



## RESEARCH ARTICLE

### METASTASIS TO ORAL CAVITY – A REVIEW

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#### ABSTRACT

Cancer is a complex disease involving multifactorial sequential processes. Metastasis is a complex biological course that begins with detachment of tumor cells from the primary tumor, spreading into the distant tissues and/or organs, invading through the lymphovascular structures followed by their survival in the circulation. Metastatic tumors to the oro-facial region are uncommon and may occur in the oral soft tissues or jawbones. The clinical presentation of metastatic tumors can be indistinct, which may lead to erroneous diagnosis or may create diagnostic difficulty. Most of the literature on oral metastases involves either single case reports or reviews of these reported cases from various geographical centres. Hence this review article is an attempt to provide a detailed review of pathogenesis, epidemiological details including clinical and radiographic presentations, microscopic features and treatment of metastatic tumors to the jaws and oral cavity.

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## INTRODUCTION

Of all the diseases *cancer* evokes the strongest emotions. This disease, being one of the major cause of death the world over, presents an enormous challenge to researchers to try and determine its cause, pathogenesis and cure (Meyer, 1965).

<sup>(1)</sup>Tumours are remarkable forms of life which parasitize the host with which they share near complete genetic identity and manifest a complex variety of biochemical, histopathological and clinical characteristics which distinguish each example as unique (Joyce, 2009). Most enigmatic of all is the capability inherent in some tumours to spread to distant sites and organs to form disseminated secondary tumours within the host, a process known as metastasis.

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The clinical significance of metastasis is that this property confers upon tumour cell population the ability to survive the excision of the primary tumour and thereby making treatment and prognosis uncertain because of the possibility of disseminated cells lying dormant or growing in numerous sites (Nguyen, 2009). Not all malignant tumours, however are capable of this behaviour. These are characteristic of certain neoplastic cells as well as host tissue that determines whether the metastasis will occur or not. Some malignant tumours are more likely to metastasize than others. Similarly certain tissues or organs are more likely to provide an ideal environment for metastasis to occur. Liver, lungs and breast are the most commonly encountered sites for metastases however, oral cavity is rare in its regard. 1% of all malignancies represent metastatic foci. Unfortunately most practitioners do not include them in their differential diagnosis. Therefore, there exists a need to increase awareness amongst the pathologists that oral metastases can occur, as diagnosis could significantly change

the treatment modality and hopefully reduce the morbidity of the patient. The present review highlights the important aspects of metastasis in the oral cavity (Naumov *et al.*, 2006).

### Pathogenesis

Metastasis unequivocally marks a tumour as a malignant because benign neoplasms do not undergo metastasis. The invasiveness of cancers permits them to penetrate blood vessels, lymphatics and body cavities providing opportunity for spread. With few exceptions all cancers metastasize except-Malignant neoplasms of glial cells of the central nervous system called as gliomas and basal cell carcinomas of skin. Both these malignant tumours are highly invasive but rarely metastasize. Therefore, next to metastasis, invasiveness is the most reliable feature that differentiates malignant from benign tumours.

Metastasis involves a series of steps from progression of the primary tumor towards site of invasion and spreading of cancer cells through the lymphatic or blood vessels. Circulating cancer cells survive and settle in the microvasculature of the target organ and extravasate through the vessel wall. These cancer cells gain path and advance towards evident metastasis with or without an superseding period of latency. These steps are supported by functions of the cancer cells themselves or of the tumor microenvironment (Joyce, 2009). Cancer cells must possess some characteristics that will allow them to survive in new environment. Thus the successful metastasis depends upon the inherent ability of cancer cells to sustain tumour microenvironment. The tumour progression depends upon angiogenesis and neovascularization. Hypoxia directs the upregulation of few transcription factors which regulates the proangiogenic signals mainly the vascular endothelial cells.

However, how tumours metastasize to jaw bones still remains enigmatic. Within the bones, the metastatic deposits favour the red bone marrow in jaw bones particularly metastasis occurs in age old adults (Zachariades, 1989).

### Epidemiologic Profile

The jaw bones undergo metastatic rate at about 1-1.5% which is very uncommon in contrast to all malignant tumours. The gender distribution reported is however 2:1. The breast is the most common primary site for tumors that metastasize to the jawbones, whereas the lung is the most common source for cancers that metastasize to the oral soft tissues. A recent literature review showed that the jawbones, particularly the mandible is more preferred site and were more frequently affected than other oral soft tissues. The most common primary tumor in male patients is from the lungs and is followed by kidneys, prostate, liver, bone, thyroid and skin (Pires *et al.*, 2004; Whitaker *et al.*, 1993). In female patients, the most common primary cancers are those in the breasts and less frequently from the female genital organs, bone and kidneys.

### Clinical Presentation

Oral metastasis is considered as a late complication and frequently associated with and receded by the metastases of multiple organs. The patient presents with symptoms like dysphagia, disfigurement, bleeding difficulty in chewing. The clinical presentation may create a dilemma in diagnosis. Presence of teeth seems to be a significant determinant on oral site preference for metastases. In the soft tissues, the attached gingiva is the most frequently involved site preceded by the tongue (Hirshberg, 1995).

**Table 1. Differences between metastasis of jaw bones and oral mucosa**

| Sr. no | Feature               | Jaw bones  | Oral mucosa   |
|--------|-----------------------|--|---|
| 1      | occurrence            | More common  | rare  |
| 2.     | gender                | Female predilection  | Male predilection   |
| 3.     | Mean age              | 45 years   | 54 years  |
| 4.     | Primary site          | Breast – most common   | Lung most common  |
| 5.     | Oral site             | Molar area affected<br>Mandible >maxilla   | Attached gingiva<br>Mandible=maxilla  |
| 6.     | Radiographic features | Presence of hematopoietic tissue is important<br>Radiographic evidence may be present<br>Metastatic lesions are difficult to recognize early and may be overlooked | Presence of inflammation is important<br>No radiographic evidence is seen<br>Metastatic lesions are more easily recognized. |

**Table 2. Histologic types of mai metastatic tumors**

| Sr. no | Primary site | Histologic site         | No of cases        |
|--------|--------------|-------------------------|--------------------|
| 1      | Lung         | Squamous cell carcinoma | 8                  |
|        |              | adenocarcinoma          | 7                  |
|        |              | Large cell carcinoma    | 4                  |
| 2.     | Kidney       | Renal cell carcinoma    | 21                 |
|        |              | skin                    | Malignant melanoma |
| 4.     | Bone         | Basal cell carcinoma    | 2                  |
|        |              | Chondrosarcoma          | 4                  |
| 5.     | Stomach      | Osteogenic sarcoma      | 1                  |
|        |              | adenocarcinoma          | 6                  |

**Table 3. Immunologic profile of metastatic epithelial malignancies**

| TUMOR  | ANTIGENIC PROFILE        |
|--------|--------------------------|
| Lung   | CK7+ /CK20-              |
| colon  | CK7-/CK20+/ Villin+      |
| Breast | CK7+ /CK20- / Villin -   |
| Kidney | CK7 - / CK 20- /villin - |

In the early stages, gingival metastases resemble hyperplastic or reactive lesions like those of pyogenic granuloma, peripheral giant cell granuloma, fibrous epulis and periodontal abscesses (Seoane *et al.*, 2009; Petteli *et al.*, 2000). Gingival metastases are shown to be polypoid or exophytic, highly vascularized, and hemorrhagic. In edentulous cases metastatic lesions are spread equally between the tongue and oral mucosa. In some cases however, metastases preceded the tooth extraction as revealed by Hirshberg in his analysis on 56 cases. In many of these cases the metastatic tumor was assumed to be present in the area before extraction. A soft tissue mass extruding from a recent extraction wound accompanied by pain are the encountered symptoms. In many of these cases the metastatic tumor is present in the area before the extraction causing pain, swelling and loosening of teeth. Thus, dental practitioners should be aware of the same and should handle the patients with utmost care. Some authors also reported that metastases may mimic an odontogenic infection and other disease conditions often delaying the prognosis. The complain of patients with numb chin or mental neuropathy should always raise the suspicion of the metastatic disease in mandible signifying the deeper tumour invasion. It is commonly referred to as mental nerve neuropathy or numb chin syndrome.

### Radiologic findings

The metastatic cases do not show a characteristic radiographic findings. Some may represent a lytic lesion or an opaque lesions with ill defined margins. However a balance between osteoblastic and osteoclastic activity determines the phenotype of the lesion. The lesions may be solitary or multiple and in mandible the entire lesion may resemble like a moth-eaten appearance. The cortical bone of adjoining structures such as mandibular canal, maxillary sinus and nasal floor may also show resorption.

### Differential Diagnosis

It includes lesions like those of osteomyelitis, granuloma, cysts, benign tumours, primary malignant tumours with or without extension to adjacent tissues, systemic diseases involving bone such as Histiocytosis X.

### Histologic findings

The histologic diagnosis is very difficult due to rarity of its occurrence. Jaw lesions are commonly presented with a known or previously treated primary. The pathologist may not provide a precise diagnosis since histologic appearance is variable. Lesion should be compared with that of the primary tumor. Usually a distinction of a metastatic tumor from a primary malignancy can be made. In some cases, special staining, immunohistochemical procedure, and electron microscopy may be performed to identify the nature of primary tumor. Though, there are many similarities between metastasis to the jaw bones and the oral mucosa, there are certain features which distinguish the two Table 1.

### Histologic types of main metastatic tumours

According to Hirshberg, most of the tumours were found to be epithelial in origin with only a few mesenchymal in origin. The following table depicts the type of organ and histologic type of the lesion Table 2.

Once a metastatic tumour is suspected, extensive oncologic workup along with imaging techniques required to correctly identify the disease and incorporate the treatment plan.

### Treatment and prognosis

The treatment and prognosis is primarily based on site of origin and degree of metastatic spread. The time of appearance of metastatic lesions is from several months to years. However, the tumour is diagnosed at a later stage in most of the cases. Management of tumours involves surgical resection followed by radiotherapy, chemotherapy and palliative care. The prognosis and overall 5- year survival rate is poor.

### Summary and Conclusion

The most fearsome aspect of cancer is metastasis and this fear is justified. Majority of the patients who die of cancer have disseminated metastasis. Despite the improvements in early diagnosis, surgical techniques, most deaths of cancer patients results from this process. Diagnosis of a tumour metastatic to the mouth or jaws is primarily of academic interest because of the poor prognosis of the condition. Therefore, a complete and accurate history of present symptoms, history of past illness, a systemic review and a complete physical examination are essential for an accurate diagnosis. Thus, perhaps the most essential part in the diagnosis of oral metastases is to think of the possibility of occurrence. Thus, it is rightly said that nothing can be produced without a cause and the effect is but the cause produced.

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