# Detection of metastases in oral squamous cell carcinoma: A diagnostic impasse

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## Abstract

Oral squamous cell carcinoma (OSCC) being the most common malignancy of the oral cavity poses a significant public health problem due to its impact on the speech, mastication, taste, swallowing and esthetics. Moreover, the presence of metastasis either regional or distant worsens the prognosis and reduces the survival rate in these patients. This makes it imperative to diagnose metastasis at an early stage to facilitate appropriate therapeutic management to reduce the morbidity and mortality associated with this disease. There have been several modalities that have been developed and in wide-use for recognition of metastasis with their inherent advantages and disadvantages making it a perplexing dilemma to the clinician and surgeon alike. This paper aims to give an insight into the diagnostic workup available for the evaluation of metastasis in patients with OSCC and reinforces the need for further research to develop more accurate methods.

**Keywords:** Oral squamous cell carcinoma, regional metastasis, distant metastasis, diagnosis

## Introduction

Oral Squamous Cell Carcinoma (OSCC) is the most common malignant neoplasm of the oral cavity. It is a significant public health problem as it can severely impact speech, mastication, taste, swallowing and cosmetics. Significant difference in incidence do exist all over the world that could be attributed to environmental differences, lifestyle and varying habits, such as betel-quid chewing, snuff dipping or the habit of reverse smoking. India has the highest incidence of oral cancer in the world and it is the most common cancer in Indian males (¹).

Primary Oral Squamous Cell Carcinoma (OSCC) is usually noticed by patients or dentists as an ulcer or a proliferating mass. Focusing on areas like floor of the mouth, ventrolateral surface of tongue and soft palate can increase the efficiency of screening examinations as most of the tumors occur in these areas (²). Although oral cancers can be easily detected and often cured in early stages, most oral cancers are already advanced in stage and demonstrate nodal metastasis at the time of diagnosis, especially in the Indian scenario. This pattern has persisted even though there has been rapid development of newer diagnostic techniques (³).

Lymphatic spread is the most important as well as the most frequent pathway for the spread of oral malignancies. Moreover, detection of nodal metastasis at the time of diagnosis is an important prognostic indicator and is associated with 50% reduction in the 5 year survival rate (⁴). The routine clinical examination and palpation of cervical lymph nodes has demonstrated only 68% accuracy in detecting metastasis. Use of CT scan increases this accuracy, but occult metastasis may still be present in about 20% to 45% of patients (⁴). The success of sentinel lymph node biopsy in this regard has been revealed in breast cancer however, its use in OSCC is still unclear due to frequent skip metastasis and proximity of lymph nodes to the primary tumor.

A further dreaded consequence of cancer is its hematogenous spread which directly leads to distant metastasis. Lungs, liver and bone are the
usual organs involved via this path and detection of distant metastasis at the time of diagnosis precludes ≥90% of patients to die within 2 years. About 10%-34% of patients present with distant metastasis at the time of diagnosis and the risk increases with advanced diseases (5). These patients are usually treated with palliative therapy, usually involving chemotherapy, radiotherapy, or both (5).

This review tries to summarize the different methods used to detect metastasis of OSCC and the various limitations that still force the need to search for newer techniques. We have used the time tested TNM staging as a scaffold on which this review will unfold starting with the primary tumors (T), regional cervical lymph nodes (N) and distant metastasis (M).

**Detection of primary tumor (T)**

The T stage or the size of primary tumor is often used to predict the stage of N or M in TNM staging. Consequently, a thorough examination of primary tumor may help in predicting metastasis of OSCC to lymph nodes or distant organs.

**History:** elucidation of a thorough history helps in determining diagnostic and treatment possibilities. Information such as time duration of lesion, difficulty in swallowing and speech, habit of tobacco (smoked and smokeless) may help in predicting spread of the primary tumor.

**Physical examination:** consists of complete evaluation of the head and neck, including a thorough examination of the oral cavity. Characteristics like size, precise location, appearance, texture, color, fixation to bone/adjacent structures of a lesion should be observed(6). For example, anatomic location of the lesion must also be considered as a metastasis indicator, since the tumor behaves differently depending on anatomic locations (6). OSCC of the tongue have a greater risk of metastasis to the cervical lymph nodes. Some patients may require examination under anesthesia, for biopsy and accurate evaluation of lesions that are not easily accessible. Paradoxically, here lies the greatest difficulty, as tumors in posterior part of the oral cavity are difficult to diagnose but they are more prone to metastasize.

**Radiographic evaluation:** evaluation of deep tissue involvement of oral cancer often requires use of several imaging modalities. Plain film radiographs, such as Panorex, occlusal view and antero-posterior and oblique views of the mandible and maxilla usually only demonstrate gross bone involvement. Contrast enhanced Computerized Tomography (CT) scan is by far the most common imaging modality used in the assessment of deep tissue extension of the tumors of the oral cavity. CT scan clearly demonstrates bone changes, such as cortical destruction of skull base and mandible as well as tumor invasion into mandibular canal. MRI can be used in conjunction with or instead of CT and is superior especially in patients with numerous dental amalgam restorations. Additionally for defining soft tissue details or demonstrating intracranial extension of the tumor, MRI is certainly a better option (7) although bony details are not clear in MRI. Ultrasound has been used with limited success in evaluation of oral cancer. With smaller ultrasound probes, one can easily determine whether a lesion is cystic or solid, if there is no bone involvement.

Positron Emission Tomography (PET), a form of nuclear medicine study, uses fluoro-deoxyglucose (FDG) as an imaging isotope. When used alone, PET has shown little advantage over CT and MRI in classifying stage of primary tumors because it lacks the spatial resolution necessary to detail structural integrity and tumor invasion (8). The ability to distinguish abnormal from physiologic FDG uptake along with tumor detection has been enhanced greatly with the development of combined PET/CT scanners. These combined anatomic CT images, along with functional PET images, have increased the efficacy of PET in accurate primary tumor detection.

It appears that use of different modalities can aid in an accurate analysis of the primary tumor and enable to predict the chances of metastasis, so as to perform further tests or treatment to detect/cure metastasis.
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Table 1: The various modalities used to detect nodal and distant metastasis from OSCC.

FNAB: fine needle aspiration biopsy; PET: Positron emission tomography; PET-CT: Positron emission tomography-Computerized tomography; SBFT: small bowel follow through; GIT: Gastrointestinal tract

Detection of nodal metastasis (N)

The head and neck are drained by a rich network of interconnected lymphatics. The pattern of lymph node involvement depends principally on the site of the primary neoplasm and the natural pathway of lymphatic drainage of the site. Usually the ipsilateral cervical lymph nodes are the primary site for metastatic deposits, but occasionally contralateral or bilateral metastatic deposits are detected. The risk of lymphatic spread is greater for posterior lesions of the oral cavity, possibly because of delayed diagnosis or increased lymphatic drainage at those sites, or both. The presence of cervical nodal metastasis is the single most reliable prognostic factor in patients who have OSCC (4). Although lymph node metastasis is not an early event, as many as 21% of individuals with oral cancer present with nodal metastasis at diagnosis (9).

Patients whose metastasis are not clinically evident (N0), the choice of management becomes very difficult (4,9). Reports show rates of occult metastasis for OSCC range from 20% to 45%(4,10).

The common modalities to detect nodal metastasis include the following: (see also Table 1)

Physical examination: it is important to note the number, size and site of lymph nodes involved. The nodal groups at risk for metastatic disease in early stage oral cancer are level I, II, III (9). Cervical nodes with metastatic deposits are firm-to-hard, non-tender enlargements. Once the tumor cells perforate the nodal capsule and invade the surrounding tissue, these lymph nodes become fixed and non-mobile. Studies have shown that sensitivity, specificity and accuracy of detection of cervical neck metastasis by clinical examination are just 70%, 65%, and 68% respectively (10).

Fine needle aspiration biopsy: has a limited diagnostic value in the metastatic evaluation in patients with known oral cancer and cervical metastasis. FNAB is useful for patients who have neck masses of unknown cause, because it may spare patients from the open biopsy (11).

Ultrasound: Though multiple studies have reported success using ultrasound guided FNAB with patients who have N0 neck (12), a study reported that 21% of their patients developed nodal disease during follow-up which were diagnosed as N0 by this technique. Moreover, diagnosing occult metastasis with ultrasound seems to be highly technique-sensitive and user specific, because other studies have been unable to replicate this success (13).

Radiographic evaluation: for assessment of cervical metastasis in patients with a clinically
negative neck node, it requires the use of CT scans of the oral cavity and neck when indicated. It has been observed that the detection rate of cervical lymphadenopathy increases from 75% with physical examination alone to 91% when physical examination is combined with CT (14). A study showed CT evidence of nodal involvement in 30% of patients with clinically N0 necks (15). Nodal necrosis, nodal size, nodal shape and nodal margins are generally the markers for nodal involvement on CT or MRI. Among these, nodal necrosis remains the most specific imaging finding. This is because, cervical node size criteria have not been validated; change in shape from ovoid to round may not correlate with malignancy; and irregular speculated margins just suggest extracapsular tumor spread. CT has been shown to perform slightly better than MRI for detection of nodes involved by metastatic OSCC (16), though MRI may be comparable with CT when axial MRI slice thickness is reduced (16). However, although presence of structural changes, such as cystic changes or necrosis-aids detection, these features are rarely present in occult disease (17).

Genetic biomarkers: cancer is a consequence of genetic and epigenetic alterations that lead to protein dysregulation affecting cell division, differentiation, immune recognition, tumor invasion and metastasis. Use of molecules to discern these tumor specific characteristics as well as to predict their phenotypes and behavior would be highly beneficial in patient management. Several potential genetic biomarkers have been identified as being involved in oral carcinogenesis and possibly metastasis, including EGFR, cyclin D1/CCND1, TP53, E-cadherin, MMP-9, TIMP1, laminin-5, MMP-1 and uPA (18-22).

One critical problem that impedes the use of any of these biomarkers is the tremendous heterogeneity among tumor genetics. Although one of these biomarkers may be found in some oral cancers, it is unlikely to be found in all, or even most oral cancers, thus reducing their sensitivity as a marker for metastasis.

Sentinel lymph node biopsy: the staging of cancer by sentinel lymph node identification and biopsy is based on the concept that metastasis from a primary tumor occurs by predictable orderly spread to the first-echelon nodes before reaching nodes in the remainder of the lymphatic basin. Therefore, histopathologic examination of the sentinel node can define the disease status of the entire regional lymphatic nodal basin. The advantage of this approach is that it is minimally invasive and can potentially be more sensitive in pathologic staging. In this technique either a radiocolloid tracer like technetium-99m-labelled sulfur colloid, or a vital blue dye like isosulfan blue in 1% aqueous solution or the combination of both is injected into the submucosa around the periphery of the entire primary tumor. The tracer and the dye travel quickly to the first echelon sentinel lymph nodes before reaching the second and third echelon nodes. Lymphoscintigraphic imaging is done by a gamma camera and the first echelon lymph node is taken out. The limited material from an SNB allows a focused analysis with a far more detailed search for metastasis than that possible from a neck dissection specimen. The procedure may thus limit morbidity caused by unnecessary neck dissections. Additionally, intra-operative frozen section analysis of sentinel lymph nodes offers the potential to decide immediately whether to perform neck dissection during the same procedure.

Nevertheless, SNB does have its limitations. Clinically positive nodes and even grossly positive nodes that are missed on clinical evaluation are difficult to identify by sentinel node mapping. This is because such diseased nodes often uptake tracer poorly or divert lymphatic flow altogether, resulting in the labeling of downstream nodes (23). Bulky or deeply infiltrative primary tumors that invade adjacent anatomic parts clearly pose technical difficulties for peritumoral injection of the dye. Therefore, the current SNB techniques are limited to the staging of the N0 neck of patients with early-stage primary tumors. It is seen that although sentinel lymph nodes were successfully identified for tumors of the tongue, retromolar trigone, buccal mucosa, lip, alveolar ridge and hard palate, the floor of the mouth still posed a dilemma (24). This may be explained by the proximity of the primary tumor to the anterior oral cavity, creative radioactive shine-through to the draining basin of level I thus obscuring
the nodes present there. Although cervical metastasis from oral cancer usually occurs in an orderly progression from the first-echelon nodes of level I to subsequent levels, cells may flow directly to level III or IV. This phenomenon known as skip metastasis from carcinoma of the tongue was reported in 15.8% of patients in a study (25). Tumor cells escaping the first draining nodes and establishing metastases at lower levels in the basin may go undetected in some patients undergoing SNB. Thus, SNB’s success in case of OSCC is still inadequate and needs additional research.

Detection of distant metastasis (M)

Though lymphatic spread is more commonly seen than hematogenous spread in OSCC, about 10%-34% of patients present with distant metastasis at the time of diagnosis (5), and 90% of patients with distant metastasis usually die within 2 years making it a dreaded consequence of cancer. Veins are penetrated readily than arteries because of the thinner walls that offer less resistance to infiltration. Following venous invasion, the blood-borne cells pursue the venous flow draining the site of the neoplasm with the tumor cells often stopping in the first capillary bed they encounter. Since all portal area drainage flows to the liver, and all caval blood flows to the lungs, the liver and lungs are the most frequently involved secondary sites in hematogenous dissemination.

Location of primary tumor, initial T and N stage of the neoplasm, have direct relation with distant metastasis (26). Distant metastasis rates reported for stage I, II, III and IV head and neck squamous cell carcinoma are 1%, 14%, 15% and 20% respectively (26). Moreover, patients with advanced nodal disease have a high incidence of distant metastasis, particularly in the presence of jugular vein invasion or extensive soft tissue disease of the neck (26). Distant metastasis in the absence of nodal metastasis is very rare in OSCC (26). The rate of early distant metastasis increases up to 16.7% for N3 disease as against 9.2% for N2 disease (27).

The most common sites of distant metastasis for OSCC includes the lungs (66%), bone (22%) and liver (9.5%) (28). Early identification of patients who may be at a high risk for development of distant metastasis and thus subjecting them to adjuvant chemotherapy, have shown improved survival rates and reduced distant metastasis (29).

The common modalities to detect distant metastasis include the following: (please refer to Table 1)

Radiographic evaluation: anteroposterior and lateral view chest radiography generally has been considered to be adequate for screening metastasis to lungs. However, pulmonary metastasis does occur in 15% to 20% of patients initially diagnosed as M0 who eventually succumb to their disease (30).

CT scan and ultrasound of the abdomen can be used to rule out metastasis to the liver. Detection of liver metastases on ultrasonography is a widely accepted technique, but it has documented limitations (31). It has shown a sensitivity and specificity of just 40% and 63% respectively. Contrast enhanced ultrasound has improved liver metastases diagnosis in comparison to ultrasound with a reported sensitivity and specificity of 83% and 84% which is almost equal to the sensitivity and specificity of contrast enhanced CT which was about 89% and 89% respectively (31). Nevertheless, FDG-PET has been shown to be the most accurate modality in detection of secondaries in liver (32).

A bone scan or bone scintigraphy may be done to diagnose metastasis to bone. In this technique technetium-99m MDP (methylene-diphosphonate) is injected in the patient and scanned with a gamma camera, a device sensitive to the radiation emitted by the injected material. Bone scans are not recommended in asymptomatic patients and are of little value in ruling out subclinical bone metastasis in case of OSCC (33). For detection of bone metastasis, FDG-PET has shown superior results than bone scan. A sensitivity, specificity and accuracy of 77.7%, 97.6% and 94.1% was shown by PET in comparison to 77.7%, 80.9% and 80.3% respectively by bone scan (33).

Imaging modalities are helpful in diagnosing small bowel metastatic disease. In this case
contrast enhanced CT remains the mainstay (34), upper GI endoscopy can be used to diagnose lesions proximal to the ligament of Treitz and can replace upper GI radiography (35). Small bowel distal to ligament of Treitz can be assessed either by enteroscopy, small bowel follow through (SBFT) or enteroclysis. A study found sensitivity of 61% for SBFT and 95% for enteroclysis, similarly demonstration of tumor was achieved in 33% of SBFT and 90% of enteroclysis in primary small bowel cancers (36).

**Tumor markers:** are substances that can be measured quantitatively by biochemical or immunochemical means, in tissue or body fluids, have been used to detect metastasis. Altered levels of Alpha fetoprotein (AFP) and skeletal alkaline phosphatase (sAP) may predict a metastasis to liver and bone respectively. But these markers cannot give a final diagnosis and can only be considered as adjuncts since alteration of these chemicals may occur in other conditions also (37).

**Circulating tumor cells:** Today, the importance of circulating tumor cells (CTCs) as an independent prognostic marker has been widely confirmed (37). CTC have a short survival time in blood, so accidental detection of tumor cells is unlikely unless there is a permanent new efflux of tumor cells. Circulating tumor cells can get lodged at any site and start multiplying to cause secondaries in that organ. CTC can therefore most likely be detected during tumor progression, which helps in diagnosis, prognosis and evaluation of therapeutic evaluation (38). A large number of studies have documented circulating tumor cells (CTCs) in peripheral blood from patients with most types of epithelial cancers (38). Still, the clinical use of CTCs has not been implemented for routine clinical practice for several reasons, like lack of standardization and automation of the technology, different reagents and methods used for staining and evaluation of immunocytochemically stained slides. Thus further studies need to be done in OSCC to prove the clinical significance of CTC in peripheral blood.

**Conclusion**

Several imaging techniques including CT, MRI, PET, ultrasound, PET/CT have been used for detection of metastasis of OSCC. Unfortunately, despite improved resolution and software analysis, these techniques are still insufficiently sensitive for revealing occult neck metastasis, as 20% to 45% of patients staged as N0 using these techniques exhibit occult nodal involvement on pathologic evaluation of the neck. For imaging techniques to be useful in treatment decisions, they must be able to detect metastatic nodes in patients with early stage tumors. In addition, these techniques must not only be sufficiently sensitive to detect microscopic disease but also specific enough so that frequent false negative results do not lead to universal prescription of elective neck treatment resulting in unnecessary patient morbidity. SNB is a technique under investigation for the staging of the regional lymph nodes in patients with OSCC that offers the potential of improving the accuracy of regional staging and thus reducing the morbidity of elective node dissection in patients without metastasis. Further, detection of distant metastasis is exceedingly complicated as tumor markers are less specific, CT, MRI bone scan are incapable for detection of occult metastasis and true clinical significance of CTC’s requires further study. Consequently, the ideal method to detect metastasis still remains elusive and opens a wide avenue for research.
References


