

METASTASIS TO OROFACIAL REGION: A REVIEW

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ABSTRACT:

The majority of cancer related deaths are due to metastasis, the process by which a malignancy spreads from a primary to a distant site. The oral presentation of metastasis may be seen before, after or simultaneously along with the malignant disease. It is generally accepted that the demonstration of metastatic lesions in the oral & maxillofacial (OMF) region involves a grave prognosis. The aim of this review is to collect the data in available literature on metastasis from extraoral sites to oral & maxillofacial region & then categorize it systematically according to age, sex, primary site & oral site which can help in early diagnosis & referral to appropriate health care facility.

Keywords: Metastasis, carcinoma, malignancies, primary site, orofacial.



INTRODUCTION:

Metastasis (meta means transformation, stasis means residence) is defined as spread of tumor by invasion in such a way that discontinuous secondary tumor mass/ masses are formed at the site of lodgement. ^[1]

Metastatic malignancies found in the oral and maxillofacial region are rare which account for only 1% of all malignancies of the jaw. In 22% to 30% of cases, the oral presentation of metastasis is the first sign of malignant disease. In about 67% of cases, metastatic lesions are detected at the same time as the primary lesion. Malignant epithelial tumours

(carcinomas) metastasize to the oral region more commonly than mesenchymal tumours (sarcomas). ^[2]

The jaw bones are involved more frequently than the oral soft tissues. The mandible is the most often affected region and the molar area, the most frequently involved site. ^[2]

Among oral soft tissues, the most common oral site was the gingiva and alveolar mucosa followed by the tongue and with much less frequency by the tonsil, palate, lip, buccal mucosa and floor of the mouth. The clinical appearance of the metastatic oral

lesions frequently resembled hyperplastic or reactive lesions. [3]

The most common sources of metastatic lesions to the oral mucosa & jaw bones were the breasts for women and lungs for men. [3,4]

GENDER AND AGE

Table 1: Comparison between cases of metastatic tumors to the jawbones and metastatic tumors to the oral mucosa in relation to age & gender.

Oral site	Number of cases	Male/female ratio	Mean Age
Oral Mucosa [Hirshberg et al (1993)] [3]	157	1.6/1	Male- 56 yrs Female- 50 yrs
Jawbone [Hirshberg et al (1994)] [4]	390	1/1.1	Male- 45.9 yrs Female- 45.2 yrs

Metastasis to the mandible was commonly seen from 4th decade onwards, whereas maxilla was the site of metastatic deposit in younger age, occurring in the first three decades of life. [5]

can give a clue to the possible primary site of a tumor that can metastasize to the jaw bones. [5]

In the younger age group (first to second decade of life), the metastasis was found to occur from adrenal neuroblastoma, medulloblastoma and osteogenic sarcoma. Thus age and sex

ORAL SITES

1. Mandible

The metastatic tumors were predominately located in the mandible (81% cases). In 5.4% cases metastatic deposits were found the both jaws. [4]

Table 2: Distribution of metastatic lesions in mandible

Hirshberg et al (1994) [4]		REINHARD et al (2010) [6]	
Molar region	55%	Corpus and alveolar process	69.2%
Premolar region	38%	Ramus	15.4%
Angle & ramus	29%	Mandibular angle/body	5.1%
Condyle	3.5%	Condylar process	7.7%
Coronoid process	1.6%	Condylar/muscular process and angle	2.6%

2. Maxilla

In only 13.6% cases the metastasis was situated in the maxilla. The tumor was

located most frequently in the maxillary premolar and molar area (58.7%). [4]

3. Oral soft tissues

In the oral soft tissues, the attached gingiva was the most common affected site, followed by the tongue. [7]

Table 3: The distribution of the metastatic lesions in the oral mucosa. [3]

Site	Percentage of cases
Gingiva (Including The Alveolar Mucosa)	54.8%
Tongue	27.4%
Tonsil	8.3%
Palate	4.4%
Lip	3.2%
Floor Of The Mouth	1.3%
Buccal Mucosa	< 1%

4. Salivary glands

The major salivary glands are regarded to be relatively frequently affected in the course of metastatic spread of malignancies. [8, 9] The parotid gland is the predominant salivary gland involved in metastasis. There are substantial differences between the parotid and the submandibular gland regarding the primary site that gives rise to their metastatic involvement. [10] According to Reinhard et al (2010) [6] parotid gland was involved in 8.7 % of cases.

The parotid gland is principally affected by tumors originating in neighboring organs, such as cutaneous melanoma, squamous cell carcinoma and the nasopharynx. [10] On the other hand, distant metastasis to the submandibular gland originates from organs more distant than those affecting the parotid, in particular below the clavicle. [11]

5. Temporomandibular joint

Metastases involving the TMJ are rare, and only 41 cases have been reported in the international literature [12,16]. The primary site of the carcinoma was the breast in 9 cases, the lung in 9, the prostate in 5 and the rectum in 3 [13], followed by the liver, cardia [14], uterus and pancreas (1 case each). In 2 cases the primary tumour was a melanoma [15], the nose being the primary site in one case and the hallux in the other. In 6 cases, the primary site was not identified. [16]

As a rule, TMJ metastases manifest clinically even years after the onset of the primary tumour. Boniello et al (2008) presented a very unusual case, unique in the literature, in which the non-reducible dislocation of the mandible was the first clinical manifestation of metastasis from pulmonary adenocarcinoma. [16]

The rarity of metastasis to the TMJ can be explained by the isolated nature of its blood supply. [17] The course of condylar metastases in general is similar to other

metastases involving the jaw. Breast cancer as the primary tumor is most frequent, followed by lung cancer.^[18]

6. Paranasal sinus

Metastases, in this area, are often secondary to renal cancer, as reported by Bernstein et al (1966)^[19] in studies on 82 patients with metastatic disease involving the paranasal sinuses and revealed that the large majority of metastases derived from renal carcinoma (40 patients) followed by testicular tumours, bronchial cancer, gastrointestinal neoplasm and breast cancer.^[19] Of note, only one case of metastatic melanoma to the ethmoid sinus has been reported in the literature.^[20]

While metastatic tumours to the paranasal sinuses have no distinctive clinical features by which to make early diagnosis, facial pain, epistaxis, nasal obstruction and facial asymmetry represent the main manifestations. These symptoms are similar to those seen in the course of upper respiratory tract infections. Conversely, diplopia, epiphora, blepharoptosis, decreased visual acuity and proptosis are the main clinical symptoms when the metastatic tumour develops in the orbit, while headache might be attributed to meningeal involvement from metastatic carcinoma.^[21]

The possibility of a primary or metastatic maxillary tumour should be suspected when treatment of a sinus infection is not effective. Given the high content of intratumoral vessels and the particular

angiostrophism of renal carcinoma, metastatic tumours originating from the kidney are usually hemorrhagic. In fact, epistaxis is present in >70% of these tumours metastatic to the paranasal sinuses.^[21] According to Yoshimura et al (1989)^[22], metastasis from renal cancer should be strongly suspected in patients with a medical history of renal carcinoma associated with epistaxis.

SIGNS AND SYMPTOMS

1. Jaw bones:

According to Hirshberg et al (1994) in 29.4% cases the oral lesion was the first sign of the metastatic disease and out of which in 37.2% cases the jaw bone metastasis was the first sign of a metastatic process. Most patients complained either of swelling (57%), pain (39%), or paresthesia (23%), which developed in a relative short time.^[4] In a review of 114 cases of metastatic jaw tumors, D'Silva et al (2006) found that the most common jaw symptom was pain.^[23]

Physical examination revealed a bony swelling, with tenderness over the affected area in most cases. Teeth mobility was noticed in 4% cases and trismus in 4% cases.^[4]

2. Oral soft tissue:

The early manifestation of the gingival metastases resembled a hyperplastic or reactive lesion, such as pyogenic granuloma, peripheral giant cell granuloma, or fibrous epulis. In other locations in the oral soft tissues the

clinical presentation was that of a submucosal mass. Only in few cases the lesion appeared as ulceration. In some cases, especially those of metastatic hepatocellular carcinoma, severe post-biopsy hemorrhagic episodes had been reported. [24]

RADIOGRAPHIC FINDINGS

Radiographic description in 86% of cases shows a lytic radiolucent lesion with ill-defined margins. Occasional osteoblastic lesions were observed as either pure or mixed radiopacity (17% of the cases). In approximately 5% of the cases, radiographs did not show any pathological changes. [7]

While metastatic prostate carcinoma gives osteoblastic appearance, and metastatic breast or renal carcinoma may be osteolytic, osteoblastic, or mixed. [23]

Breast cancer metastases are frequently osteolytic and this has been attributed to overexpression of osteoclast inducing factors such as Parathyroid Hormone Related Protein (PTHrP), interleukin (IL)-8 and IL-11. [25,26,27]

Predominantly, osteoblastic metastasis is mediated by osteoblast promoting factors like bone morphogenetic proteins (BMPs), Wnt family ligands, endothelin-1 and platelet-derived growth factor (PDGF). Furthermore, the release of matrix embedded growth factors such as insulin-like growth factor (IGF) and transforming growth factor-β (TGF-β) upon osteolysis promotes the induction of osteoclast promoting factors. [25,26]

SURVIVAL RATE

The average survival time for patients with metastatic tumors in the oral cavity is six to seven months, with approximately 70% of patients dying within one year of diagnosis. Most patients with oral metastases have already developed generalized metastases by the time of diagnosis. [4,7,28] The mean time between detection of primary tumor and diagnosis of metastasis was 42.7 months. [5]

PRIMARY SITES

According to the studies mentioned below, breast cancer patients constituted the largest subgroup of these patients.

Table 4: The primary site of the metastatic tumors according to different authors

Hirshberg et al (1994) (390 cases) [4]		D’Silva et al (2006) (114 cases) [23]		REINHARD et al (2010) (92 cases) [6]		Daley and Darling, (2011) (n = 38) [29]	
Breast	21.8 %	Breast	20.17%	Breast	2.2%	Prostate	21.05 %
Lung	12.6%	Lung	13.15%	Lung	4.8%	Lung	18.42 %
Adrenal	8.7%	Prostate	9.64%	Rectal	5.6%	Breast	13.15 %
Kidney	7.9%	Colon	7.01%	Prostate	3.7%	Kidney	7.89 %
Bone	7.4%	Kidney	2.63%	Thyroid	1.9%	Colon	5.26 %
Colorectal	6.6%	Thyroid	2.63%	Colon	1.9%	Liver	5.26 %
Prostate	5.6%	--	--	--	--	--	--
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METASTASIS FROM DIFFERENT SITES

Different frequencies of metastasis from various extra-oral sites to the oral & maxillofacial regions has been mentioned which are discussed below.

1. Metastasis from Lung

In Yellin's study (1986), which spanned 40 years from 1943 to 1983 & included 1,900 patients for lung cancer, the incidence of secondary primary upper airway was only 0.05 %. This suggests that patients with lung cancer may be not at a high risk of developing upper airway cancer, including oral cavity.^[30]

Yoshii et al (2002) estimated that the probability of lung cancer involving a diagnosis of gingival metastasis is about 10% to 20%.^[31] Hirshberg et al (1994) reviewed cases of oral metastases reported from 1916 to 1991 & found that in 25.5% of cases, primary tumors were located in the lung.^[4]

2. Metastasis from Breast

According to Epker and colleagues, breast cancer may metastasize to the bone and progress without signs, symptoms, or radiographic changes.^[32]

The primary site from which metastasis to the oral mucosa occur in women are the breasts, and metastasis usually involves the jaw bones,^[33] whereas soft tissues are involved in only 0.1% of all oral lesions.^[34]

Poulias et al (2011) reported a case of metastatic breast cancer mimicking a periodontal abscess.^[35] John Horton et al (1973) observed unilateral numbness of the chin in 400 patients with breast cancer, but according to them reason for breast cancer to cause this symptom was not clear.^[36]

3. Metastasis from Kidney

Despite being reported infrequently, head and neck region metastasis may be linked to renal cell carcinoma (RCC) in up to 8–15% of cases. The nose and paranasal sinuses are most commonly affected followed by the oral cavity. Within the oral cavity, the tongue is a frequent target for RCC metastasis while isolated cases spread to the floor of mouth are rarely reported.^[37] The metastasis from renal cell carcinoma presented as an ulcero-proliferative growth with soft tissue involvement.^[5]

A comprehensive review of the relative literature from 1914 to 2008 includes only 21 cases of renal tumors with lingual metastasis.^[38] As a rule, primary lesions metastasizing to the tongue are uncommon, with an incidence as low as 0.2% in a series of 6881 autopsies performed on cancer patients.^[39] Also when the tongue is involved, it is most often at the base, because of its rich vascularization.^[40]

5. Metastasis from Liver

Hepatocellular carcinoma (HCC), with an estimated 1 million cases per year, is the 5th most common cancer in the world, particularly in the Southeast Asia. [41] The mandible is a rare site of HCC metastasis. [42]

Two modes of spread were ever proposed for the tumor spreading from the liver to the maxillofacial territory. The metastatic dissemination reaches the lungs first, and possibly the maxillofacial area later through the communication between the hepatic artery and portal vein. It has been postulated that there is a connection between the azygos and hemiazygos veins and the vertebral venous plexus (Batson's plexus). [43,44]

There is the existence of free communication between the neck, thorax, abdomen and pelvis venous systems with the non-valve vertebral venous plexus that extends from cranial base to coccyx. Any pressure increment inside the abdomen can create an ascendant flow through the vertebral venous plexus. The HCC cells could reach maxillofacial territory through these two hematogenous connections and grow into a metastatic lesion in the mandibular region. [42]

6. Metastasis from Prostate

Prostate cancer is the most frequently diagnosed cancer in men, the most common site of prostate cancer metastasis is the bone. The literature suggests that jaws are not a common site of prostatic metastasis (1 % of all metastatic bone lesions). This low rate is

linked to low active bone marrow content in jaw bones of adult patients [4,28,45] ; only 40 cases have been reported in the international literature. [16]

7. Metastasis from Colorectal region

Colonic carcinoma is the most frequent malignant gastrointestinal neoplasm, and one of the commonest tumors in the general population. Colorectal cancers commonly metastasize to the liver or lungs [46] and it is not uncommon that multiple sites are involved before the oral presentation.

Metastasis from a colorectal carcinoma to the oral cavity is primarily to the bone, but there have also been a few case reports of oral metastasis to soft tissue sites such as the gingiva. [47] Tejinder Singh et al (2011) reported a case of metastasis to the floor of mouth from colorectal carcinoma. [48]

8. Metastasis from Thyroid

Thyroid carcinoma is the most frequently diagnosed endocrine carcinoma and the most common cause of death among patients with these tumours. [49] Bone metastases are found in 1-3 % of well-differentiated thyroid carcinomas, occurring more often in follicular carcinoma and in patients more than 40 years of age. The presence of a distant metastasis in an adult is associated with poor prognosis with an overall mortality of 50 per cent within 1-6 years post-operatively. [50]

A review by Batsakis showed that out of 115 metastasizing jaw tumors 6.1 %

constituted thyroid tumors metastasizing to the jaws [51] & according to Hirshberg et

al (1994) thyroid carcinoma constitutes about 3.85% of all jaws metastases. [4]

Table 5: Origin and site of metastatic tumors to the oral region in men. [52]

Soft tissue	Jawbones
Lung - 31%	Lung - 25%
Kidney - 14%	Kidney - 10%
Skin - 12%	Liver - 8.6%
Liver - 7.5%	Prostate - 7.5%
Colorectum - 5.2%	Bone - 7.5%
Bone - 5.2%	Adrenal gland - 5.3%
Testis - 4.5%	Colorectum - 4.7%
Esophagus - 4.5%	Testis - 4.4%
Stomach - 3.7%	Esophagus - 3.6%
Rare tumors - 12.4%	Stomach - 2.5%
--	Bladder - 2.5%
--	Rare tumors - 17.6%

Table 6: Origin and site of metastatic tumors to the oral region in women. [52]

Soft tissue	Jawbones
Breast - 24%	Breast - 36.6%
Genital organs* - 14%	Genital organs* - 9.5%
Kidney - 12%	Kidney - 8.5%
Lung - 9.4%	Colorectum - 7.1%
Bone - 9.4%	Bone - 6.7%
Skin - 6.8%	Adrenal gland - 5.8%
Colorectum - 6.8%	Thyroid - 5.4%
Rare tumors - 16.8%	Rare tumors - 20.4%

*Uterus, ovaries, cervix, and fallopian tubes.

Metastasis in the Post-extraction site

A peculiar site for metastasis is the post extraction site. Hirshberg et al (1994) reported 55 cases out of 390 cases, in which metastatic tumor was found in post extraction site. The average time between extraction and appearance of the metastasis was 2 months. [4]

DISCUSSION:

The most common sources of metastatic lesions to the oral mucosa were the breasts for women and lungs for men. This is not surprising, since malignant tumors of the breast and lungs are common. However, there were differences between the incidence of

certain primary malignant tumors and their incidence as metastases in the oral mucosa. In part, this can be explained on the basis of different biologic behavior of the primary malignancy. [53,54]

Prostatic carcinoma, for example, which is a common malignant tumor in men, prefers bone as its metastatic target. Therefore, it rarely colonizes in the oral mucosa (only one case reported in the literature). On the other hand, renal cell carcinoma, a relatively uncommon malignant tumor, is the second most prevalent malignant tumor metastasizing to the oral mucosa. This is probably due to its tendency to disseminate widely early in the course of the disease. [53,54]

Metastasis to orofacial region

The metastasis to orofacial region can be discussed depending on the involvement of jaw bones & oral soft tissues. In majority of cases mandible is commonly affected as compared to maxilla, whereas in soft tissues gingiva is the most common site of involvement both in mandible & maxilla.

a) Jaw bones

Possible routes of metastasis to the oral cavity include arterial, venous and lymphatic circulations. In the case of head and neck metastasis without lung involvement, several theories exist to address a route of dissemination that avoids pulmonary vascular filtration. These include spread via Batson's venous plexus or through the thoracic lymphatic duct. Batson's para-spinal plexus is a

valve-less, venous system extending from the skull to the sacrum allowing tumor emboli to bypass the pulmonary venous system with minimal resistance resulting in metastasis to the head and neck region in the absence of obvious lung lesions. [55]

The pathogenesis of the metastatic process in the jawbones is not clear. Most likely it is not a simple mechanical process because of the uneven distribution of the metastatic spread in the jawbones and oral mucosa, even though these oral structures share a common blood supply. In the skeleton, bones with an active marrow, such as the trunk, ribs, skull, femur, and humerus are the preferential sites for metastatic deposits. [56, 57]

Hematopoietically active marrow represents an attractive site of metastatic involvement because the vascular spaces are sinusoidal in nature and present a relatively easy barrier for tumor cells to penetrate. [57] In addition, the marrow contains growth factors (TGF- β , IGF-I, IGF-II) which may enhance colonization of some metastatic tumors. [4]

The jawbones, especially in old age, are poor in active marrow, which is usually found in the posterior part of the mandible. However, remnants of hematopoietic marrow can also be detected in edentulous mandibles, in cases of focal osteoporotic bone marrow defects. [4] Hashimoto et al (1987), from a study of autopsy cases, suggested that hematopoietic areas in the mandible favor the early deposition of tumor cells. [58]

It is not clear why the jaws are less affected by metastases of osteotropic primary cancers than other bones. However, it may be owing to the fact that the jaws are not rich in hematopoietically active red bone marrow where sinusoidal vascular spaces favour the establishment of metastasis. Moreover breast cancer and prostate cancer often occur in older people in whom the bone marrow of the jaw is even more reduced.^[4]

It is probable that the mandible is more affected by bone metastatic growth than the maxilla because of the pattern of its blood supply. Also the mandibular retromolar area, the jaw site most affected by metastases, has more red bone marrow than other jaw sites.^[59]

Data reported in literature highlight a low incidence in mandibular condyles owing to their low red bone marrow (hematopoietic active) content in adulthood.^[60]

In the maxilla, the metastases were from neuroblastoma, osteosarcoma (common in younger age) and renal cell carcinoma (presented in older age). The lesions involving maxilla presented with variable degree of gross facial asymmetry. The metastatic lesions from neuroblastoma and osteogenic sarcoma presented as expansile lesions of upper alveolus with comparatively less soft tissue involvement. However the metastasis from renal cell carcinoma presented as an ulceroproliferative growth with soft tissue involvement.^[5]

In the younger age group maxilla can be a common site of deposition of the disease due to higher vascularity and hematopoietically active bone marrow. According to Muttagi et al (2011) bone involvement precedes soft tissue involvement in metastatic tumors of the jaw bones.^[5]

b) Soft tissues

The gingiva is the most common oral site for the colonization of metastatic tumor cells. The presence of teeth seems to have a crucial effect on the oral site preference of metastases. In the dentulous patient, 79% exhibited their metastasis in the attached gingiva, whereas in the edentulous patient metastatic lesions were equally distributed between the tongue and the alveolar mucosa.^[3]

Batson^[44] proposed the valve-less vertebral venous plexus as a mechanism for by-passing filtration through the lungs. Once circulating tumor cells reach the oral region, they may be entrapped in the rich capillary network of chronically inflamed attached gingiva. The entrapment may be a simple mechanical one or enhanced by specific local factors. Such local factors may be adhesive molecules on the endothelial surface and exposed basement membrane.^[61-64]

In addition, the new proliferating capillaries in the inflamed gingiva have a fragmented basement membrane and are leaky, making them more penetrable by tumor cells than are mature vessels.^[65] The tumor cells that escape from the capillaries may adhere and degrade the

extracellular matrix elements by tumor proteolytic enzymes, especially collagenase. [66-68] Further growth and proliferation of the metastatic colony may be induced by the tumor cells themselves and by the cleavage products of the matrix components which have growth promoting, angiogenic and chemotactic activities. The latter may promote the migration of tumor cells into the loosened extracellular matrix. [68-70]

Finally, the pathologist must exercise great caution not to mistake a normal microscopic structure for malignancy, particularly metastatic carcinoma. An excellent example is the correct recognition of the juxtaoral organ of chievitz. This is a cluster of nests of squamous epithelial cells, sometimes with a duct-like pattern, found microscopically in tissues taken from the approximate site used by the dentist for the injection of the inferior alveolar nerve. This site is just medial to the mandibular internal oblique

ridge and the pterygomandibular raphe, and from where the biopsy, for one reason or another, might be taken. These epithelial islands are usually intimately associated with myelinated nerves and the suggestion has been made, but not universally accepted, that they might represent neuroepithelial structures with a neuroendocrine receptor function. [71]

CONCLUSION:

Comprehensive knowledge about metastasis to oral and maxillofacial region is of paramount importance from diagnostic as well as prognostic point of view. In the present review an attempt was made to summarize the same based on available literature. Dental surgeons as well as general practitioners should be able to detect oral metastatic cases, as their early referral to appropriate health care facilities will reduce the burden associated with cancer mortality of healthy society.

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