

# Possible Pathogenetic Mechanisms And Overview Of Metastatic Tumours To The Oral Cavity.

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## Abstract

Metastasis to the oral region are uncommon and account for about 1% of the oral malignant tumors and it may occur in the oral soft tissue or jaw bones. In 25% of cases, oral metastasis were found to be the first sign of the metastatic spread and in 23% it was the first indication of an undiscovered malignancy at a distant site. So we can say that oral cavity is the mirror of whole body. Oral lesions and manifestations suspect the possibility of metastasis from distant sites and that initiate the necessary investigations. This article has emphasised on various pathogenetic mechanisms related to tumours metastasizing to oral cavity.

## INTRODUCTION

Cancer is a complex disease in which many basic processes, such as cell division, apoptosis, and cell migration are dysregulated. It is the process of metastasis that results in morbidity and eventual mortality.<sup>1</sup> After a quarter century of rapid advances, cancer research has generated a rich and complex body of knowledge, revealing cancer to be a disease involving dynamic changes in the genome. The foundation has been set in the discovery of mutations that produce oncogenes with dominant gain of function and tumor suppressor genes with recessive loss of function; both classes of cancer genes have been identified through their alteration in human and animal cancer cells and by their elicitation of cancer phenotypes in experimental models.<sup>2</sup>

Cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth 1): self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Each of these physiologic changes novel capabilities acquired during tumor development represents the successful breaching of an anticancer defence mechanism hardwired into cells and tissues. It has been proposed that these six capabilities are shared in common by most and perhaps all types of human tumors. This multiplicity of defences may explain why cancer is relatively rare during an average human lifetime.<sup>2</sup>

Incidence of the metastatic involvement of oral cavity shown in literature ranges from 1% to 8%. These occur in the soft as well as in the osseous tissue of the upper and lower jaw. Meyer and Shklar (1965) reported, out of 2,400 malignancies in the mouth and jaws, only 25 were accepted as metastatic tumours.<sup>5</sup> Because of their rarity, metastatic tumours to the oral region are challenging to diagnose. Therefore, they should be considered in the differential diagnosis of inflammatory and reactive lesions that are common to the oral region.<sup>3</sup> In some cases, the oral lesion is the first and only symptom of malignant disease of a primary which might be growing silently elsewhere in the body<sup>4,5,6</sup> (Clausen and Poulsen, 1963 ; McDaniel R.K et al 1971; Meyer and Shklar, 1965).

The criteria for considering a malignant neoplasm to be metastatic are as follows<sup>7,8</sup> (Bertelli A.P. et al, 1970, Solomon and Gardner, 1975, Zichariades N, 1989).

1. There must be a histologically verified primary.
2. The secondary lesion must be histologically the same as primary.
3. The possibility of direct extension from the primary must be excluded.

## PATHOPHYSIOLOGY OF METASTATIC TUMOURS

The oral region is an uncommon site for metastatic lesions. However, several factors can enhance metastatic

colonization in the oral region. Pathogenesis of metastasis to jaw bones is unclear. Jaw bones have very little red bone marrow and remnant haematopoietic tissue in the posterior areas may be the site for metastasis.<sup>9</sup> The type of interaction between the bone microenvironment and the tumour cells can potentially give rise to osteolytic (bone resorbing) or osteoblastic (bone forming) metastasis. Osteolytic bone metastases are characteristic for most malignancies, and indeed, over 90% of jawbone metastases presented as osteolytic lesion. It should be noted, however, that about 5% of the reported cases of metastases to the jawbones, lacked any radiographic change.<sup>10</sup> Hanahan and Weinberg, have brilliantly described the processes involved in the detachment of tumour cells from the primary cancer site, its transport through the lymphatics or blood stream and establishment of a metastatic tumour site. The literature indicates that metastases are more frequent in the mandible than the maxilla due to paucity of active red marrow in the latter. Tumour metastases to the jaws occur via the blood stream by embolization as the jawbones lack lymphatics.<sup>11</sup>

Metastases are common from carcinoma (83%) compared to sarcomas (17%). Lung and breast carcinomas account for the majority that metastasize to oral cavity constituting 50-6% of all tumours.<sup>12,13</sup>

Presence of teeth seems to be an important determinant on oral site preference for metastases. In dentulous patients, 80% of the metastatic tumors to the oral soft mucosa are found in the attached gingiva, whereas in edentulous patients, metastatic lesions are equally distributed between the tongue and the alveolar mucosa. Inflammation may play a role in the attraction of metastatic cells towards the attached gingiva. Malignant cells may be entrapped by the rich capillary network of the chronically inflamed gingiva. The microenvironment present in the chronically inflamed gingiva may favour the progression of the metastatic cells. Chronic inflammation has been linked to various steps involved in tumour genesis, including cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis.<sup>1,10</sup>

Possible routes of metastatic spread to the tongue are the arterial, venous and lymphatic circulation. Metastases are mostly located on the base of the tongue possibly due to its rich vascular supply, through the dorsal lingual artery, and due to immobility as compared to other parts of the tongue. Head and neck metastasis is commonly associated with lung metastases. If there are no signs of pulmonary disease, it is

possible that spread has been via Batson's venous plexus or via the thoracic duct. Batson's venous plexus extends from the skull to the sacrum. This valveless system theoretically offers less resistance to the spread of tumour emboli, especially when there is an increase in intrathoracic and intra-abdominal pressure, allowing retrograde flow by-passing pulmonary filters.<sup>14,15</sup>

Esophageal carcinoma represents 1.5% of all malignancies, with an annual incidence of approximately 10 cases / 100,000 population<sup>16,17</sup> (Ellis G. L. et al. 1977; Cukingnan RA et al, 1978; Bucin E. et al. 1982). Metastatic esophageal lesion can be disseminated via the lymphatics or blood vessels. Tumor emboli may enter the caval system and subsequently metastasize to distant sites<sup>18,19,20,21</sup> The low incidence of metastasis to the oral cavity from esophageal sites is perhaps best explained by the tendency of these cancers to remain localized and to progress rapidly, leading to death before metastatic lesion have developed significantly.

**Mortality/Morbidity:** The prognosis is grave for metastatic neoplasms to the oral cavity. The time from the appearance of the metastasis to death is several months.

**Race:** Race has not been studied as a factor in the metastatic process in the oral region; however, changes can occur in different parts of the world, depending on the local prevalence of a particular malignant tumor. For example, in Japanese women, the uterus rather than the breast is reported to be the most common primary sites of cancers that metastasize to the oral cavity. Metastatic tumors originating in cancers of the lung, thyroid, liver, esophagus, and stomach were encountered more commonly in China than in United States.<sup>22</sup>

**Age:** Most metastatic tumors to the oral region occur in patients aged 40-70 years. On average, patients with metastases to the jawbones are younger (ie, aged 45 y) than those with metastases to the oral soft tissues (ie, aged 54 y). The mean ages of these 2 groups differ probably because of cases of metastatic neuroblastoma to the jawbones in children; these cancers have a propensity to metastasize to bones.<sup>23</sup>

**Sex:** The male-to-female ratio is almost equal for metastatic neoplasms to the oral cavity; however, sites within the oral cavity differ. For the jawbones, the male-to-female ratio is 1:1.1; for the oral mucosa, the ratio is 2:1. The primary site differs between the sexes.<sup>1,10,23</sup>

**PRIMARY SITE OF METASTASIS**

The origin of metastasis to the oral mucosa and jaw bones in man and women:

**Figure 1**

	ORAL MUCOSA	JAW BONES
<b>MEN</b>	<ul style="list-style-type: none"> <li>• Lung - 31%</li> <li>• Kidney - 14%</li> <li>• Skin - 12%</li> <li>• Liver - 7.5%</li> <li>• Colorectum - 5.2%</li> <li>• Bone - 5.2%</li> <li>• Testis - 4.5%</li> <li>• Esophagus - 4.5%</li> <li>• Stomach - 3.7%</li> <li>• Rare tumors - 12.4%</li> </ul>	<ul style="list-style-type: none"> <li>• Lung - 25%</li> <li>• Kidney - 10.8%</li> <li>• Liver - 8.6%</li> <li>• Prostate - 7.5%</li> <li>• Bone - 7.5%</li> <li>• Adrenal gland - 5.3%</li> <li>• Colorectum - 4.7%</li> <li>• Testis - 4.4%</li> <li>• Esophagus - 3.6%</li> <li>• Stomach - 2.5%</li> <li>• Bladder - 2.5%</li> <li>• Rare tumors - 17.6%</li> </ul>
<b>WOMEN</b>	<ul style="list-style-type: none"> <li>• Breast - 24%</li> <li>• Genital organs (uterus, ovaries, cervix, fallopian tubes) - 14.8%</li> <li>• Kidney - 12%</li> <li>• Lung - 9.4%</li> <li>• Bone - 9.4%</li> <li>• Skin - 6.8%</li> <li>• Colorectum - 6.8%</li> <li>• Rare tumors - 16.8%</li> </ul>	<ul style="list-style-type: none"> <li>• Breast - 36.6%</li> <li>• Genital organs (uterus, ovaries, cervix, fallopian tubes) - 9.5%</li> <li>• Kidney - 8.5%</li> <li>• Colorectum - 7.1%</li> <li>• Bone - 6.7%</li> <li>• Adrenal gland (cases of neuroblastoma, including cases from retroperitoneum and mediastinum) - 5.8%</li> <li>• Thyroid - 5.4%</li> <li>• Rare tumors - 20.4%</li> </ul>

According to the Western literature, metastatic tumours in the oral region mainly originate from the breast, followed by the lung, kidney, thyroid gland, intestine, prostate gland, stomach, testis and bladder.

**CLINICAL PRESENTATION OF VARIOUS ORAL METASTATIC TUMOURS**

Primary carcinomas metastasizing most frequently to the oral region are those of the breast and lung. The clinical presentation of metastatic tumors can be variable, which may lead to erroneous diagnosis or may create diagnostic dilemma. In some cases, the oral lesion is the first and only symptom of malignant disease of a primary which might be growing silently elsewhere in the body<sup>4,5,6</sup>

Oral metastasis is considered a late complication and is commonly associated with multiple organ metastases. Oral metastases can grow rapidly causing pain, difficulty in chewing, dysphagia, disfigurement and intermittent bleeding, leading to poor quality of life. In some cases metastases is discovered after a recent dental extraction at the site.

In the jawbones most patients complained of rapidly progressing swelling, pain and paresthesia.

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 a few cases the lesion appeared as ulceration. In some cases, especially those of metastatic hepatocellular carcinoma, severe post-biopsy hemorrhagic episodes had been reported.<sup>23</sup>

A peculiar site for metastasis is the post-extraction site. Analysis of the literature by Hirshberg revealed 56 cases in which tooth extraction preceded the discovery of the metastases. In many of these cases the metastatic tumour was assumed to be present in the area before extraction.<sup>1,10</sup>

Metastatic lesions may mimic odontogenic infections and other disease conditions in the oral cavity in presentation leading to late diagnosis by the unwary clinician.

**Figure 2**

Table1: Demographic analysis of 10 cases reviewed from literature which were diagnosed by the sign and symptoms appeared in the oral cavity

s. No.	References	Age/ Sex	Primary site	Secondary site	Signs and symptoms	Clinical outcome
1	Tamiolaki et al (2008) <sup>24</sup>	60y/ F	Thyroid gland	Mandible	facial swelling, pain, oral ulceration, bleeding and nasal obstruction.	Died 1 month after diagnosis
2	Stavropoulos and Ord (1993) <sup>25</sup>	60/F	Breast	Mandibular condyle	Pain in TMJ	Survived
3	Azam F et al (2008) <sup>15</sup>	78/M	Renal carcinoma	Tongue	Difficulty in swallowing with pain in his pharynx. 3 × 2 cm solitary pedunculated lesion on the anterior two thirds of tongue.	Patient survived after radiotherapy, with nephrectomy
4	Dhanrajani P et al (2001) <sup>3</sup>	35/F	Oesophagous	Alveolus	soft tissue pedunculated mass in the region of right maxillary alveolus.	Survived
5	Dhanrajani P et al (2001) <sup>3</sup>	6 months F	Kidney	Maxilla	Rapidly growing soft tissue mass over right maxilla resembling an epulis.	Died 18 months after diagnosis
6	Rajappa S (2005) <sup>9</sup>	59y/ M	Retrperitoneal leiomyosarcoma	Palate	3 months history of constipancy, hesitation in micturation, dysuria, weight loss. 1×1 cm nodule in hard palate.	Died 15 weeks after the appearance of palatal swelling
7	Rajappa S (2005) <sup>9</sup>	40y/ M	Lungs	Gingiva	Exertional dypnea and non productive cough of 3 months duration. 1×1 cm non ulcerated nodule over lower gingival.	Succumbed of disease 18 weeks after diagnosis
8	Adebayo et al (2004) <sup>11</sup>	45y/ M	Breast	Maxilla	Facial swelling, pain	Survived after radiotherapy and resection
9	Adebayo et al (2004) <sup>11</sup>	60y/ F	Thyroid	Maxilla	Facial swelling, nasal obstruction, epistaxis	Succumbed two months after diagnosis
10.	Llanes (1996) <sup>26</sup>	66/M	Liver	Gingiva	Non ulcerated nodule over lower gingival	Survived

All the cases which were diagnosed based upon the first sign and symptoms in the oral cavity, are screened in the pubmed from 1993 to 2008. These cases are collected and reviewed; details of which are tabulated in table 1.

Special attention should be given to patients with “numb chin syndrome” or mental nerve neuropathy, a symptom which should always raise the suspicion of a metastatic disease in the mandible. With the progression of the disease, oral metastatic lesions, especially those located in the soft tissues, cause progressive discomfort. Pain, bleeding,

superinfection, dysphagia, interference with mastication, and disfigurement are some of the main complaints of patients. In some cases, the metastasis is discovered in a recent extraction site. A soft tissue mass extruding from a recent extraction wound accompanied by pain are the main symptoms. In many of these cases the metastatic tumour is present in the area before the extraction causing pain, swelling and loosening of teeth. Theses symptoms lead the clinician to extract the affected tooth. however, in some cases, metastasis probably develops after extraction. Tooth extraction can serve as a promoting factor in the metastatic process.

In patients with a known malignant disease, the clinical presentation may favour the pre-operative diagnosis of metastasis. However, in 24% of patients, the metastatic lesion in the oral region is the first indication of an undiscovered malignancy at a distant site.<sup>1,4,23</sup>

**ORAL CAVITY TUMOURS WHICH CAN MIMIC METASTATIC TUMOURS**

**ORAL SOFT TISSUES**

- Oral Soft TMalignant Melanoma
- Pyogenic Granuloma (Lobular Capillary Hemangioma)
- Oral Fibromas and Fibromatoses
- Peripheral Giant Cell Granuloma
- Squamous Cell Carcinoma

**JAW BONE (DIFFERENTIAL DIAGNOSIS DEPENDS ON LOCATION)**

- Malignant tumors (eg, primary intraosseous carcinoma, other malignant odontogenic tumors)
- Central malignant salivary gland tumors
- Sarcoma (eg, malignant fibrous histiocytoma, fibrosarcoma)

**BONY LESION CAN MIMIC BENIGN LESION (SOME CASES)**

- Periapical pathology
- Infected odontogenic cyst or tumor
- Osteomyelitis

## **DIAGNOSIS**

The following steps constitute the diagnostic algorithm for evaluation of oral metastases:

Review the clinical history.

Review the available radiographic findings.

If a history of a previous tumor exists, obtain the slides and reports for review.

Perform a biopsy of the lesion.

Evaluate the light microscopic features of the neoplasm. On the basis of the histologic features, determine the need for special studies (eg, histochemical staining, immunohistochemical tests, electron microscopy). (cancer journal)

The histologic diagnosis is a keystone in evaluating patients with cancer of unknown primary. Attention should be given to differentiating primary intraoral malignancies from metastatic tumours. Several primary intraoral malignancies, especially those originating from salivary glands, have similar histological features to tumours occurring in distant organs. For example, primary ductal carcinoma of salivary gland origin versus metastatic breast carcinoma; primary intraoral clear cell tumour of salivary gland origin or intraosseous clear cell carcinoma versus metastatic renal cell carcinoma; and primary squamous cell carcinoma versus metastatic squamous cell carcinoma from the lung. In addition, malignant soft tissue tumours may originate intraorally but, because of their relatively uncommon occurrence in the oral region, metastatic origin should be considered. Plan the treatment protocol based on the clinical, pathological, and radiographic informations.

## **CONCLUSION**

Misdiagnosis of a metastatic lesion as a benign reactive lesion may delay diagnosis and treatment. Metastatic tumors should always be considered in the differential diagnosis of benign-looking lesions in the oral cavity, especially in patients with a previous history of a malignant disease. Biopsy is mandatory to establish an accurate diagnosis.

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