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REVIEW ARTICLE

METASTATIC CANCERS TO THE ORAL CAVITY: AN OVERVIEW

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Abstract

Metastasis is a complex biological process that begins when cancer cells separate from the original tumor and spread to other tissues and organs, causing morbidity and death. Metastatic cancers to the oral cavity are rare and frequently associated with widespread disease. The diagnosis of these tumors is challenging, and their prognosis is poor. The purpose of this paper is to review the pathogenesis, clinical and histological features, treatment options, and prognosis of metastatic cancers that affect the oral cavity.

Keywords: Cancer, metastasis, oral cavity.

INTRODUCTION

According to the National Cancer Institute, cancer is a disease in which some of the body's cells grow uncontrollably and may spread to other parts of the body.[1] It is characterized by complex, sequential, and irreversible dysregulated processes. Metastasis is a complex biological process that initiates with the detachment of cancer cells from the primary tumor, followed by dissemination into distant tissues and organs, resulting in morbidity and mortality.[2]

Metastatic cancers to the oral cavity are rare (1% to 3% of all malignant oral neoplasms) and frequently associated with widespread disease and poor prognosis. They can affect the soft tissues of the mouth, the jawbones, or both of them.[2,3] The kidney, the lung, the breast, the prostate, the bone, the colon, and the adrenal gland are among the initial sites of malignancies that spread to the oral region, and the mandible, especially the molar region, is the most frequently involved site.[4,5]

The distribution of primary tumors and their typical oral metastatic patterns is summarized in Table 1.

Table 1. Primary Tumor Sites and Frequency of Oral Metastasis

Primary tumor site	Relative frequency	Common oral location	Typical pattern
Lung	High	Gingiva, jawbones	Osteolytic, fast-growing
Breast	High	Mandible, soft tissue	Mixed lytic/blastic
Kidney	Moderate–High	Gingiva, tongue	Highly vascular soft tissue mass
Prostate	Moderate	Mandible	Osteoblastic lesions
Colon/Rectum	Low–Moderate	Jawbones	Osteolytic lesions
Thyroid	Low	Jawbones/soft tissue	Vascular lesion, bleeding tendency
Adrenal gland	Rare	Mandible	Osteolytic destructive lesion

Clinically, metastatic cancers to the oral cavity often show non-aggressive signs that look like harmless or reactive lesions or even simple odontogenic infections; consequently, it may be difficult for both the pathologist and the dentist to diagnose them.[2] Actually, the pathologist must identify the location of the tumor's origin, and the clinician must recognize the possibility that a lesion could be a metastasis. These tumors are very important from a clinical perspective because they could represent the first symptom of an undetected cancer at a distant primary site or the first sign of a known tumor spreading from its originating site.[2,5,6] The aim of this paper was to review the pathogenesis and clinical and histological features, as well as the treatment and prognosis of metastatic cancers to the oral cavity.

Epidemiology

Metastatic cancers to the oral cavity are rare, occurring in about 1% to 3% of cases.[7-9] They are mostly patients aged between 40 and 70 years. Generally, in young patients, metastases are in jaw bones more than in soft tissues. The male-to-female ratio of metastases in oral soft tissues was 2:1, while the distribution in the jawbone was nearly equal by gender.[2] A systematic review conducted by Macedo et al. and published in 2023 found that male patients represented the majority (1.7:1), and most of them were in their sixth decade of life. In 51% of cases, the oral metastatic lesion was the initial indication of malignancy. Furthermore, 60% of them developed metastases to other locations by the time of clinical evaluation.[10] Soft tissues, especially the gingiva, account for 58% of oral cavity metastases; the jaws account for 42%, with the mandible having the highest prevalence (89%). The lungs were the most frequently reported primary site of metastatic lesions in the jaws and oral soft tissues.[7,10]

Pathogenesis

Metastasis refers to the process by which a primary tumor invades surrounding tissues and disseminates cancer cells through lymphatic or blood vessels. As these circulating cancer cells travel throughout the body, they can survive and eventually settle in the microvasculature of target organs, where they extravasate through the walls of blood vessels.

These cancer cells enter and progress toward visible metastases. The tumor microenvironment and/or the functions of the cancer cells themselves support these phases.[2,11] Cancer cells must have specific characteristics that enable them to survive in new environments. In fact, the establishment of a successful metastatic area depends on these cells' ability to maintain distinct microenvironments throughout the metastatic process. Furthermore, angiogenesis and revascularization, which involve creating new blood vessels, are essential for tumor growth.[2,11-13] The formation of the tumor vasculature depends on numerous proangiogenic and antiangiogenic, inflammatory, and coagulation factors.[2,14,15] Additionally, hypoxia within the tumor mass stimulates angiogenesis during the early stages of tumor growth by promoting the up-regulation of specific transcription factors that regulate proangiogenic signals, primarily the vascular endothelial growth factors (VEGFs).[14-17] Considerable evidence suggests that the spread of various types of cancer to distant organs is a controlled, site-specific process rather than an accidental occurence.[2,12] Several studies show that many molecular pathways are involved in the lymphatic and hematogenous dissemination of various malignancies.

The oral region is not a favored site for the initial spread of a cancer from its original site but is usually the result of secondary spread from other metastatic lesions. In fact, it is unclear what causes the metastatic cancers in the jawbones. Bone, especially the one with red marrow, is often regarded as a preferred site for the metastatic process by many primary malignancies, particularly those originating in the lungs, breast, prostate, and kidneys.[2,18] Although jawbones typically contain minimal active marrow, particularly in older adults, remnants of hematopoietic active marrow can still be found in the posterior regions of the mandible. These areas are known to attract metastatic tumor cells.[2] As for the oral soft tissues having a rich complex of capillaries, they can easily capture malignant cells. Additionally, chronic inflammation is associated with various stages of tumorigenesis, such as cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis.[4,19]

Clinical features

The clinical features of metastatic cancers to the oral cavity are variable. A comparative overview of the main differences between soft tissue and jawbone metastases is presented in Table 2.

Table 2. Clinical Features: Oral Soft Tissue vs Jawbone Metastases

Feature	Soft tissue metastasis	Jawbone metastasis
Most common site	Gingiva, tongue	Posterior mandible
Growth rate	Rapid	Moderate–rapid
Pain	Variable	Common
Swelling	Exophytic mass	Intraosseous expansion
Ulceration	Frequent	Less frequent
Bleeding	Very common	Occasional
Paresthesia	Rare	Common (“numb chin syndrome”)
Misdiagnosis	Pyogenic lesion, hyperplasia	Osteomyelitis, cyst, periodontitis

Metastatic cancers to the oral cavity can grow fast, causing pain, dysphagia, disfigurement, and intermittent bleeding.

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The majority of them presented as tumors, masses, and swelling, mostly larger than 10 mm in diameter. In the soft tissues, the most commonly involved site is the attached gingiva, preceded by the tongue. The lesions are typically firm and irregular, with or without an ulcerated surface, and they are more often associated with bleeding compared to those in the jaws, which were frequently linked to pain, paresthesia, and sometimes pathological fractures.[8,10] In some cases, metastases are discovered after a recent dental extraction; a painful soft mass extruding from the extraction site is the main symptom.[2]

This schematic illustrates the distribution and key clinical characteristics of oral metastatic lesions, divided into two main categories: soft tissue and jawbone involvement. Soft tissue metastases account for approximately 58% of cases and most commonly affect the gingiva, followed by the tongue and palate. These lesions typically present as rapidly growing exophytic masses with frequent ulceration and bleeding. Jawbone metastases represent approximately 42% of cases, with the posterior mandible being the most commonly involved site, while the maxilla is less frequently affected. Clinically, jawbone lesions are associated with pain, paresthesia (including "numb chin syndrome"), pathological fractures, and radiographic "moth-eaten" radiolucency. This comparison highlights the distinct clinical behavior and diagnostic features of soft tissue versus osseous metastatic involvement in the oral cavity (figure1).

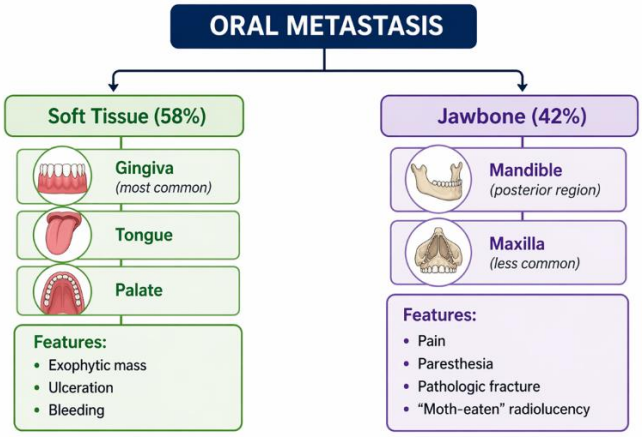

Figure 1. Oral Metastasis Clinical Pattern Map

According to many studies, tooth extraction can serve as a promoting factor in the metastatic process.[8,9,10] Furthermore, the oral metastatic lesion may be the first sign of an undiscovered malignancy at a distant site.[20,21]

Radiological features

Traditional oncology imaging techniques, such as echography, X-ray, CT, and MRI, have been utilized for radiological assessments of cancers, but diagnostic decisions were often limited by low precision. Subsequently, significant advancements in oncologic imaging have revolutionized cancer diagnosis, treatment planning, and monitoring, offering the clinicians valuable insights into tumor characteristics and their responses to therapies. For instance, dual-modality imaging like PET/CT and SPECT/CT combines anatomical, metabolic, and functional information for more accurate disease assessment.[22]

As for the radiographic appearance, metastatic cancers to the oral cavity do not possess a specific one. They can be anything from an osteolytic or opaque lesion with unclear borders to the absence of any signs.[2] The balance between osteoblastic and osteoclastic activity generally determines the characteristics of metastatic bone lesions.[23] Metastases originating from prostate cancer almost always result in the formation of osteoblastic lesions within the bone. In contrast, bone metastases from kidney, lung, or breast cancers tend to be more osteolytic. Furthermore, these lesions may occasionally show up as a single radiolucency of the jawbone that mimics osteomyelitis or an infected cyst. A summary of radiographic characteristics according to primary tumor type is provided in Table 3.

Table 3. Radiographic Characteristics by Primary Tumor Type

Primary tumor	Radiographic pattern	Key diagnostic clue
Prostate	Osteoblastic (radiopaque)	Dense sclerotic bone
Kidney	Osteolytic	"Moth-eaten" destruction
Lung	Osteolytic / mixed	Poorly defined radiolucency
Breast	Mixed pattern	Cortical destruction + expansion
Thyroid	Radiolucent, vascular	Bleeding tendency
Colon	Osteolytic	Aggressive bone loss

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The bone may have a moth-eaten look, which is characterized by numerous tiny, ill-defined holes. The cortical bone of adjacent structures, including the nasal floor, maxillary sinus, and mandibular canal, could be resorbed.[2]

Histological features

The diagnosis of metastatic cancers to the oral cavity is challenging. An incisional biopsy and histopathologic examination are essential to confirm the malignancy of the lesion and potentially its metastatic origin. Furthermore, these lesions present variable histological appearances. In case of a previous tumor history, the microscopic findings of the oral lesion should be compared with those of the primary tumor. However, due to the heterogeneity and sometimes nonspecific features of these lesions, adjunctive techniques are frequently necessary. Special staining aids in identifying specific cellular components, while immunohistochemistry plays a central role in detecting tumor-specific markers and narrowing the primary site. In diagnostically challenging cases, electron microscopy may provide additional ultrastructural detail. [2,24,25]

Table 4 summarizes the integrative approach to histological diagnosis of oral metastatic lesions.

Table 4. Histological Diagnostic Approach for Oral Metastatic Lesions

Diagnostic Method	Purpose	Key Findings / Role	Clinical Relevance
Incisional Biopsy	Initial tissue sampling	Confirms presence of malignant cells	Essential first step in diagnosis
Histopathologic Examination	Microscopic evaluation	Identifies tumor type, differentiation pattern	Helps distinguish primary vs metastatic lesion
Comparison with Primary Tumor	Correlation analysis	Similar morphology with known primary cancer	Strong evidence of metastatic origin
Special Staining	Cellular characterization	Highlights mucin, keratin, or other components	Supports tumor subtype identification
Immunohistochemistry (IHC)	Detection of tumor markers	Expression of CK7, CK20, TTF-1, PSA, etc.	Critical for identifying primary site
Electron Microscopy	Ultrastructural analysis	Detailed cellular architecture	Used in difficult or ambiguous cases

Overall, accurate diagnosis of oral metastatic disease requires a multidisciplinary and multimodal approach, integrating conventional histopathology with advanced diagnostic techniques to ensure precise tumor identification and appropriate clinical management.

Prognosis and management

Metastatic cancers to the oral cavity are usually evidence of a widespread disease and represent a poor prognosis.[26,27] As for the treatment, if the primary tumor has been successfully treated and the patient's medical condition allows, the metastatic lesion should be treated aggressively. Treatment options may include surgical resection, radiation, chemotherapy, or a combination of these methods. However, if the primary tumor has recurred or if there are widespread metastases, the approach to managing the jaw lesion should be more conservative, aiming to relieve the patient's pain while preserving oral function. This approach may include methods such as radiotherapy, chemotherapy, or local surgical excision to reduce the size of the tumor.[2,28]

Stepwise Diagnostic Approach for the Evaluation of Oral Metastatic Lesions

The diagnostic workup of oral metastatic lesions follows a structured, stepwise approach that integrates clinical evaluation, imaging modalities, and histopathological confirmation. Initially, a thorough clinical examination is essential to identify suspicious lesions and assess their morphology, location, and associated symptoms. Radiographic evaluation, including orthopantomogram (OPG) and computed tomography (CT), is then used to detect bone destruction and evaluate the extent of osseous involvement. Magnetic resonance imaging (MRI) provides superior soft tissue contrast and is particularly useful for assessing tumor extension into adjacent anatomical structures.[29,30] Positron emission tomography/computed tomography (PET/CT) plays a critical role in whole-body staging by identifying both the primary tumor and additional metastatic sites. Definitive diagnosis relies on biopsy and

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histopathological examination of the lesion. Subsequently, immunohistochemical analysis is employed to determine the tumor's tissue of origin. In selected cases, molecular markers such as cytokeratin profiles (CK7, CK20), prostate-specific antigen (PSA), and other tumor-specific markers are used to further confirm the primary source of the metastasis.[22, 3] The complete diagnostic pathway is summarized in Table 5.

Table 5. Diagnostic Approach to Oral Metastatic Lesions

Step	Diagnostic tool	Purpose
1	Clinical examination	Identify suspicious lesion
2	Radiography (OPG, CT)	Detect bone destruction
3	MRI	Soft tissue extension
4	PET/CT	Identify primary tumor + metastases
5	Biopsy	Histopathological confirmation
6	Immunohistochemistry	Tumor origin identification
7	Molecular markers	Confirm primary site (CK7, CK20, PSA, etc.)

CONCLUSION

Diagnosing a metastatic lesion in the oral region is challenging, and the prognosis for these lesions is poor; alleviating symptoms is the aim of the therapeutic modality needed. Adequate clinical and histopathological assessments are required for a definitive diagnosis of the lesion and its origin.

Limitations

DECLARATIONS

Ethical Approval

Not applicable.

Consent to Participate

Not applicable.

Competing Interests

The authors declare no conflict of interest.

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