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Metastatic Tumors to the Oral Soft Tissues and Jawbones: A Retrospective Analysis of 40 Cases and Review of the Literature

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Abstract

Background Metastasis to the oral soft tissues and jawbones is rare and frequently associated with wide spread disease and dismal prognosis. Herein, we report the clinicopathologic characteristics of 40 intraoral metastatic neoplasms and perform a comprehensive review of the pertinent literature.

Methods Criteria for inclusion included: (a) archived cases from the UMN Oral Pathology laboratory with available tissue blocks and/or H&E-stained preparations diagnosed between 2003 and 2021, (b) proper documentation of the clinico-radiographic characteristics of oral metastasis along with confirmed history of primary malignancy, or (c) microscopic findings consistent with metastatic disease with or without discovery of the primary site.

Results Intraoral metastases comprised 0.03% of all accessioned cases; 22 (55%) occurred in men and 18 (45%) in women (median age = 66.5; range = 18–94 years). Eighteen cases (45%) involved the gingiva, 16 (40%) the gingiva and jawbones, 5 (12.5%) were exclusively intraosseous, and 1 affected (2.5%) the tongue. The lung was the two most frequent primary site in both men (n = 6, 27.3%) and women (n = 5, 27.7%), followed by the colon (n = 4, 18.2%) and kidney (n = 3, 13.7%) in men, and colon (n = 4, 22.2%) and breast (n = 3, 16.6%) in women. Analysis of 1,084 metastatic cases from the literature (male-to-female ratio = 1.2; mean = 52.3; range = 0.6–90 years) indicated strong preference for the jawbones (69.5%) and significant site-specific predilection of certain primary malignancies.

Conclusions Oral and gnathic metastases are rare but demonstrate a clear predilection for the gingiva and mandible. Clinicians should remain cognizant of such lesions since they frequently mimic inflammatory, reactive or benign neoplastic processes and, in certain cases, are the first indication of occult disease.

Keywords Metastasis · Oral soft tissues · Jawbones · Gingival tumors · Osteolysis · Metastatic neoplasms · Lung · Breast

Introduction

Metastatic lesions to the oral cavity are exceedingly rare representing 1–1.5% of all intraoral malignancies [1–4]. When present, such metastases may involve the oral soft tissues,

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jaw bones, or both [2, 4–6]. The most common sites for oral soft tissue metastases are the gingiva followed by the tongue accounting for 54% and 23% of all cases, respectively [7]. When involving the gingiva, the lesions usually appear as a nodular exophytic mass mimicking other benign, hyperplastic or reactive lesions, i.e. pyogenic granuloma (PG) or peripheral giant cell granuloma (PGCG) [7, 8]. Ulceration of the overlying mucosa surfacing the lesion can be, occasionally, seen. Mobility of adjacent teeth may present as the sequela of alveolar bone destruction with concomitant chewing difficulties, dysphagia and intermittent bleeding [4, 6]. According to previously reported cohorts, lung cancer is responsible for approximately one-third of oral soft tissue metastases in males, while breast adenocarcinoma accounts for 25% of all cases in women [1, 5, 7].

Metastasis to the jaws, albeit reported in a broad age range, is most commonly encountered in older individuals without a frank gender predilection [1, 5, 7]. Symptomatology may include pain, swelling, tenderness, paresthesia, pathologic fractures and trismus [5]. Often, osseous metastases can impede healing at sites of dental extractions [4, 5]. Radiographically, metastatic tumors to the jaws present as solitary or multiple, unilocular radiolucencies with poorly-defined, "moth-eaten" borders [4]. Less frequently, mixed radiopaque/radiolucent features can be seen as, for example, in metastatic prostate or breast adenocarcinomas with osteoblastic activity [7, 9]. The non-pathognomonic radiographic characteristics of jawbone metastatic tumors frequently lead to erroneous interpretations as inflammatory processes [4, 5, 10].

Although in most instances a diagnosis of primary malignancy is already established when metastases are detected, in approximately 25–30% of the patients the oral lesions are the first manifestation of underlying disease [1–3, 5, 7, 11]. Oral soft tissue and gnathic metastases are associated with dismal prognosis and survival rates of less than 1 year [4]. Herein, we perform a retrospective analysis of the epidemiologic and clinicopathologic features of 40 examples of oral metastatic tumors along with a comprehensive review of the pertinent literature.

Materials and Methods

Retrospective Cohort Case Identification and Inclusion Criteria

The archives of the Oral and Maxillofacial Pathology Laboratory, School of Dentistry, University of Minnesota, were retrospectively searched for cases diagnosed as metastatic tumors to the oral soft tissues or gnathic bones between January of 2003 and March of 2021. Criteria for inclusion were as follows: (a) availability of the original tissue paraffin blocks and/or hematoxylin and eosin-stained preparations of the specimens, along with any immunohistochemical (IHC) stains requested at the time of diagnosis, (b) oral metastatic lesions with proper documentation of their clinical and radiographic characteristics, along with confirmation of a pre-existing primary malignancy from the patients' medical history, or (c) lesions with histopathologic and/or IHC findings suggestive of metastatic disease with or without subsequent discovery of the primary site or presence of other metastatic foci. Cases with insufficient clinicopathologic documentation and unavailable blocks and histopathologic slides were excluded from this study. Forty cases were identified and are presented herein. The age and gender of the patients, site of primary malignancy, location of metastatic lesion(s) (i.e. soft tissues and/or gnathic bones), clinical impression as well as histopathologic diagnosis and ancillary IHC stains for each case were collected and tabulated.

Literature Review

Pubmed and Medline were researched for well-documented, original case series or review studies on metastatic tumors to the oral cavity and/or jawbones using the following keywords: "oral metastasis", "metastatic oral cancer", "jaw metastases", "metastasis to the head and neck", "metastasis to the oral cavity", "gingival metastasis", "metastasis to oral soft tissues". Exclusion criteria included: (a) studies with small number of reported cases ($n < 5$) or singular case reports, and (b) lack of adequate documentation of the primary site or the clinicopathologic characteristics of the intraoral metastasis. Thirteen original case series and one previously published literature review [1, 3, 8, 10, 12–21] were utilized for the current study leading to a total number of 1084 metastatic cases. Information regarding the patients' age and gender as well as site of primary tumor and location of metastases was collected. In review studies where the age of each individual patient was not disclosed, the reported mean age was utilized for further analysis.

Statistical Analysis

Demographic and clinical characteristics of cases in the retrospective cohort and literature review were separately summarized using descriptive statistics. Among cases identified in the literature review, the associations between primary malignancy diagnosis (each tumor site separately versus all other tumor sites) and location of metastases (oral soft tissue, gnathic bone) were assessed using Chi-squared and Fisher's exact tests as appropriate. Analyses were conducted using SAS 9.4 (Cary, NC) and p-values < 0.05 were considered statistically significant.

Results

Retrospective Cohort

Forty metastatic tumor cases were identified out of 127,984 diagnoses, accounting for 0.03% of all accessioned specimens during that period (Table 1). Of 40 lesions, 22 presented in men (55.0%) and 18 in women (45.0%) with a median of 66.5 years at the time of diagnosis and age range = 18–94 years. Nineteen of 40 (47.5%) metastatic tumors affected the oral soft tissues without evidence of bone involvement. Specifically, 18 of 40 (45%) involved the gingiva and 1 of 40 (2.5%) the tongue. The gingival lesions varied in size, were soft to palpation, generally asymptomatic, presented as pink or erythematous, occasionally ulcerated and exophytic masses (Fig. 1A, B and D).

Metastases confined only to the jawbones comprised 5 of 40 cases (12.5%, Table 1) and they were all located in the mandible. Furthermore, in 16 of 40 (40%) cases the gingival metastatic growths were accompanied by bone osteolytic lesions (Fig. 1E). Radiographically, jawbone metastatic lesions presented as solitary or multifocal, radiolucencies with irregular, ill-defined borders (Fig. 1G).

Regarding the organ of primary malignancy, lung was the most frequent primary location in both men and women alike with 6 of 22 (27.3%) and 5 of 18 (27.7%) cases, respectively (Fig. 2A and B). In males, the second most common primary site was the colon (4 of 22, 18.2%), followed by the kidneys (3 of 22, 13.7%), prostate and pancreas (2 of 22 each, 9.1%, Fig. 2A). More rare anatomic locations for the primary tumor included the heart, esophagus, and sublingual gland (1 of 22 each, 4.5%). In females, besides the lung, common primary sites comprised the colon (4 of 18, 22.2%), breast (3 of 18, 16.6%), and kidneys (2 of 18, 11.1%), while less frequently the adrenal glands, bone, central nervous system (CNS) and female genital organs (FGO) were also reported (1 of 18 each, 5.6%, Fig. 2B). In two cases, both affecting men, identification of the primary site was not available at the time of diagnosis.

With regards to clinical impression at the time of biopsy, possibility of metastatic disease was considered in approximately two thirds of the cases by the clinicians, while either reactive, inflammatory or other neoplastic processes were considered in the remaining cases (see Table 1). Microscopically, the striking majority of oral and gnathic metastases were carcinomas (37 of 40, 92.5%, Fig. 1C, F, H and I) with only 3 of 40 (7.5%) cases representing sarcomas.

Literature Review

A comprehensive review of the English-written literature resulted in 1084 reported cases of intraoral soft tissue and jawbone metastatic lesions that fulfilled the inclusion criteria of the current study (Table 2). Of 1084 cases, 578 (53.3%) affected men (mean age = 54.5 years) and 476 (43.9%) women (mean age = 50.1 years; male-to-female ratio = 1.2); the gender of the patients was not reported in 30 cases (2.8%). The mean age for both genders was 52.3 years (age range = 0.6–90 years), with a stronger predilection for the 6th and 7th decades of life. The majority of metastases occurred in the jawbones (n = 753, 69.5%; mean age = 53.9 years), while the remaining cases involved the intraoral soft tissues (n = 331, 30.5%; mean age = 49.2 years).

The majority of oral and jawbone metastases originated from primary malignancies of the lung (n = 202, 18.6%) and the breast (n = 183, 16.9%), followed by the kidney (n = 105, 9.7%), colo-rectum (n = 67, 6.2%) and liver (n = 58, 5.4%). Less common primary locations included the skeletal system (n = 51, 4.7%), skin (n = 48, 4.4%), adrenal glands and prostate (n = 42 each, 3.9%), thyroid (n = 36, 3.3%) and female genital organs (n = 34, 3.1%). Metastatic lesions from the testes, esophagus, eyes, stomach, brain and bladder were less frequently reported and comprised less than 3% of the total each. The two most rare organs or tissues of origin were the skeletal and smooth muscles and pancreas with 7 (0.6%) and 2 (0.2%), respectively. However, in 90 (8.3%) reported cases the location of primary malignancy could not be determined. The distribution of all 1084 metastatic cases according to their primary tissue or organ is tabulated (Table 2) and depicted in Fig. 3A. Significant associations between primary malignancy site and jawbone versus oral soft tissues metastases were observed. Notably, malignancies originating from the breast ($p < 0.0001$), adrenal glands ($p < 0.0001$), female genital organs ($p = 0.0006$), prostate ($p < 0.0001$) and eyes ($p = 0.03$) were more likely to metastasize to the jawbones rather than the oral soft tissues (Fig. 3B). In contrast, lung ($p < 0.00001$), kidney ($p = 0.0012$), skin (< 0.0001) and stomach ($p = 0.0055$) primary cancers tended to metastasize more frequently to the oral soft tissues (Fig. 3B). Statistical differences in other sites were not observed.

When stratified based on gender, lung (n = 160, 27.7%) was the most frequent primary site for men, followed by the kidney (n = 66, 11.4%), prostate and liver (n = 42 each, 7.3%), colo-rectum (n = 32, 5.5%), skeletal system (n = 30, 5.2%) and testes (n = 29, 5.0%; Fig. 4A). On the other hand, brain, breast and pancreas were the least common primary tumor locations in male individuals with 5 (0.9%), 5 (0.9%) and 2 (0.4%) examples, respectively (Fig. 4A). In contrast to men where the majority of intraoral and gnathic metastases derived from the lungs, in women metastatic lesions

Table 1 Presentation of the epidemiologic, histopathologic and immunohistochemical characteristics of the metastatic lesions (N = 40) to the oral soft tissues and jawbones included in the current cohort

Case	Gender	Age	Site of primary tumor	Site of oral metastasis	Clinical impression	Histopathologic diagnosis	Positive immunohistochemical markers
1	M	60	Colon	Gingiva (Mn) and Mandible (Posterior)	Metastasis	Metastatic AdCa	N/A
2	M	58	Sublingual gland	Mandible (Anterior)	Metastasis	Metastatic Adenoid Cystic Ca, solid variant	N/A
3	M	51	Kidney	Gingiva (Mn) and Mandible (Anterior)	PG	Metastatic Kidney Ca	N/A
4	M	75	Colon	Gingiva (Mn)	PG, SCC	Metastatic AdCa	CDX2, CK20
5	M	81	Lung	Gingiva (Mx)	SCC	Metastatic AdCa	CK7
6	F	18	Bones	Gingiva (Mn) and Mandible (Posterior)	N/A	Metastatic Ewing's Sarcoma	CD99
7	F	70	Colon	Gingiva (Mx)	PG, SCC	Metastatic AdCa	AE1/AE3, CK7, CK20, Myogenin, CDX2, CA125
8	M	77	Lung	Gingiva (Mn) and Mandible (Posterior)	Osteosarcoma, Metastasis	Metastatic Small Cell Neuroendocrine Ca	Chromogranin, Synaptophysin, AE1/AE3, TTF-1
9	M	73	NOS	Gingiva (Mn)	Fibroma, Metastasis	Metastatic Ca	AE1/AE3, Vimentin
10	M	51	Pancreas	Mandible (Posterior)	SCC, Metastasis	Metastatic Ca	CK7
11	M	80	Prostate	Mandible (Posterior)	Metastasis	Metastatic AdCa	N/A
12	F	60	CNS	Gingiva (Mx) and Maxilla (Posterior)	PG, Metastasis	Metastatic Ca	N/A
13	M	65	Pancreas	Gingiva (Mn)	SCC	Metastatic AdCa	CK7, CEA, CDX2, CA19-9
14	F	78	Lung	Gingiva (Mn) and Mandible (Posterior)	PG, Metastasis	Metastatic Small Cell Neuroendocrine Ca	AE1/AE3, CK7, CK20, Chromogranin, Synaptophysin, NSE, TTF-1
15	M	77	Kidney	Gingiva (Mx)	PG, Metastasis	Metastatic Renal Cell Ca	AE1/AE3, Vimentin, CD31
16	F	56	Lung	Gingiva (Mx and Mn, Posterior)	PG, Metastasis	Metastatic AdCa	AE1/AE3
17	F	92	Colon	Gingiva (Mx)	Metastasis	Metastatic AdCa	N/A
18	F	63	Kidney	Gingiva (Mn) and Mandible (Posterior)	Ameloblastoma	Metastatic Renal Cell Ca	RCC, AE1/AE3
19	M	59	Kidney	Tongue	Metastasis	Metastatic Renal Cell Ca	N/A
20	M	70	Heart	Gingiva (Mx)	Metastasis	Metastatic Angiosarcoma	N/A
21	M	88	Colon	Gingiva (Mn) and Mandible (Posterior)	Osteomyelitis, SCC	Metastatic AdCa	CDX2, CK7, CK20
22	F	83	Adrenal gland	Gingiva (Mn) and Mandible (Posterior)	Metastasis	Metastatic Ca	N/A
23	M	65	Lung	Gingiva (Mn)	Metastasis	Metastatic AdCa	TTF-1
24	F	57	Lung	Gingiva (Mx)	PG, Metastasis	Metastatic AdCa	AE1/AE3, TTF-1, WT1, Calretinin
25	F	94	Breast	Gingiva (Mn)	SCC	Metastatic Ductal AdCa	ER, PR
26	M	69	Esophagus	Gingiva (Mn)	PG	Metastatic AdCa	N/A
27	F	66	Lung	Gingiva (Mn)	SCC, Metastasis	Metastatic Small Cell Neuroendocrine Ca	Synaptophysin, Chromogranin
28	F	50	Lung	Gingiva (Mx)	Fibroma, POF	Metastatic Non-Small Cell Ca	N/A

Table 1 (continued)

Case	Gender	Age	Site of primary tumor	Site of oral metastasis	Clinical impression	Histopathologic diagnosis	Positive immunohistochemical markers
29	F	58	FGO	Gingiva (Mn)	PG, PGCG, Metastasis	Metastatic High-grade Sarcoma, Malignant Mixed Müllerian Tumor	N/A
30	F	94	Breast	Gingiva (MN) and Mandible (Posterior)	N/A	Metastatic Ca	AE1/AE3, CK7, ER, PR, GATA3
31	M	57	Colon	Gingiva (Mx) and Maxilla	Metastasis	Metastatic AdCa	N/A
32	F	81	Colon	Mandible (Anterior)	Periodontal disease, Metastasis	Metastatic AdCa	Mucicarmine, CK7, Inhibin, CEA, CDX2
33	F	71	Kidney	Gingiva (Mn)	PGCG, PG, POF, Metastasis	Metastatic Clear Cell Ca	AE1/AE3, Vimentin, EMA, PAX8, CD10
34	M	63	Lung	Gingiva (Mn) and Mandible (Anterior)	PG, PGCG, Fibroma, SCC	Metastatic Ca	AE1/AE3
35	M	67	Lung	Gingiva (Mn) and Mandible (Posterior)	Metastasis	Metastatic AdCa	CK7
36	M	62	Lung	Gingiva (Mn)	PGCG, PG, POF, Metastasis	Metastatic AdCa	TTF-1
37	F	42	Breast	Gingiva (Mx) and Maxilla (Posterior)	Metastasis	Metastatic Ductal AdCa	ER, PR, HER2, GATA3
38	M	50	NOS	Mandible (Posterior and Anterior)	Langerhans Histiocytosis, CGCG, Metastasis	Metastatic AdCa	CK7, CK20, TTF-1, CDX2, CEA
39	F	85	Colon	Gingiva (Mn) and Mandible (Anterior)	PG	Metastatic AdCa	N/A
40	M	70	Prostate	Gingiva (Mn) and Mandible (Posterior)	Osteosarcoma	Metastatic AdCa	CK7, CK20, TTF-1, GATA3, NKX3.1

Male-to-Female ratio = 22:18; Median age = 66.5 years; Age range = 18–94 years

Mn mandibular, *Mx* maxillary, *PG* pyogenic granuloma, *SCC* squamous cell carcinoma, *POF* peripheral ossifying fibroma, *PGCG* peripheral giant cell granuloma, *CGCG* central giant cell granuloma, *AdCa* adenocarcinoma, *Ca* carcinoma, *CEA* carcinoembryonic antigen, *NSE* neuron specific enolase, *RCC* renal cell carcinoma, *ER* estrogen, *PR* progesterone, *N/A* not available, *NOS* not otherwise specified, *CNS* central nervous system, *FGO* female genital organs

from the breast were predominant (n = 178, 37.4%; Fig. 4B). Other less frequent primary locations in women comprised the kidneys (n = 38, 8.0%), lung (n = 36, 7.6%), female genital organs (n = 34, 7.1%), colo-rectum (n = 33, 6.9%), thyroid (n = 28, 5.9%) and bones (n = 21, 4.4%), whereas least common were the bladder (n = 3, 0.6%) and muscles (n = 1, 0.2%; Fig. 4B).

Discussion

Carcinogenesis represents a multistep and convoluted process characterized by a multitude of biological changes enabling the neoplastic cells to exert functions and acquire attributes that clearly separate them from their normal cell of origin [22, 23]. These properties, frequently referred to as the "hallmarks" of cancer, encompass sustaining proliferative signaling, avoiding programmed cell death and destruction by immune cells, enabling replicative immortality along with increased genomic instability and mutation burden, in addition to inducing angiogenesis and activating the invasion–metastasis cascade [22, 24]. It is now well-established that the process of "epithelial–mesenchymal transition" is prominently involved and broadly regulates invasion and metastasis [22, 25]. By assimilating capabilities important in embryonic tissue and organ morphogenesis and wound healing, transformed epithelial cells can acquire the capacity to invade and disseminate [26–29]. Tumor cells invade the underlying or surrounding extracellular matrix mainly using enzymatic collagen degradation by matrix metalloproteinases (MMPs). Subsequent tumor growth is highly dependent on angiogenesis; the latter is promoted by intralesional hypoxia which serves as a key stimulus for upregulation of proangiogenic signals, i.e. vascular endothelial growth factors (VEGFs) [4, 5, 30–33]. Tumor neovasculature is characterized by immature capillary sprouting, excessive vessel branching, distorted and enlarged vessels, increased blood flow,

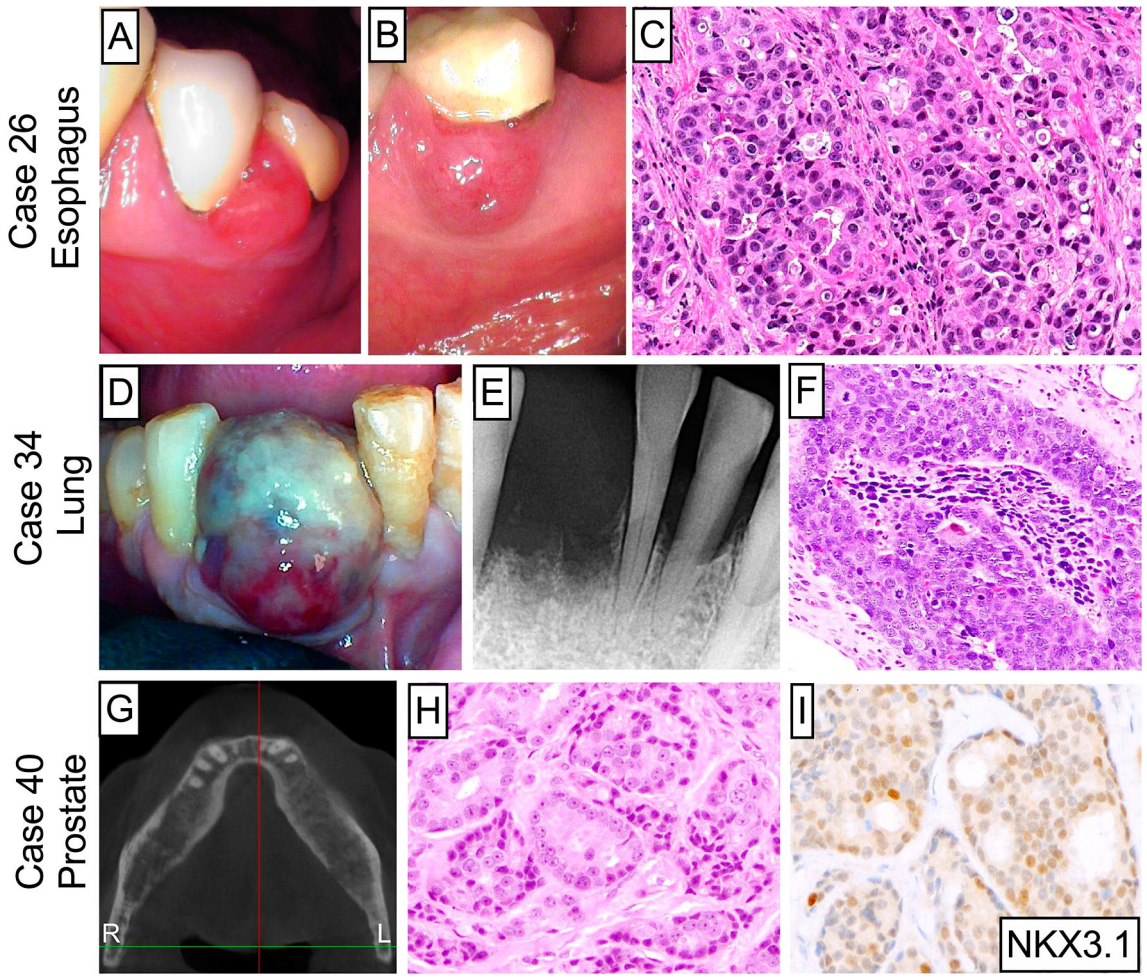

Fig. 1 **A**-**C** Clinical photos of an esophageal AdCa (Case 26, Table 1) metastasizing to the buccal (**A**) and lingual (**B**) gingiva associated with the left mandibular first and second premolars (teeth #20–21); **C** Medium-power photomicrograph depicting the histopathologic features of the tumor (H&E; original magnification × 20); **D**–**F** Clinical, radiographic and histopathologic characteristics of a lung Ca metastasizing to the oral cavity (Case 34). The lesion presented as a large, erythematous, focally ulcerated, tumorous growth of the anterior mandible (**D**) associated with significant irregular and asymmetric bone loss (**E**) (teeth #23, 24 and 27); **F** Medium-power photomicrograph displaying the histopathologic properties of the tumor featuring marked atypia, cellular and nuclear pleomorphism, hyperchromasia and increased number of mitotic figures (H&E; original magnification × 20); **G**–**I** Radiologic, histopathologic and immunohistochemical characteristics of a metastatic AdCa from the prostate (Case 40). **G** Computed tomography scan (axial plane) revealed diffuse, bilateral, mixed radiopacities and radiolucencies of the posterior mandible with thinning of the cortical plates and areas of perforation; **H** The neoplastic cells form ductal structures and solid nests, and show weak to moderate, nuclear immunoreactivity for NKX3.1 **I** (H&E and immunoperoxidase; original magnification × 20)

microhemorrhaging, and abnormal levels of endothelial cell proliferation [22].

The neoplastic cells intravasate either physiologic lymphovascular structures located in anatomic proximity with the growing tumor or the newly formed and largely immature intralesional blood vessels that exhibit weak endothelial-cell barrier [34]. Circulating tumor cells (CTCs) that survive, actively adhere to the microvasculature of a downstream site, extravasate through the lumina of blood vessels into the parenchyma of the distant organ, adapt to the new microenvironment and establish micrometastases [5, 35]. The growth of such micrometastatic foci into macroscopic, clinically detectable, lesions represents the final step of the invasion–metastasis cascade and is termed "colonization" [22]. Many of the micrometastases remain in a state of clinical dormancy and appear years after the manifestation of the primary tumor. Disruption of the balance between proliferative and apoptotic cellular signaling is hypothesized to trigger tumor awakening, albeit the exact mechanisms regulating tumor dormancy and reactivation remain largely unexplored [36].

Metastases to the oral soft tissues and jawbones are extremely uncommon constituting 1–1.5% of all intraoral malignant neoplasms [1, 4, 5, 20]. In our cohort, metastatic

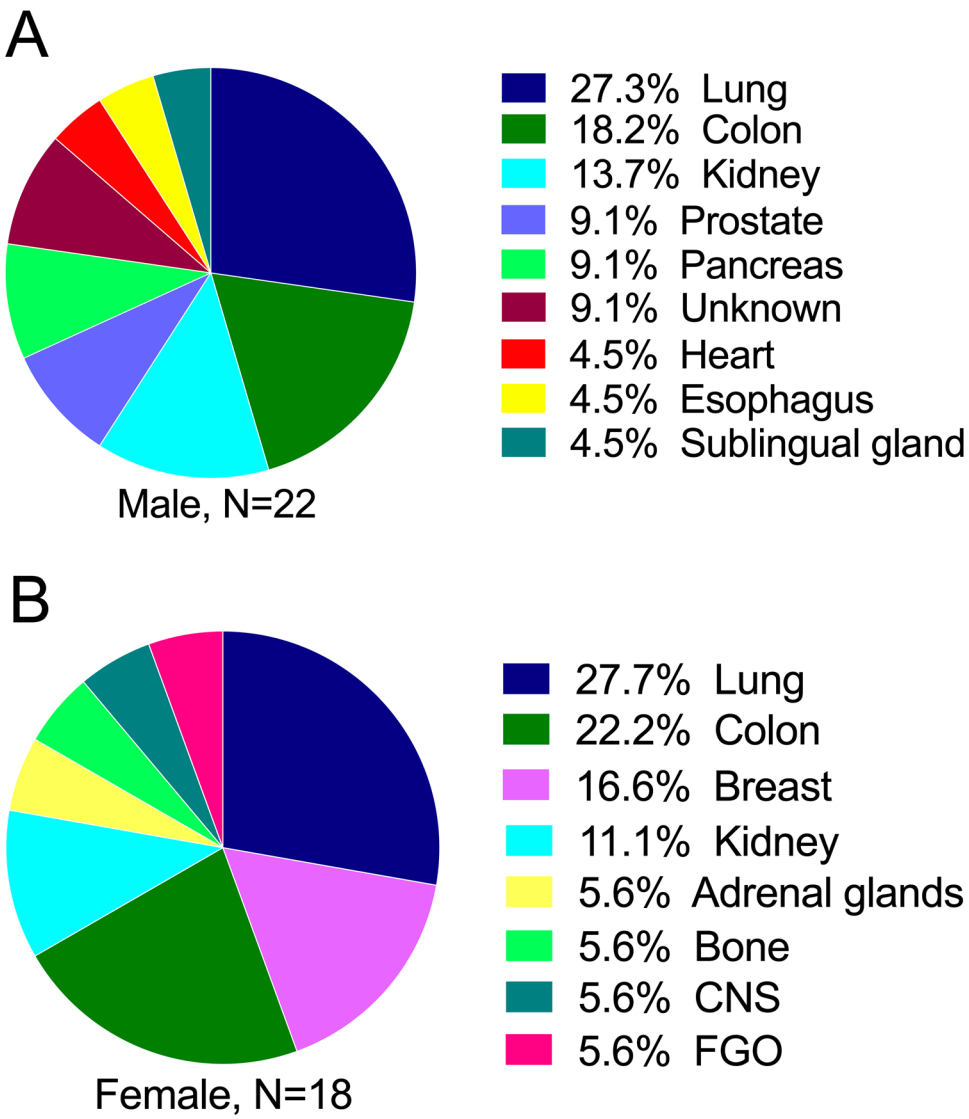

Fig. 2 Distribution of the primary sites of malignancy for men (**A**) and women (**B**) with metastases to the oral soft tissues and jawbones identified in this study

tumors (N = 40) represented only a small fraction (0.003%) of all cases diagnosed in this laboratory during a 19-year period. Review of the literature for such lesions is vexing since most of existing data are in the form of single case reports or short-scaled case series. Furthermore, there appears to be a bias for examples with unusual presentation or rare primary tumors [1, 5]. Few previously published studies [2, 3, 5, 11], which we also utilized for our current analysis, have performed a thorough review of the English-written literature since 1916. However, one should take into consideration that the means for proper histopathologic documentation and radiologic identification of the primary tumors were not as developed or reliable as in the modern era. Regarding the location, analysis of 1084 metastatic cases showed a predilection for the gnathic bones compared to the oral mucosa (69.5% and 30.5%, respectively) [1, 3, 8, 10, 12–21]. However, as shown herein, lesions confined only to the jawbones were less frequent than those of the soft tissues. Notably, in 40% of our cases there was concomitant bone and gingival involvement. It is likely that at least a subset of the metastatic tumors described in the literature as intraosseous may have also presented with soft tissue lesions.

The oral cavity is an uncommon location for metastasis due to various filtration systems that prevent the spread of disease [5]. Batson's valveless vertebral venous plexus has been proposed as a potential pathway for distant metastases which would allow CTCs to bypass lung filtration [5, 37]. As we show here and in agreement with previously published case series, the gingiva represent the most common site for metastatic colonization to the oral mucosa [5, 8, 38, 39], whereas other locations such as the tongue are only rarely affected. The high predilection of metastases for the gingiva is not random. A significant association between gingival metastasis and presence of teeth [39] strongly supports the role of chronic inflammation and dense capillary network in

Table 2 Review of the English literature on metastatic tumors to the oral cavity and jawbones; the gender of patients, metastatic location, and organ or site of primary malignancy are presented

Primary site	Total	Jawbones				Oral mucosa			
		Total	M	F	N/A	Total	M	F	N/A
Lung	202	109	89	19	1	93	71	17	5
Breast	183	156	3	153		27	2	25	0
Kidney	105	58	34	24		47	32	14	1
Bone	51	36	22	14		15	8	7	
Colo-rectum	67	46	20	24	2	21	12	9	
Skin	48	20	10	9	1	28	16	9	3
Adrenal	42	42	22	20		0			
Liver	58	44	30	13	1	14	12	2	
FGO	34	21		21		13		13	
Prostate	42	40	40			2	2		
Thyroid	36	28	5	23		8	3	5	
Eye	21	19	8	9	2	2		1	1
Testes	29	22	22			7	7		
Stomach	17	6	4	2		11	6	4	1
Esophagus	23	15	12	3		8	6	2	
Brain	14	12	4	8		2	1	1	
Bladder	13	10	8	2		3	2	1	
Other	90	64	39	13	12	26	18	8	
Muscle	7	4	4			3	2	1	
Pancreas	2	1	1			1	1		
Total	1084	753	377	357	19	331	201	119	11

FGO female genital organs, *N/A* not available

the recruitment, transportation and settling of CTCs in the gingival tissues [5, 39]. The microenvironment of chronically inflamed gingiva rich in soluble cytokines, i.e. interleukin-1 and TNF-α, serves as a prosperous niche for metastatic colonization and growth [5, 8, 38, 39]. Of clinical importance is the fact that gingival metastatic tumors can often mimic benign neoplastic, inflammatory or reactive lesions, including PG, PGCG, peripheral ossifying fibroma (POF) and hemangiomas or vascular malformations [5, 38, 39].

Bone represents the preferred site of metastasis for numerous solid tumors mainly originating from the breast, prostate, thyroid gland and kidneys [40, 41], albeit bone-only metastases are rare [5]. In our analysis of 1084 intraoral metastatic tumors, we observed a significant affinity of malignancies from the breast, prostate, adrenal glands and female reproductive genital organs towards the jawbones (see Fig. 3B). In contrast, lung metastases which are the most common when cases are not stratified based on gender, exhibit a strong predilection for the oral soft tissues. Regarding jawbones, there exists a strong predisposition for metastatic colonization of the mandible compared to the maxilla or other craniofacial bones [1–3, 5, 10, 11]. This may be attributed either to the presence of residual hematopoietic bone marrow or the sinusoidal and perplexed morphology of the vasculature of the posterior mandible, which allows for settling of metastatic cells [1, 5, 37]. Metastases to the mandible account for up to 80% of bony metastatic lesions, of which 55% involve the molar and 38% the premolar regions [5]. In our study, we report involvement of the mandible with or without gingival lesions in 45% of the cases. Notably, involvement of both jawbones may occur in up to 5% of reported metastases [13, 42], while another 5% of the cases lack any radiographic changes [5].

Our data also suggest that the most common types of metastatic tumors encountered in the oral cavity generally mirror the most frequent human malignancies. For example, lung was the most common primary tumor site in our cohort in both men and women (27.3% and 27.7%, respectively). Furthermore, review of the cases from the literature revealed the lung as the most frequent primary site in males (27.7%) and the breast in females (37.4%). Although kidney and renal pelvis malignancies account for only 4% of all cancers with 76,080 estimated new cases in 2021 in the United States [43], renal metastases comprised the second most frequent intraoral metastatic lesion in both men and women (11.4% and 8.0%, respectively). Interestingly, metastases from the kidneys were more commonly encountered than those originating from the prostate and colo-rectum (see Fig. 4), although prostatic and colorectal tumors are more prevalent among human cancers. Such discrepancies most likely reflect differences in the biologic behavior and level of aggressiveness of the primary malignancy, as well as

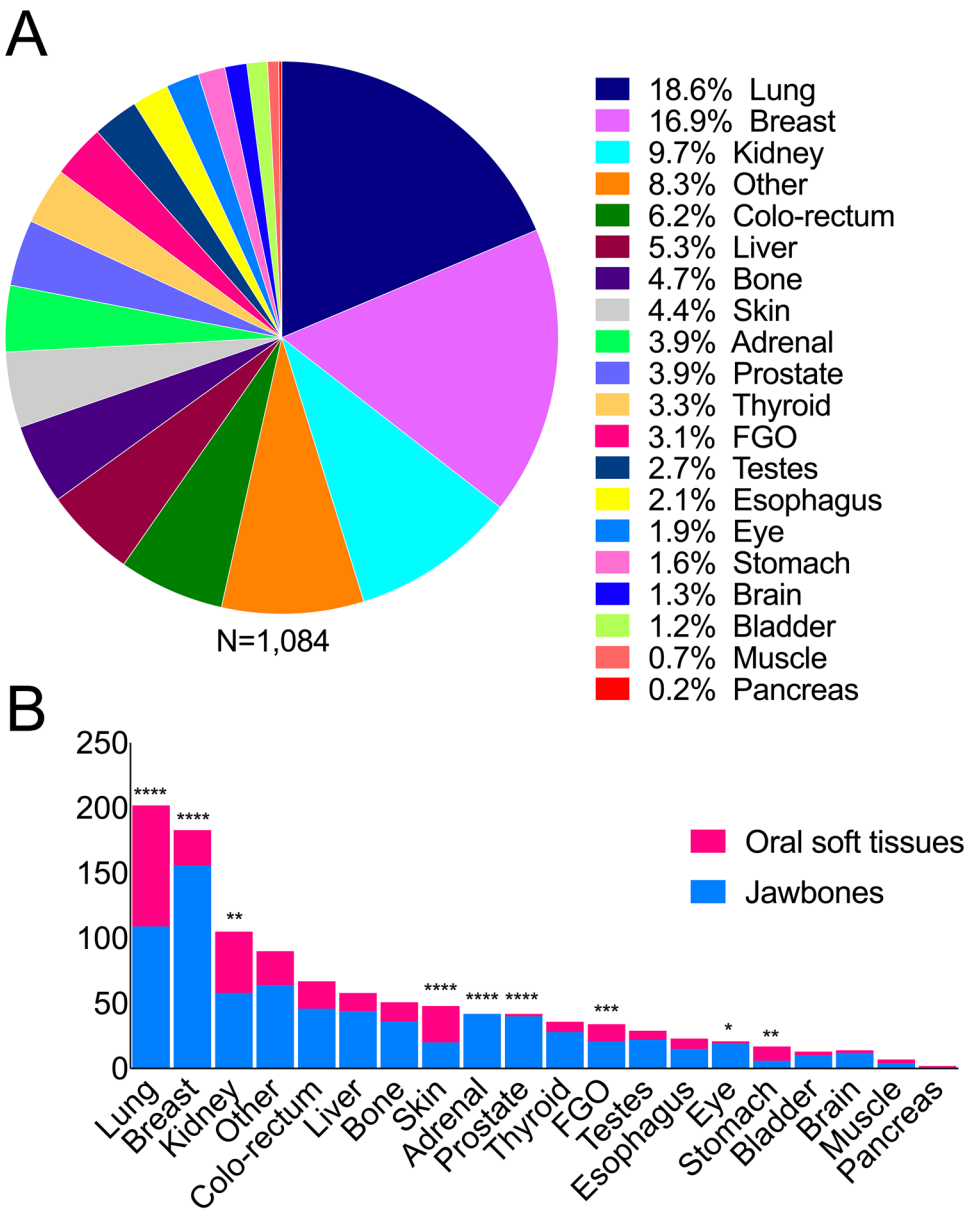

Fig. 3 **A** Distribution of the primary sites of malignancy with metastasis to the oral soft tissues and jawbones collected from the literature (N = 1084); **B** Summation of metastases to the oral soft tissues and jawbones (N = 1084) stratified by location of primary tumor as reported in the literature review. Associations between primary malignancy diagnosis and location of metastases were assessed using Chi-squared and Fisher's exact tests. Statistically significant associations between primary malignancy site and jawbone versus oral soft tissues metastases were observed; tumors originating from the breast, adrenal glands, female genital organs, prostate and eyes were more likely to metastasize to the gnathic bones, whereas lung, kidney, skin and stomach primary cancers tended to metastasize more frequently to the oral soft tissues. Statistically significant relationships are depicted (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001)

possible affinity towards oral tissues [3, 5, 44]. Certain types of primary cancer, such as skeletal and smooth muscle sarcomas (0.7%) and pancreatic carcinomas (0.2%), only rarely metastasize to the oral cavity. The latter may be attributed to the fact that the patients succumb to the disease before oral metastases can manifest.

From a diagnostic standpoint, the more recent availability of lineage specific immunohistochemical markers may aid in the identification of occult primary tumors when metastasis to the oral cavity is suspected and the primary site is unknown. Depending on the histologic characteristics of the tumor, stains against pancytokeratin (i.e. AE1/AE3, Cam 5.2, OSCAR) and p63, S100 protein, vimentin or desmin, and leukocyte common antigen (LCA; CD45) usually comprise the initial screening panel to rule out metastatic carcinoma, melanoma, sarcoma and lymphoma, respectively [1, 5, 45]. For metastatic adenocarcinomas, the differential expression of CK7 and CK20 followed by relevant site-specific markers can help localize the primary site of malignancy. For instance, a CK7 + /CK20- immunoprofile with TTF1 positivity would be suggestive of lung primary, whereas a CK7-/CK20 + , CDX2 + or SATB2 + immunophenotype indicates colorectal origin [1, 46]. Positivity for CK7, ER/PR, GATA3 and mammaglobin is helpful in identifying metastatic adenocarcinomas of the breast, while NKX3.1 along with other prostate-restricted markers, such as PSA or PSAP, can be valuable in determining prostatic origin [1, 5, 47]. Finally, CK7/CK20 negativity with RCC, PAX8 and CD10 positivity would highlight a renal metastatic tumor [1, 5], while

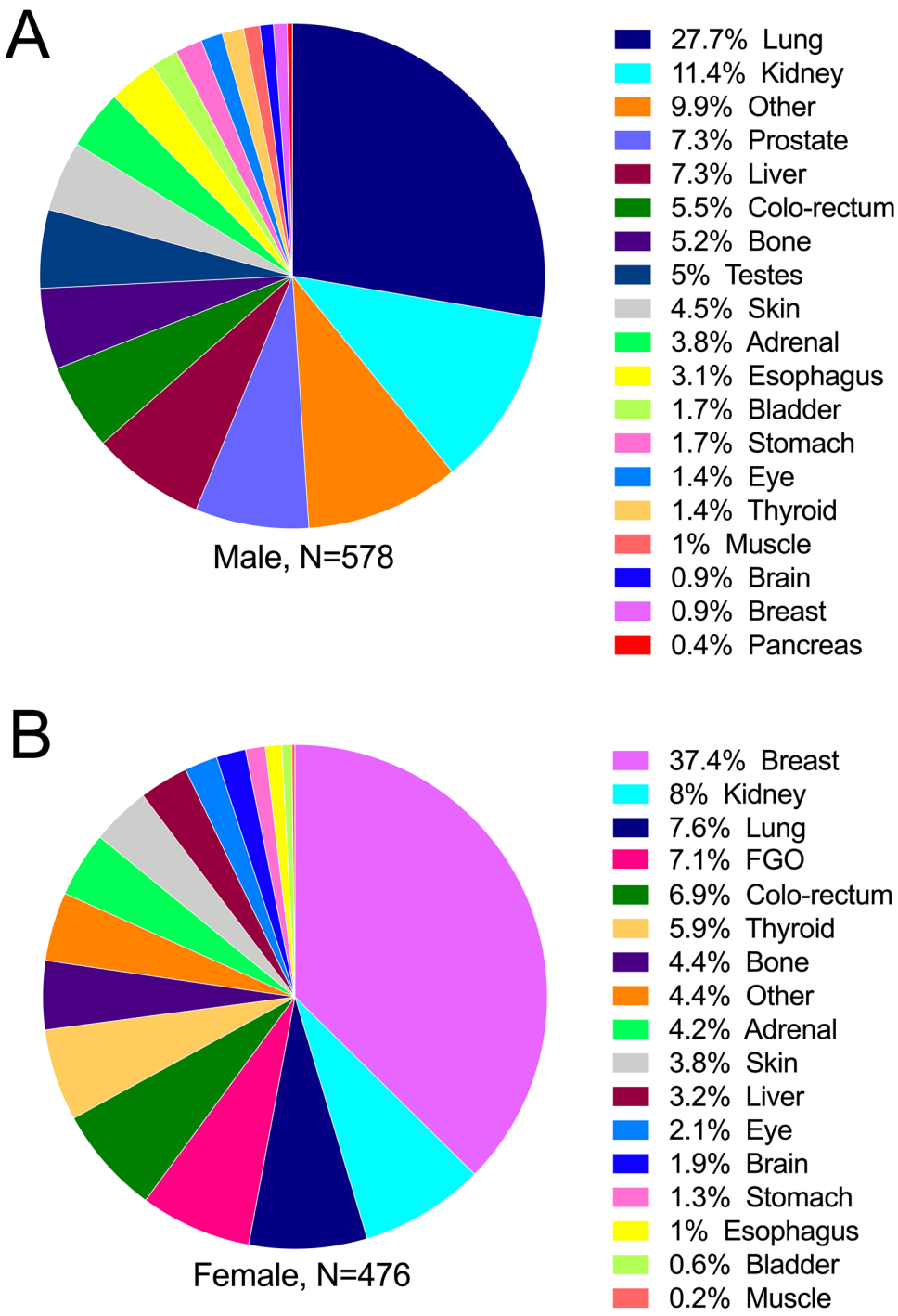

Fig. 4 Distribution of the primary sites of malignancy for men (**A**) and women (**B**) with metastases to the oral soft tissues and jawbones identified in the review of the literature

a CK7 + /CK20-, WT1 + and PAX8 + immunophenotype is consistent with an ovarian primary [48, 49]. It is worth mentioning that despite extensive immunohistochemical investigation, discovery of the primary location may not be feasible for certain metastatic neoplasms. Since metastases of unknown primary may retain the molecular signature of the primary tumor, DNA- and RNA- based molecular techniques can be implemented to elucidate the profile and origin of such lesions [50].

Intraoral metastatic lesions usually signify late-stage disease, although in approximately 25% of the cases metastases to the oral soft tissues and jawbones were the first indication of underlying malignancy [5, 37]. Oral metastasis in individuals younger than 40 years of age is quite unlikely and mainly associated with neuroendocrine neoplasms [18, 20]. In the cohort from our institution only one patient younger than 40 was found, an 18 year-old female, who presented with gingival and intraosseous lesions of the mandible

consistent with metastatic Ewing's sarcoma. Furthermore, in agreement with previous studies [1, 2, 11], the striking majority of metastases (> 92%) represented carcinomas with only 3 examples of primary sarcoma metastasizing to the oral soft tissues and jawbones identified. The latter most likely mirrors the overall rarity of soft tissue sarcomas when compared to epithelial malignancies [1].

Survival rates of patients with metastasis to the head and neck are dismal. Patients with evidence of maxillofacial metastatic disease have a 30% survival rate after the first year of diagnosis [20] and a mean survival time of approximately 7 months [3, 5, 51]. Unique to this statistic are the pediatric patients with a reported 5-year survival rate approaching 80% [18]. The latter is attributed to the nature and biologic behavior of their primary tumors which include neuroblastoma and retinoblastoma [18, 20]. Available therapeutic regimens are dependent on several factors including location of the lesion, site of origin, and severity of metastatic spread [19], and encompass local resection with or without chemotherapy and/or radiotherapy. However, in most cases treatment is mainly palliative and aims to improve the quality of life of the patients [3, 5].

In conclusion, herein we shared our single—institution experience regarding metastatic neoplasms affecting the oral cavity and jawbones by contributing 40 additional examples of such tumors to the literature. Although oral soft tissue and jawbone metastases are exceedingly uncommon, they demonstrate a clear predilection for the gingiva and the mandible. Clinicians should remain cognizant of such lesions since they frequently mimic inflammatory, reactive or benign neoplastic processes and, in certain cases, are the first and only indication of occult disease.

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Code Availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflict of interest to disclose.

Ethical Approval This retrospective cohort is exempt from institutional IRB approval.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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