon	P (L)
28	50	M	Y/R	N	Rapidly increasing painful mass for 2 Mon	P (L)
29	52	M	Y/R	NA	Intraoral mass	P (R)
30	63	M	Y/NA	NA	Rapidly growing masses on both sides of face	P (BL)
31	83	F	Y/NA	NA	Mass x2 Mon. on left preauricular region	P (L)
32	61	M	N	NA	Left facial mass	P (L)
33	59	F	Y/L	NA	Swelling on left side of face	P (L)
34	67	M	N	N	Mass on left side of mouth for 4 Mon	P (L)
35	83	M	Y/NA	N	Swelling in mouth	SMG (SNA)
36	NA	NA	NA	NA	NA	P (SNA)
37	NA	NA	Y/L	NA	Rapidly growing mass in mouth	P (SNA)
38	NA	NA	Y/L	NA	Growth on face	P (SNA)
39	74	M	Y/N	N	Painful swelling on right side of face	SMG (R)
40	78	M	Y/NA	N	Painful swelling on right side of face	SMG (R)
41	74	F	Y/R	N	Right side preauricular swelling for 3 Mon	P (R)
42	68	M	N	S	Gradually increasing painless mass in right periauricular region for 1 Yr.	P (R)
43	58	F	N	NA	Tender mass on right side of mouth	P (R)
44	75	F	Y/NA	NA	Painful mass on the left side of the face	P (L)
45	62	M	YNA	NA	Painful mass on the left side of the face for a few years	P (L)
46	67	M	Y/R	CRF	Right preauricularSwelling	P (R)
47	64	M	Y/L	N	Swelling in the right auricle	P (R)
48	75	M	N	N	Swelling in the right preauricular region for 6 Mon	P (R)
49	78	M	Y/R	Cholecystectomy	Rapidly increasing facial swellingfor 2 Mon	P (SNA)
50	61	F	Y/L	Mastectomy, BC	Painless and palpable swellings in the thyroid and mid-mouth region	SMG (R)

Contd...

Table 2: Contd...

PT NO.	Age (in years)	Gender	Previous history of RCC/ Side of Kidney	Medical history	Chief complaint	Site of metastasis
51	61	F	N	N	Mass on left side of face	P (L)
52	60	M	Y/R	N	Swelling on right side of mouth	P (R)
53	35	M	N	Abdominal lump	Gradually increasing facial swelling	P (L)
54	82	M	Y/R	CLL, Left adrenalectomy	Mass on right preauricular region for 18 Mon.	P (R)
55	79	F	Y/L	NA	Difficulty in eating	P (L)
56	71	M	Y/R	HT, S	Mass on right side of ear for 2 years	P (R)
57	NA	NA	Y/NA	NA	Hard mass in mouth	SMG (SNA)
58	57	F	Y/R	N	Painless swelling in the left preauricular region	P (L)
59	61	M	Y/R	Drug allergy, Anaemia, Family history of RCC	Painless mass on the right side of the mouth	P (R)
60	44	F	N	N	Painless mass on the left side of the mouth	P (L)
61	62	M	N	HT	Palpable swelling in the left preauricular region	P (L)
62	NA	NA	Y/NA	NA	Mass on left side of face	P (L)
63	67	M	N	N	Rapidly growing mass in the left side of the mouth for 1 Yr.	P (L)
64	64	F	N	N	Slowly progressive left facial swelling for few Mon	P (BL), SMG (L)
65	70	M	Y/L	IHD, Bypass surgery	Left cheek swelling, haematuria,	P (L)
66	64	M	Y/L	NA	Mass under his right ear for several weeks	P (R)
67	77	F	Y/BL	FNP (R side, hemi cranial pain (R side)	Right neck mass extending to right parotid and thyroid glands	P (R)
68	83	M	Y/R	N	Rapidly growing mass on right side of face	P (R)
69	53	F	Y/L	Dialysis	Firm mass in the mouth	SMG (L)
70	82	F	Y/L	NA	Rapidly enlarging mass on left side of face	P (L)
71	56	F	Y/R	Thyroid resection	Right preauricular painless mass present for 6 Mon	P (R)
72	66	F	Y/L	N	Painful swelling in the right side of mouth	P (R)
73	70	M	Y/R	HT	Growing lesion in the right side of mouth	P (R)
74	65	M	Y/R	SCC of right pinna	Right preauricular swelling	P (R)
75	66	F	N	NA	Painless, enlarging, hard, immobile facial mass, FNP	P (R)
76	76	F	N	NA	Painless, enlarging, immobile facial mass	P (R)
77	97	F	N	NA	Hard, immobile mass in mouth	SMG (R)
78	68	M	N	NA	Growing firm painless preauricular mass for 4 Mon	P (L)
79	69	M	N	NA	Palpable mass on left side of mouth	P (L)
80	NA	M	Y/NA	NA	Painless slowly growing mass for 3 Mon	P (R)
81	NA	F	Y/NA	NA	Tumour growth in left side of mouth	Minor glands, left retromolar)
82	NA	F	Y/NA	NA	Palpable tumor on right side	P (R)
83	60	F	N	NA	Swelling on right side of face	P (R)
84	74	F	N	N	Swelling on the left side of the mouth	P (L)
85	74	NA	Y/NA	NA	NA	P (SNA)
86	NA	NA	NA	NA	Swelling on face	P (SNA)
87	74	F	Y/L	Colorectal cancer	Rapidly growing painless mass in the left preauricular region.	P (L)
88	80	F	Y/L	Colorectal cancer, parotid metastasis of left side	Rapidly growing painless mass in the right preauricular region.	P (R)
89	74	F	Y/L	N	Hard nodule on the right side of the mouth	SMG(R)
90	75	F	Y/L	S, A,Recurrent RCC	Mass growing for 18 Mon on the left side of the mouth	P (L)
91	50	M	NA	NA	Rapidly growing mass on one side of face	P (SNA)
92	50	M	N	N	Pain radiating to right ear for 5 Mon	P (R)
93	NA	NA	NA	NA	NA	P (SNA)
94	69	M	N	S, A	Nodule in the right parotid region for 3 Mon	P (R)
95	72	M	Y/R	N	Facial swelling for 1 Yr.	P (SNA)

Contd...

Table 2: Contd...

PT NO.	Age (in years)	Gender	Previous history of RCC/ Side of Kidney	Medical history	Chief complaint	Site of metastasis
96	81	M	Y/L	HT, Glaucoma, osteoarthritis	Tumor mass on left side of mouth	SMG (L)
97	84	M	Y/L	HT, Glaucoma	Tumor mass on the right side of the mouth	SMG (R)
98	54	M	N	HT, Nicotine	Painless rapidly growing mass on the left preauricular region for 6 months	P (L)
99	75	F	N	HT, DM, Colon cancer, CAD, Diabetic nephropathy	Painful swelling on the left preauricular region	P (L)
100	59	M	Y/R	N	Preauricular swelling right side	P (R)

PT NO.	Clinical findings	Provisional diagnosis	Oral soft tissue as the initial site of metastasis?	Time of diagnosis of metastasis after nephrectomy	Any other organs involved in metastasis	Final diagnosis of metastatic RCC
1	Soft, fluctuant swelling	SGT	Y	-	NA	CCC
2	Firm, fixed mass	SGT	N	1 Yr.	Bone	CCC
3	Soft mass	SGT	Y	-	NA	CCC
4	Pulsatile, mobile swelling	SGT	Y	-	Liver, lung	CCC
5	Swelling	SGT	Y	-	NA	CCC
6	Firm, non-tender swelling	SGT	Y	-	N	CCC
7	Firm, non-tender swelling	SGT	N	8.5 Yr.	SMG	NA
8	Soft, fluctuant swelling	SGT	Y	-	lungs, ribs, lumbar spine, and brain	CCC
9	Swelling	SGT	N	10 Yr.	N	CCC
10	Pulsatile, mobile mass	SGT	NA	NA	NA	CCC
11	Soft, firm swelling	NA	Y	-	Thyroid, Max sinus	NA
12	Painful swelling	SGT	N	NA	NA	CCC
13	Swelling	SGT	Y	-	Liver, lungs, mediastinum, adrenal	NA
14	Swelling	SGT	Y	-	Chest, brain, bone	CCC
15	Swelling	SGT	N	8 Yr.	Recurrent renal disease	CCC
16	Soft fluctuant, tender swelling	SGT	Y	-	Perirenal LN	CCC
17	Soft swelling	SGT	N	7 Yr.	Lungs, axillary lymph nodes	CCC
18	Firm swelling	SGT	Y	-	Cerebellum, vertebrae	CCC
19	Firm swelling	SGT	N	5 Yr.	NA	CCC
20	Firm swelling	SGT	N	4 Mon	Radius	CCC
21	Painful swelling	SGT	N	7 Yr	NA	CCC
22	Soft mass	SGT	Y	-	Liver, pancreas	CCC
23	Soft mass	SGT	Y	-	Perirenal lymphnodes	CCC
24	Soft mass	SGT	Y	-	NA	CCC
25	Soft mass	SGT	Y	-	NA	CCC
26	NA	NA	NA	NA	NA	CCC
27	Soft, painless mass	SGT	Y	-	Right adrenal	CCC
28	Enlarged parotids, a solid, well-circumscribed tumor, deeply adhering without FN involvement.	SGT	N	5 Yr	N	CCC
29	Rapidly increasing painless mass	SGT	N	5 Mon	LN	CCC
30	3×2.5 cm firm mass in both glands	SGT	N	14 Yr	NA	CCC
31	Firm, nodular swelling	SGT	N	10 Yr	N	CCC
32	Firm, nodular swelling	SGT	Y	-	N	CCC
33	Firm, nodular, swelling	SGT	N	10 Yr	Other Kidney	CCC
34	Firm, nodular, swelling	SGT	Y	-	Adrenals, lung, LN	CCC
35	Firm, nodular lesion	SGT	N	10 Yr	N	CCC
36	NA	NA	NA	NA	NA	CCC
37	NA	NA	N	5 Yr	NA	CCC
38	NA	NA	N	10 Yr	NA	CCC

Contd...

Table 2: Contd...

PT NO.	Clinical findings	Provisional diagnosis	Oral soft tissue as the initial site of metastasis?	Time of diagnosis of metastasis after nephrectomy	Any other organs involved in metastasis	Final diagnosis of metastatic RCC
39	Firm mass	NA	N	NA	NA	CCC
40	Firm mass, non-fixed	NA	N	NA	NA	CCC
41	Painful, firm, 2×2 cm, no FN involvement	SGT	N	7 Yr	Ad gland	CCC
42	Hard, firm, nontender, deeply adhering mass	SGT	Y	-	Lung, liver	CCC
43	Painful swelling	SGT	Y	-	Meatus	CCC
44	Tender mass	SGT	N	9 Yr	Contralateral kidney, lung, bone	CCC
45	Tender mass	SGT	N	5 Yr	N	CCC
46	Deeply adherent painless mass	NA	N	15 Yr	LN	CCC
47	Round, painless, immobilized mass, 2×2 cm	SGT	N	10 Yr	N	CCC
48	Firm nodular mass, 4×3 mm	SGT	Y	-	Liver, vertebrae, lungs, adrenals	CCC
49	Hard, painless mass of 3×3 cm	SGT	N	3 Yr	N	CCC
50	Firm mass	Thyroid tumor	N	7 Yr.	Thyroid	CCC
51	Enlarged size of parotid region	SGT	Y	-	Skin, pancreas	CCC
52	Painful swelling	SGT	N	3 Yr	N	CCC
53	Firm swelling	SGT	Y	-	N	CCC
54	Swelling	lymphoma	N	19 Yr	N	CCC
55	Non tender soft swelling	SGT	N	16 Yr	N	CCC
56	Non tender soft swelling without lymphadenopathy	NA	N	5 Yr	Pancreas	CCC
57	NA	NA	N	9 Yr	NA	CCC
58	A 30-mm flexible elastic hard mass	SGT	N	10	Lung	CCC
59	Firm, painful mass	SGT	N	5 Yr	Lung, Adrenal	CCC
60	Painless swelling	SGT	Y	-	Lung, Liver, Bone	CCC
61	Bony hard mass	SGT	Y	-	N	CCC
62	Nodular, firm swelling	SGT	N	11 Yr	NA	CCC
63	Painless mass 2×2 cm	SGT	Y	-	N	CCC
64	Painless masses	SGT	Y	-	Thyroid	CCC
65	Hard, fixed tender mass of size 2×2 cm	SGT	N	15 Yr	Contralateral kidney, right adrenal	CCC
66	1.0×1.0 cm firm, painless, mobile mass	SGT	N	6 Yr	Lung	CCC
67	Hyper vascular mass, lymphadenopathy	Metastatic	N	3 Yr	Thyroid	CCC
68	Firm swelling	SGT	N	10 Yr	Cerebellum	CCC
69	Hard, round, fixed	SGT	N	4 Yr	NA	CCC
70	Firm, nodular swelling	SGT	N	6 Yr	NA	CCC
71	Smooth, firm, immobile and non□tender mass 3 x 3 cm	SGT	N	11 Yr	N	CCC
72	Well-defined, 37×21 mm in size, hypoechoic heterogeneous solid mass	NA	N	15 Yr	N	CCC
73	Painless, soft, smooth 3×4 cm mass	NA	N	11 Yr	N	CCC
74	Nodule	SGT	N	8 Yr	N	CCC
75	Non-tender, firm mass 5×4 cm, FNP	SGT	Y	-	N	CCC
76	Non-tender soft mass, 5×5 cm	SGT	Y	-	N	CCC
77	Firm, nodular swelling	SGT	N	(At time of diagnosis)	N	CCC
78	Non-tender, firm swelling, 2.6×1.8×1.3 cm	SGT	Y	-	N	CCC
79	Firm hard swelling, 1.8×1.5×2 cm	SGT	Y	-	N	CCC
80	Non-tender mass	SGT, Metastatic	N	NA	Lung	CCC
81	Soft, fluctuant swelling	SGT, Metastatic	N	NA	N	CCC
82	Firm, nodular mass, 1.5 cm	SGT	N	NA	N	CCC

Contd...

Table 2: Contd...

PT NO.	Clinical findings	Provisional diagnosis	Oral soft tissue as the initial site of metastasis?	Time of diagnosis of metastasis after nephrectomy	Any other organs involved in metastasis	Final diagnosis of metastatic RCC
83	Multinodular palpable mass in the area of cicatrix	SGT	Y	-	N	CCC
84	A well-demarcated painless mass	SGT	Y	-	N	CCC
85	NA	NA	N	6.5 Yr	N	CCC
86	NA	Oncocytoma	NA	NA	NA	CCC
87	Mobile mass	SGT/ Metastatic	N	11 Yr	Lungs, liver	CCC
88	Vascular mass 1.5 cm	Metastasis	N	17 Yr	N	CCC
89	Firm Vascular swelling	NA	N	11 Yr	N	CCC
90	Painless swelling,4×4 cm.	PA	N	10 Yr	N	CCC
91	NA	NA	NA	NA	NA	CCC
92	Non tender swelling, trismus, lymphadenopathy	TN	Y	-	LN	CCC
93	NA	NA	NA	NA	NA	CCC
94	Nodule, vascular	SGT	Y	-	N	CCC
95	Nodular growth	SGT	N	8 Yr	N	CCC
96	Vascularized, solid mass, 24 x 21 x 26 mm in diameter	SGT	N	8 Yr	N	CCC
97	Painless, soft, movable tumor, approx. 2 x 2 cm in diameter	Metastatic	N	11 Yr	N	CCC
98	Palpable mass with lymphadenopathy	SGT	Y	-	Lung, neck, rib	CCC
99	Firm, nodular growth	SGT	Y	-	Vertebrae	CCC
100	6×4 cm nodular, vascular, mass	NA	N	4 Yr	N	CCC

A: Alcohol, Ant: Anterior, BL: Bilateral, BPA: Benign prostate atrophy, CAD: Coronary artery disease, CCC: Clear cell carcinoma, CLL: Chronic lymphocytic leukemia, CRF: Chronic renal failure, DM: Diabetes mellites, F: Female, FNP: Facial nerve palsy, HT: Hypertension, I: Ischaemic heart disease, L: Left, M: Male, Mon: Months, N: No, NA: Not available, P: Parotid, Post: Posterior, R: Right, RCC: Renal cell carcinoma, S: Smoking, SCC: Squamous cell carcinoma, SGT: Salivary gland tumour, SMG: Submandibular gland, SNA: Site not available, TN: Trigeminal neuralgia, Y: Yes, Yr: Years

Multiple risk factors favor the development of RCC, which include smoking, tobacco chewing, alcohol, obesity, hypertension, cardiac, liver, and renal diseases, urinary stones, diabetes mellites, drug usage, and malnutrition.[4] Studies have reported that cigarette smoke contains many carcinogens as well as a highly addictive substance called nicotine. As they are filtered through the nephron, these particles are metabolized and promote inflammation and induce deoxyribonucleic acid damage, paving the way for carcinogenesis. Smokers are known to exhibit more risk of RCC than non-smokers.[39] Patients with underlying comorbidities are at a higher risk of developing cancer owing to a lack of immunity.[4] In this research, we found that 23% of cases had a history of associated risk factors and comorbidities, the most common of which were hypertension and a history of other treated malignancies. One patient revealed a family history of RCC. Very few patients reported a history of smoking and tobacco habit [Table 4].

Distant spread of RCC most often occurs in the lungs, bones, lymph nodes, liver, adrenal glands, brain, and skin. SG is the rarest uncommon site of distant metastasis from RCC. And if this occurs, the parotid is the most affected gland. According to the current research, the first case of SG metastasis from RCC was reported in 1965 by Patey *et al*.[11] Since then, we could find only 100 such cases reported in the last 57 years (1965–2022). Parotid was the most common gland affected (85%), whereas 13% of metastatic sites were in SMG. No case of the sublingual gland was documented. The right side of both glands was predominantly affected than the left. Minor SG is very rarely affected by metastasis. In one case, minor glands of the retromolar region were affected and in another, only the Wharton duct was involved.

The route of secondary metastasis to the SG may be either lymphatic, homogeneous, or direct invasion. Abundant lymphatic tissue in the parotid leads to lymphatic spread. However, metastatic RCC spreads to the SG predominantly following the hematogenous route, because of the highly vascular nature of the tumor and its association with multiple arteriovenous shunts. It is hypothesized that the kidneys receive about 25% of the circulating blood volume per minute, in addition to the release of vascular endothelial growth factors and other angiogenic factors, all resulting in the hypervascularity of these tumors.[6] The majority of cases of RCC involve dysfunction of the Von–Hippel–Lindau gene, which promotes ubiquitination and inactivation of hypoxia-induced factors in healthy individuals, which creates a pre-angiogenic environment.[6] Angiogenesis plays a crucial role in the development of tumor metastasis.

Table 3: Data describing treatment and prognosis of patients with renal cell carcinoma metastasizing to salivary glands (1965 to 2022)

Pt. No.	Treatment done	Prognosis	Survival Time from diagnosis of oral metastasis (in months)
1	S, R	NA	NA
2	NA	Fav/Alive	-
3	Parotidectomy (Superficial)	NA	NA
4	S, R	Fav	-
5	Parotidectomy (Deep)	NA	NA
6	Sub maxillectomy	NA	NA
7	S	NA	NA
8	Parotidectomy (Superficial)	NA	NA
9	NA	NA	NA
10	S	NA	NA
11	S	D	NA
12	Parotidectomy (Partial)	NA	NA
13	Palliative radiotherapy	NA	NA
14	Parotidectomy (Superficial)	NA	NA
15	Parotidectomy (Complete)	NA	NA
16	Parotidectomy (superficial)	D	20
17	S, R	D	46
18	Parotidectomy (superficial)	NA	NA
19	Parotidectomy (TNA)	NA	NA
20	Parotidectomy (superficial)	NA	NA
21	Parotidectomy (superficial)	Fav	-
22	Parotidectomy (Partial)	NA	NA
23	Parotidectomy (superficial)	NA	NA
24	NA	NA	NA
25	NA	NA	NA
26	NA	NA	NA
27	Parotidectomy (Superficial)	NA	NA
28	Parotidectomy (Complete)	Fav	-
29	S	NA	NA
30	NA	NA	NA
31	Parotidectomy (TNA) and nephrectomy	NA	NA
32	Parotidectomy (Superficial)	NA	NA
33	Parotidectomy (Superficial)	NA	NA
34	Parotidectomy (Superficial)	NA	NA
35	Parotidectomy (Superficial)	NA	NA
36	Parotidectomy (TNA)	NA	NA
37	NA	NA	NA
38	NA	NA	NA
39	S	NA	NA
40	S	NA	NA
41	Parotidectomy (Superficial)	NA	NA
42	R, I	D	2
43	Parotidectomy (Superficial)	NA	NA
44	NA	NA	NA
45	Parotidectomy (Superficial)	NA	NA
46	Parotidectomy (Complete), R	NA	NA
47	Parotidectomy (Complete), Further Tt RBP	Fav	-
48	Parotidectomy (Superficial)	NA	NA
49	S, R	Fav	-
50	S	NA	NA
51	Parotidectomy (Superficial)	Fav	NA
52	Parotidectomy (Superficial)	NA	NA

Contd...

Table 3: Contd...

Pt. No.	Treatment done	Prognosis	Survival Time from diagnosis of oral metastasis (in months)
53	Palliative	D	2
54	Parotidectomy (Complete), R, C	Fav	-
55	Parotidectomy (Superficial)	NA	NA
56	Parotidectomy (Complete)	Fav	-
57	Gland resection with preservation of the FN	Fav	-
58	S, Cytokines, Parotidectomy with FN resection and reconstruction	Fav	-
59	S	Fav	-
60	IL	UFU	-
61	Parotidectomy (Complete), further Tt RBP	NA	-
62	NA	NA	NA
63	Parotidectomy with preservation of FN, R	UFU	-
64	Parotidectomy (Partial), nephrectomy, Sunitinib	Fav	-
65	Parotidectomy (Complete), adrenalectomy, nephrectomy	Fav	-
66	Systematic	NA(Size increased)	-
67	Total parotidectomy sacrificing FN, RND, and hemithyroidectomy with isthmusectomy	NA	-
68	Parotidectomy (Superficial)	Fav	-
69	S	NA	NA
70	NA	NA	NA
71	Parotidectomy (Superficial)	Fav	-
72	S, C, R	NA	NA
73	S, I	NA(MM)	-
74	R, TKI, S	Fav	-
75	Parotidectomy (Complete)	NA	NA
76	Parotidectomy (Complete)	NA	NA
77	NA	NA	NA
78	Tumor resection	NA	NA
79	Parotidectomy (Superficial)	NA	NA
80	Parotidectomy (Complete)	NA	NA
81	Tumor resection	NA	NA
82	Parotidectomy (Complete)	NA	NA
83	Tumor resection	NA	NA
84	Parotidectomy (Complete)	NA	NA
85	S	D	3
86	NA	NA	NA
87	Parotidectomy with preservation of FN	NA	NA
88	Parotidectomy	Fav	-
89	S, R	Fav	-
90	Parotidectomy (Partial)	UFU	-
91	Planned for R, C	D	12
92	RBP	D	12
93	NA	NA	NA
94	Parotidectomy (TNA)	Fav	-
95	Parotidectomy (TNA), RTO	NA	NA
96	Radical excision of the gland	Fav/TGO	-
97	Radical excision of the gland	Fav/TGO	-
98	Nephrectomy	TGO	-
99	R	TGO	-
100	Targetoid	UFU	-

C: Chemotherapy, D: Death, Fav: Favourable, FN: Facial nerve, I: Interferon, IL: Interleukin, NA: Not available: NG: Not given, R: Radiotherapy, RBP: Refused by patient, Referred to oncologist, S: Surgery, TGO: Treatment going on, TKI: Tyrosine kinase inhibitor, TNA: Type not available, Tt: Treatment, UFU: Under follow up

The tumor-derived microvesicles break off from the primary site. These microvesicles appear to carry a cancer stem cell phenotype and micro-ribonucleic acids, which stimulate angiogenesis.[6] One of the proposed pathways is via Batson's valve plexus system.

Table 4: Summary of results documented from literature research describing the characteristics of renal cell carcinoma metastasizing to Salivary glands (1965-2022)

Feature	Number
Total number of papers published	83 • Case reports-71 • Case series- 4 • Retrospective analysis -4 • Clinicopathological study-2 • Systematic reviews-1 • Prospective study-1
Total number of patients	100
Worldwide distribution of cases	• USA-17 (17%) • Poland-11 (11%) • UK=Turkey-10 (10%) • Japan=Italy-8 (8%) • Spain-5 (5%) • India - 4 (4%) • Germany=Brazil=Finland=3 (3%) • China=Greece=Saudi Arabia-2 (2%) • Argentina=Australia=Canada=Cretz republic=Europe=France=Jorden=Korea=Netherland=Romania-1 (1%)
Gender	• M -55 (55%) • F- 35 (35%) • NA-10 (10%) • M: F=1.6:1
Average age of patients (Mean, Range)	• Total- 65.1 Yr. (35-97 Yr.) • M- 63.3 Yr. (35-84 Yr.) • F- 68.4 Yr. (44-97 Yr.)
Previous history of RCC	• Y-55 (55%) • (L-20, R-17, Both-1, NA-17) • N –33 (33%) • NA-12 (12%)
Associated risk factors	• Y- 23 (23%) • N-32. (32%) • NA-45 (45%) • HT-9 (39.1%) • Other malignancies – 7 (30.4%) • Smoking=Cardiac diseases=Renal diseases=3 (13%) • Alcohol=Tobacco=DM=Drug allergy=Anaemia=Adrenalectomy=Thyroid resection=recurrent RCC=Family history of RCC=Glaucoma=FNP-1 (4.3%)
Salivary gland involved in metastasis	• Parotid – 85 (85%). • (R-36, L-35, BL-1, SNA-13) • Submandibular – 13 (13%) • (L-4, R-6, BL-0, SNA-3) • Minor glands retromolar-1 (1%) • Wharton duct-1 (1%)
Salivary gland as the initial site of metastasis	• Y- 37 (37%) • N- 56 (56%) • Detected at same time- 1 (1%) • NA- 6 (6%)
Any other site of metastasis	• Y-40 (40%) • N- 37 (37%) • NA- 23 (23%)
Average mean time of detection of salivary gland metastasis after nephrectomy	• 8.5 Yr. (4 Mon-19 Yr.)
Final diagnosis of metastatic RCC	• CCC-98 (98%) • NA-2 (2%)
Treatment aids	• Surgical aids – 72 (72%) • (Parotidectomy – 50, Not specified- 9, Excision-6, Tumor resection-3, Radical excision of gland-3, Sub maxillectomy-1) • Combined therapy-14 (14%) • Systematic=Interleukins=Palliative radiotherapy=Palliative treatment=Targetoid therapy 1 (1%)

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Table 4: Contd...

Feature	Number
	• Tt planned but died before-1 (1%) • RBP-1 (1%) • NA- 15 (15%)
Prognosis	• Deaths- 8 (8%) • Favorable- 21 (21%) • UFU- 4 (4%) • TGO- 2 (2%) • NA-65 (65%)
Average mean time of death from diagnosis of salivary gland metastasis	1.3 Yr. (2 Mon- 3.8 Yrs. appx.)

BL: Bilateral, CCC: Clear cell carcinoma, DM: Diabetic mellites, F: Female, FNP: Facial nerve paralysis, HT: Hypertension, L: Left, M: Male, Mon: Months, N: No, NA: Not available, R: Right, RBP: Refused by patient, RCC: Renal cell carcinoma, SCC: SNA: Site not available, TGO: Treatment going on, Tt: treatment, UFU: Under follow up, Y: Yes, Yr.: years

Oral metastatic tumors are of high clinical importance because they may be the only symptom of an undiagnosed underlying malignancy or the first sign of metastasis. In our study, SG was the initial site of metastasis in 37% of cases, whereas, in 56% of cases, metastasis was detected after the nephrectomy performed for RCC, with an average mean time of 8.5 years. The longest interval observed between SGM and nephrectomy was 19 years.

Clinically, metastatic RCC to SG is characterized by rapidly growing painful or asymptomatic highly vascular palpable mass accompanied by pulsations, tinnitus, facial weakness, difficulty in chewing, and dysphagia.[31,32] In some cases, there may be a history of facial nerve palsy (FNP). Multiple masses in the thyroid, SMG, and sublingual glands may also be present. One-third of the patients with advanced stage have bony metastasis causing substantial morbidity including pain, pathological fractures, spinal cord compression, enlargement of lesions, and hypercalcemia.[32] These metastatic lesions often become difficult to diagnose because their variable appearance bear close resemblance to primary neoplastic or non-neoplastic SG lesions. In the present research, rapidly increasing swelling was the most predominant clinical feature observed. Other lesions appeared as nodular, firm, and vascular masses. To exclude the primary malignancies of SG, a history of primary metastatic RCC in the patient could be a guiding tool for detecting the secondary deposits. Before the metastatic spread to the oral cavity, the majority of patients are often aware of their primary tumors. However, metastasis to SG via RCC is a late indication and patients may manifest the symptoms even after a long time of nephrectomy. In the current research, 55% of patients had a previous history of primary RCC with nephrectomy, whereas 33% of patients did not reveal such a history.

SG tumors need a proper evaluation for diagnosing the type of malignancy, whether it is benign or malignant. Ultrasonic examination is the prime choice in the diagnosis of SG swellings. Fine needle aspiration biopsy is another diagnostic aid used for these lesions; however, its diagnostic value is controversial due to the high false-negative rate.[34] A biopsy is recommended for the histopathological examination to provide a conclusive diagnosis of the type of metastatic lesion. However, it might be difficult to make an exact diagnosis because of varied histological appearance, particularly when the major focus of the primary site is unknown. Histopathologically, RCC is divided into various subgroups. The World Health Organization's classification of urogenital tumors in 2022 has introduced many new entities in the RCC.[40] CCC is the most predominant type and has been discovered to be the most prevalent metastasizing to the SG. Histopathologically, many SG primary malignancies such as mucoepidermoid carcinoma, hyalinizing clear cell carcinoma, acinic cell carcinoma, myoepithelial carcinoma, pleomorphic adenoma, and oncocytoma are characterized by the presence of clear cells.[33] Thus, it becomes difficult to differentiate from the secondary tumor. In that case, immunohistochemistry (IHC) plays a crucial role in providing the final diagnosis.

Classically, RCC presents positive IHC staining for vimentin, cytokeratin (CK), and epithelial membrane antigen (EMA), and negative staining for CK-7, CK-20, and S-100. Positive IHC staining for CK is important to exclude melanoma as the primary malignancy because most parotid metastases originate from this neoplasm. Negative IHC staining for CK-7 assists in excluding the thyroid origin of the carcinoma.[25] Most studies in this research demonstrated tumor cell positivity for vimentin, CD-10, CK-8, CK-10, and EMA and negative for S-100, CK-7, and CK-20. A high proliferative index of Ki67 was also observed in tumor cells. All these findings accorded the final diagnosis of metastatic renal CCC.

Imaging techniques such as computerized tomography scans (CT scans) and magnetic resonance imaging (MRI) can help in the assessment for possible extension or invasion. Positron emission tomography (PET) is useful in detecting distant organ metastasis.

Although RCC entails multiorgan distant metastases, SG might occasionally be the only site of metastasis many times. Also, 37 out of 100 instances in this study had SG as the only location of RCC metastasis, whereas 40 had metastasis to other regions as well such as the lungs, brain, adrenals, liver, vertebrae, spine, pelvis, skin, and skeletal muscles.[4]

The treatment of choice for primary RCC ranges from partial to radical nephrectomy, or even cytoreductive therapy, However, options for metastatic RCC to SG include biopsy, surgery, chemotherapy, radiotherapy, brachytherapy, and/or combination therapy. Superficial parotidectomy with preservation of the facial nerve (FN) and with disease-free margins is the optimal procedure for isolated parotid metastasis, provided the FN is not adhering to the tumor. Lymph node dissection may be performed in cases with the involvement of surrounding tissues. The treatment of diffuse metastatic disease is mainly palliative and includes a combination of chemotherapy, immunotherapy, hormone treatment, and radiation; this is due to the fact that metastatic RCC is often resistant to chemotherapy and radiotherapy. Surgical excision is provided to alleviate pain and discomfort along with an aim to avoid complications such as infection and bleeding. Bone-targeted therapy using bisphosphonates and denosumab can reduce skeletal complications; however, it has no role in improving survival. The most commonly used therapeutic aids in this study were surgical aids (39.6%) and combination therapy. Parotid lesions were treated by parotidectomy (either superficial, deep, partial, or total depending on the site) with preservation of FN. In SMG involvement, radical excision of the gland was performed in most cases.

Unfortunately, metastatic RCC has a bad prognosis with a maximum survival rate of approximately 5 years. In some cases, a patient's terminal stage of disease results in a loss of follow-up or death.

However, according to the current study, only 8% of individuals died with an average survival time of 1.3 years. Also, 21% of patients had a good prognosis with no signs of recurrence. In two patients, treatment is going on; four cases are under follow-up. These results may be because of the lack of information available in many papers included in this review.

Limitations of the current study

One of the limitations of current research was small sample size. Most studies included were case reports and case series. In many included studies, individual data of patients were not available.

CONCLUSIONS

During the last 57 years (1965–2022), we found only 100 cases of RCC metastasizing to SG. This signifies a rare occurrence of SG metastasis from RCC. Also, 8% of patients died with a mean survival rate of 1.3 years. Parotid was the most affected gland followed by SMG. Because of their resemblance to primary neoplastic and non-neoplastic SG lesions, metastatic lesions go unnoticed the majority of the time. Their diagnosis is a challenging task for clinicians and pathologists. A thorough examination of the metastatic lesions is required, including a review of the patient's medical history, clinical presentation, and early diagnosis to identify the primary site of metastasis and choose the best course of treatment. Current review adds an evidence of rarity of RCC metastasizing to SG and making clinicians and pathologists aware about the accurate diagnosis of such unnoticed lesions for a long time, so that their timely management may lead to reduction in the mortality rate. Although during our research, we could find mostly case reports and case series for the data analysis, robust research is still needed for documenting more evidence in such aspect.

Abbreviations

CCC: Clear cell carcinoma, CEA: Carcinogenic embryonic antigen, CK: Cytokeratin, CT: Computerized tomography, EMA: Epithelial membrane antigen, FN: Facial nerve, FNP: Facial nerve palsy, HP: Hard palate, IHC: Immunohistochemistry, MRI: Magnetic resonance imaging, NA: Not available, OST: Oral soft tissues, OSTM: Oral soft tissue metastasis, PET: Positron emission tomography, RCC: Renal cell carcinoma, SG: Salivary glands, SGT: Salivary gland tumors, SMG: Submandibular gland

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Conflicts of interest

There are no conflicts of interest.

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